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HENRY FORD HEALTH

Henry Ford Health Publication List – August 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 111 unique citations listed this month. 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

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Allergy and Immunology
Anesthesiology
Behavioral Health Services/Psychiatry/Neuropsychology
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Orthopedics/Bone and Joint Center
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Pulmonary and Critical Care Medicine
Radiation Oncology
Research Administration
Rheumatology
Sleep Medicine
Surgery
Urology

Articles

Administration
Aghi MK, Brastianos PK, Kim AH, **Kalkanis SN**, and Tonn JC. Introduction. Update on brain metastases. *Neurosurg Focus* 2023; 55(2):E1. PMID: 37527676. Full Text

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2Division of Hematology/Oncology, Massachusetts General Hospital, Harvard Medical School, Boston, Massachusetts.
3Department of Neurosurgery, Washington University School of Medicine, St. Louis, Missouri.
4Henry Ford Health, Detroit, Michigan.
5Department of Neurosurgery, Ludwig Maximilian University, Munich, Germany; and.
6German Cancer Consortium (DKTK), Partner Site Munich, Germany.

Administration
Jamil M, Salam A, Joseph Benher BM, **Rehman S**, Jamil J, and **Suleyman G**. A Case of Alcohol Withdrawal-Induced Central and Extrapontine Myelinolysis. *Cureus* 2023; 15(7):e41640. PMID: 37565130. Full Text

Internal Medicine, Henry Ford Health System, Detroit, USA.
Internal Medicine, Khyber Teaching Hospital, Peshawar, PAK.
Internal Medicine, Wayne State University, Detroit, USA.
Internal Medicine, Henry Ford Health System, Detriot, USA.
Internal Medicine, Gulf Medical University, Ajman, ARE.
Infectious Disease, Henry Ford Health System, Detroit, USA.

A 40-year-old female with a history of chronic alcohol use disorder presented with an acute intractable left-sided headache for three days and progressively worsening unsteady gait requiring a wheelchair to ambulate. The patient had a history of chronic alcoholism since 2019 but reported abstinence since September 2021. One month after quitting alcohol, she experienced a sudden deterioration in bilateral extremity neuropathy, forgetfulness, difficulty writing, and severe mood swings, which continued to worsen until her presentation in July 2022. Laboratory tests, including complete blood count and electrolyte levels, were within normal ranges. A previous MRI performed during the investigation for alcoholic neuropathy a few months before she quit drinking showed no abnormalities. However, a subsequent MRI during work-up for the current acute symptoms revealed significant signal abnormalities involving the central pons, bilateral cerebral peduncles, and medullary pyramids, consistent with chronic central pontine myelinolysis (CPM) with extrapontine myelinolysis (EPM) extending into the peduncles. The patient received treatment with folate and multivitamins and was scheduled for outpatient follow-up with physical therapy for rehabilitation. This case highlights CPM as a consequence of alcohol withdrawal and emphasizes the importance of timely diagnosis and appropriate management in such patients.

Administration
Li JH, Perry JA, Jablonski KA, Srinivasan S, Chen L, Todd JN, Harden M, Mercader JM, Pan Q, Dawed AY, Yee SW, Pearson ER, Giacomini KM, Giri A, Hung AM, **Xiao S**, **Williams LK**, Franks PW, Hanson RL, Kahn SE, Knowler WC, Pollin TI, and Florez JC. Identification of Genetic Variation Influencing Metformin Response in a Multiancestry Genome-Wide Association Study in the Diabetes Prevention Program (DPP). *Diabetes* 2023; 72(8):1161-1172. PMID: 36525397. Full Text

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Diabetes Unit, Department of Medicine, Massachusetts General Hospital, Boston, MA.
Programs in Metabolism and Medical and Population Genetics, Broad Institute of Harvard and MIT, Cambridge, MA.
Department of Medicine, Harvard Medical School, Boston, MA.
Department of Medicine, University of Maryland School of Medicine, Baltimore, MD.

Department of Epidemiology and Biostatistics, George Washington University Biostatistics Center, Washington, DC.
Division of Pediatric Endocrinology and Diabetes, Department of Pediatrics, University of California, San Francisco, San Francisco, CA.
Division of Endocrinology, Department of Pediatrics, Boston Children's Hospital, Boston, MA.
Division of Population Health and Genomics, Ninewells Hospital and School of Medicine, University of Dundee, Dundee, U.K.
Department of Bioengineering and Therapeutic Sciences, University of California, San Francisco, San Francisco, CA.
Division of Quantitative Sciences, Department of Obstetrics and Gynecology, Vanderbilt University Medical Center, Nashville, TN.
Division of Nephrology and Hypertension, Department of Medicine, Vanderbilt University Medical Center, Nashville, TN.
Center for Individualized and Genomic Medicine Research, Department of Internal Medicine, Henry Ford Health System, Detroit, MI.
Genetic and Molecular Epidemiology Unit, Lund University Diabetes Centre, Lund University, Malmö, Sweden.
Diabetes Epidemiology and Clinical Research Section, National Institute of Diabetes and Digestive and Kidney Diseases, Phoenix, AZ.
Division of Metabolism, Endocrinology and Nutrition, Department of Medicine, VA Puget Sound Health Care System and University of Washington, Seattle.

Genome-wide significant loci for metformin response in type 2 diabetes reported elsewhere have not been replicated in the Diabetes Prevention Program (DPP). To assess pharmacogenetic interactions in prediabetes, we conducted a genome-wide association study (GWAS) in the DPP. Cox proportional hazards models tested associations with diabetes incidence in the metformin (MET; n = 876) and placebo (PBO; n = 887) arms. Multiple linear regression assessed association with 1-year change in metformin-related quantitative traits, adjusted for baseline trait, age, sex, and 10 ancestry principal components. We tested for gene-by-treatment interaction. No significant associations emerged for diabetes incidence. We identified four genome-wide significant variants after correcting for correlated traits ($P < 9 \times 10\text{-}9$). In the MET arm, rs144322333 near ENOSF1 (minor allele frequency [MAF]AFR = 0.07; MAFEUR = 0.002) was associated with an increase in percentage of glycated hemoglobin (per minor allele, $\beta = 0.39$ [95% CI 0.28, 0.50]; $P = 2.8 \times 10\text{-}12$). rs145591055 near OMSR (MAF = 0.10 in American Indians) was associated with weight loss (kilograms) (per G allele, $\beta = -7.55$ [95% CI -9.88, -5.22]; $P = 3.2 \times 10\text{-}10$) in the MET arm. Neither variant was significant in PBO; gene-by-treatment interaction was significant for both variants [$P(G\times T) < 1.0 \times 10\text{-}4$]. Replication in individuals with diabetes did not yield significant findings. A GWAS for metformin response in prediabetes revealed novel ethnic-specific associations that require further investigation but may have implications for tailored therapy.

Administration

Wu B, Yee SW, **Xiao S**, Xu F, Sridhar SB, **Yang M**, **Hochstadt S**, **Cabral W**, **Lanfear DE**, Hedderson MM, Giacomini KM, and **Williams LK**. Genome-Wide Association Study Identifies Pharmacogenomic Variants Associated With Metformin Glycemic Response in African American Patients With Type 2 Diabetes. *Diabetes Care* 2023; Epub ahead of print. PMID: 37639712. Full Text

Center for Individualized and Genomic Medicine Research (CIGMA), Department of Internal Medicine, Henry Ford Health System, Detroit, MI.
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OBJECTIVE: Metformin is the most common treatment for type 2 diabetes (T2D). However, there have been no pharmacogenomic studies for T2D in which a population of color was used in the discovery analysis. This study sought to identify genomic variants associated with metformin response in African American patients with diabetes. RESEARCH DESIGN AND METHODS: Patients in the discovery set were adult, African American participants from the Diabetes Multi-omic Investigation of Drug Response

(DIAMOND), a cohort study of patients with T2D from a health system serving southeast Michigan. DIAMOND participants had genome-wide genotype data and longitudinal electronic records of laboratory results and medication fills. The genome-wide discovery analysis identified polymorphisms correlated to changes in glycated hemoglobin (HbA1c) levels among individuals on metformin monotherapy. Lead associations were assessed for replication in an independent cohort of African American participants from Kaiser Permanente Northern California (KPNC) and in European American participants from DIAMOND. RESULTS: The discovery set consisted of 447 African American participants, whereas the replication sets included 353 African American KPNC participants and 466 European American DIAMOND participants. The primary analysis identified a variant, rs143276236, in the gene ARFGEF3, which met the threshold for genome-wide significance, replicated in KPNC African Americans, and was still significant in the meta-analysis (P = 1.17 × 10-9). None of the significant discovery variants replicated in European Americans DIAMOND participants. CONCLUSIONS: We identified a novel and biologically plausible genetic variant associated with a change in HbA1c levels among African American patients on metformin monotherapy. These results highlight the importance of diversity in pharmacogenomic studies.

Allergy and Immunology

Bochkov YA, Devries M, Tetreault K, Gangnon R, Lee S, Bacharier LB, Busse WW, Camargo CA, Choi T, Cohen R, De R, DeMuri GP, Fitzpatrick AM, Gergen PJ, Grindle K, Gruchalla R, Hartert T, Hasegawa K, Khurana Hershey GK, Holt P, Homil K, Jartti T, Kattan M, Kercsmar C, **Kim H**, Laing IA, Le Souëf PN, Liu AH, Mauger DT, Pappas T, Patel SJ, Phipatanakul W, Pongracic J, Seroogy C, Sly PD, Tisler C, Wald ER, Wood R, Lemanske RF, Jr., Jackson DJ, and Gern JE. Rhinoviruses A and C elicit long-lasting antibody responses with limited cross-neutralization. *J Med Virol* 2023; 95(8):e29058. PMID: 37638498. Full Text

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Telethon Kids Institute, The University of Western Australia, Perth, Australia.
University of Turku and Turku University Hospital, Turku, Finland.
PEDEGO Research Unit, University of Oulu and Oulu University Hospital, Oulu, Finland.
Columbia University, New York, New York, USA.
Henry Ford Health Systems, Detroit, Michigan, USA.
University of Western Australia, Perth, Australia.
Children's Hospital Colorado, University of Colorado, Aurora, Colorado, USA.
Penn State University, Hershey, Pennsylvania, USA.
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Child Health Research Centre, The University of Queensland, Brisbane, Queensland, Australia.
Johns Hopkins University, Baltimore, Maryland, USA.

Rhinoviruses (RVs) can cause severe wheezing illnesses in young children and patients with asthma. Vaccine development has been hampered by the multitude of RV types with little information about cross-neutralization. We previously showed that neutralizing antibody (nAb) responses to RV-C are detected twofold to threefold more often than those to RV-A throughout childhood. Based on those findings, we hypothesized that RV-C infections are more likely to induce either cross-neutralizing or longer-lasting antibody responses compared with RV-A infections. We pooled RV diagnostic data from multiple studies of children with respiratory illnesses and compared the expected versus observed frequencies of

sequential infections with RV-A or RV-C types using log-linear regression models. We tested longitudinally collected plasma samples from children to compare the duration of RV-A versus RV-C nAb responses. Our models identified limited reciprocal cross-neutralizing relationships for RV-A (A12-A75, A12-A78, A20-A78, and A75-A78) and only one for RV-C (C2-C40). Serologic analysis using reference mouse sera and banked human plasma samples confirmed that C40 infections induced nAb responses with modest heterotypic activity against RV-C2. Mixed-effects regression modeling of longitudinal human plasma samples collected from ages 2 to 18 years demonstrated that RV-A and RV-C illnesses induced nAb responses of similar duration. These results indicate that both RV-A and RV-C nAb responses have only modest cross-reactivity that is limited to genetically similar types. Contrary to our initial hypothesis, RV-C species may include even fewer cross-neutralizing types than RV-A, whereas the duration of nAb responses during childhood is similar between the two species. The modest heterotypic responses suggest that RV vaccines must have a broad representation of prevalent types.

Anesthesiology

Blum RH, Mai CL, **Mitchell JD**, Saddawi-Konefka D, Cooper JB, Shorten G, and DunnGalvin A. Measuring deliberate reflection in residents: validation and psychometric properties of a measurement tool. *BMC Med Educ* 2023; 23(1):606. PMID: 37626350. Full Text

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Department of Anesthesia and Intensive Care, Cork University Hospital, Cork, Ireland.
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Department of Paediatrics and Child Infectious Diseases, I.M. Sechenov First Moscow State Medical University, Moscow, Russia.

PURPOSE: Reflective capacity is "the ability to understand critical analysis of knowledge and experience to achieve deeper meaning." In medicine, there is little provision for post-graduate medical education to teach deliberate reflection. The feasibility, scoring characteristics, reliability, validation, and adaptability of a modified previously validated instrument was examined for its usefulness assessing reflective capacity in residents as a step toward developing interventions for improvement. METHODS: Third-year residents and fellows from four anesthesia training programs were administered a slightly modified version of the Reflection Evaluation for Learners' Enhanced Competencies Tool (REFLECT) in a prospective, observational study at the end of the 2019 academic year. Six written vignettes of imperfect anesthesia situations were created. Subjects recorded their perspectives on two randomly assigned vignettes. Responses were scored using a 5-element rubric; average scores were analyzed for psychometric properties. An independent self-report assessment method, the Cognitive Behavior Survey: Residency Level (rCBS) was used to examine construct validity. Internal consistency (ICR, Cronbach's alpha) and interrater reliability (weighted kappa) were examined. Pearson correlations were used between the two measures of reflective capacity. RESULTS: 46/136 invited subjects completed 2/6 randomly assigned vignettes. Interrater agreement was high ($k = 0.85$). The overall average REFLECT score was 1.8 (1-4 scale) with good distribution across the range of scores. ICR for both the REFLECT score (mean 1.8, sd 0.5; $\alpha = 0.92$) and the reflection scale of the rCBS (mean 4.5, sd 1.1; $\alpha = 0.94$) were excellent. There was a significant correlation between REFLECT score and the rCBS reflection scale ($r = .44$, $p < 0.01$). CONCLUSIONS: This study demonstrates feasibility, reliability, and sufficiently robust psychometric

properties of a modified REFLECT rubric to assess graduate medical trainees' reflective capacity and established construct/convergent validity to an independent measure. The instrument has the potential to assess the effectiveness of interventions intended to improve reflective capacity.

Anesthesiology
Cohen S, Patel SJ, Grosh T, Augoustides JG, Spelde AE, Vernick W, Wald J, Bermudez C, Ibrahim M, Cevasco M, Usman AA, **Folbe E**, **Sanders J**, and Fernando RJ. Surgical Placement of Axillary Impella 5.5 With Regional Anesthesia and Monitored Anesthesia Care. *J Cardiothorac Vasc Anesth* 2023; Epub ahead of print. PMID: 37574337. Full Text

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Anesthesiology
Nizar R, **Cazacu S**, **Xiang C**, Krasner M, Barbiro-Michaely E, Gerber D, Schwartz J, Fried I, Yuval S, Brodie A, Kazimirsky G, Amos N, Unger R, **Brown S**, **Rogers L**, **Penning DH**, and **Brodie C**. Propofol Inhibits Glioma Stem Cell Growth and Migration and Their Interaction with Microglia via BDNF-AS and Extracellular Vesicles. *Cells* 2023; 12(15). PMID: 37566001. Full Text

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Anesthesiology, Pain Management & Perioperative Medicine, Henry Ford Health, Detroit, MI 48202, USA.

Glioblastoma (GBM) is the most common and aggressive primary brain tumor. GBM contains a small subpopulation of glioma stem cells (GSCs) that are implicated in treatment resistance, tumor infiltration, and recurrence, and are thereby considered important therapeutic targets. Recent clinical studies have suggested that the choice of general anesthetic (GA), particularly propofol, during tumor resection, affects subsequent tumor response to treatments and patient prognosis. In this study, we investigated the molecular mechanisms underlying propofol's anti-tumor effects on GSCs and their interaction with microglia cells. Propofol exerted a dose-dependent inhibitory effect on the self-renewal, expression of mesenchymal markers, and migration of GSCs and sensitized them to both temozolomide (TMZ) and radiation. At higher concentrations, propofol induced a large degree of cell death, as demonstrated using microfluid chip technology. Propofol increased the expression of the lncRNA BDNF-AS, which acts as a tumor suppressor in GBM, and silencing of this lncRNA partially abrogated propofol's effects. Propofol also inhibited the pro-tumorigenic GSC-microglia crosstalk via extracellular vesicles (EVs) and delivery of BDNF-AS. In conclusion, propofol exerted anti-tumor effects on GSCs, sensitized these cells to radiation and TMZ, and inhibited their pro-tumorigenic interactions with microglia via transfer of BDNF-AS by EVs.

Behavioral Health Services/Psychiatry/Neuropsychology
Cheng Z, Cai Y, Zhang K, Zhang J, **Gui H**, Luo YS, Zhou J, and DeVeale B. MAP3K19 regulatory variation in populations with African ancestry may increase COVID-19 severity. *iScience* 2023; 26(9):107555. PMID: 37649700. Full Text

Center for Applied Bioinformatics, St Jude Children's Research Hospital, 262 Danny Thomas Pl, Memphis, TN 38105, USA.
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To identify ancestry-linked genetic risk variants associated with COVID-19 hospitalization, we performed an integrative analysis of two genome-wide association studies and resolved four single nucleotide polymorphisms more frequent in COVID-19-hospitalized patients with non-European ancestry. Among them, the COVID-19 risk SNP rs16831827 shows the largest difference in minor allele frequency (MAF) between populations with African and European ancestry and also shows higher MAF in hospitalized COVID-19 patients among cohorts of mixed ancestry (odds ratio [OR] = 1.20, 95% CI: 1.10-1.30) and entirely African ancestry (OR = 1.30, 95% CI: 1.02-1.67). rs16831827 is an expression quantitative trait locus of MAP3K19. MAP3K19 expression is induced during ciliogenesis and most abundant in ciliated tissues including lungs. Single-cell RNA sequencing analyses revealed that MAP3K19 is highly expressed in multiple ciliated cell types. As rs16831827∗T is associated with reduced MAP3K19 expression, it may increase the risk of severe COVID-19 by reducing MAP3K19 expression.

Behavioral Health Services/Psychiatry/Neuropsychology

Ferber M, **Hecht LM**, **Martens KM**, **Hamann A**, **Carlin AM**, and **Miller-Matero LR**. Examining differences in long-term weight loss outcomes after bariatric surgery: The role of romantic relationship status. *Fam Syst Health* 2023; Epub ahead of print. PMID: 37616105. Request Article

Department of Family and Community Medicine, Medical Family Therapy Program, Saint Louis University.
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Department of Behavioral Health, Henry Ford Health System.
Department of Surgery, Henry Ford Health System.

INTRODUCTION: This study tested for differences based on relationship status at the time of surgery in baseline body mass index (BMI), weight loss outcomes (change in BMI [ΔBMI], percent total weight loss [%TWL], percent excess weight loss [%EWL]), and rates of successful weight loss (defined as ≥ 50%EWL) up to 4-year postbariatric surgery. METHOD: Data came from a secondary analysis of patients (N = 492) who were up to 4-year postsurgery and completed a presurgical psychological evaluation and postsurgical survey. RESULTS: Sixty-nine percent of participants were patients in committed relationships and 31% were single/divorced/widowed patients. Single patients had higher presurgical BMIs than those who were partnered (t = 2.28, p = .02). There were no differences between those who were partnered and singles regarding ΔBMI and %TWL, although singles had smaller %EWL (t = -2.08, p = .04), which became nonsignificant after controlling for covariates. Most participants had successful weight loss (76.8%); however, this was not related to romantic relationship status. DISCUSSION: The results suggest those who were partnered undergo surgery at better-starting weights than singles and maintain this advantage in the long term. Providers working with patients considering bariatric surgery could inquire about how their romantic and social relationships play a part in their decision-making process. (PsycInfo Database Record (c) 2023 APA, all rights reserved).

Behavioral Health Services/Psychiatry/Neuropsychology

Miller-Matero LR, **Yeh HH**, **Maffett A**, **Mooney JT**, **Sala-Hamrick K**, **Frank CB**, Simon GE, Rossom R, Owen-Smith AA, Lynch FL, Beck A, Waring S, Daida YG, Lu CY, and **Ahmedani BK**. Racial-Ethnic Differences in Receipt of Past-Year Health Care Services Among Suicide Decedents: A Case-Control Study. *Psychiatr Serv* 2023; Epub ahead of print. PMID: 37554000. Full Text

Behavioral Health (Miller-Matero, Maffett, Mooney, Frank, Ahmedani) and Center for Health Policy and Health Services Research (Miller-Matero, Yeh, Sala-Hamrick, Ahmedani), Henry Ford Health, Detroit; Kaiser Permanente Washington Health Research Institute, Seattle (Simon); HealthPartners Institute, Minneapolis (Rossom); Department of Health Policy and Behavioral Sciences, School of Public Health, Georgia State University, and Center for Research and Evaluation, Kaiser Permanente Georgia, Atlanta (Owen-Smith); Center for Health Research, Kaiser Permanente Northwest, Portland, Oregon (Lynch); Institute for Health Research, Kaiser Permanente Colorado, Aurora (Beck); Essentia Institute of Rural Health, Duluth, Minnesota (Waring); Center for Integrated Health Care Research, Kaiser Permanente Hawaii, Honolulu (Daida); Department of Population Medicine, Harvard Medical School, and Harvard Pilgrim Health Care Institute, Boston (Lu).

OBJECTIVE: Suicide remains an urgent public health crisis. Although some sociodemographic characteristics are associated with greater suicide risk in the general population, it is unclear whether individuals utilizing health care in the United States have similar suicide incidence patterns. The authors examined whether race-ethnicity is associated with suicide death among patients seeking health care and investigated health care utilization patterns. METHODS: Data were collected from electronic health records and government mortality records for patients seeking health care across nine health care systems in the United States. Patients who died by suicide (N=1,935) were matched with patients in a control group (N=19,350) within each health care system. RESULTS: Patients who died by suicide were significantly more likely to be White, older, male, living in low-education areas, living in rural areas, or diagnosed as having mental health conditions or were significantly less likely to have commercial insurance ($p<0.05$). Among most racial-ethnic groups, those who died by suicide had a higher number of past-year mental health, primary care, and total health care visits; for American Indian/Alaska Native patients, the number of health care visits tended to be lower among suicide decedents. CONCLUSIONS: These findings suggest that higher past-year health care utilization was associated with increased likelihood of suicide death across several racial-ethnic groups. This observation underscores the need for identifying and managing suicide risk in health care settings, including outside of mental health visits, among most racial-ethnic groups.

Behavioral Health Services/Psychiatry/Neuropsychology

Segal A, **Pearl E**, **Fatabhoy M**, **Zohr SJ**, **Bryce K**, **Gonzalez HC**, and **Miller-Matero LR**. Factors associated with a positive phosphatidylethanol test during liver transplantation evaluation. *Clin Transplant* 2023; e15100. Epub ahead of print. PMID: 37577900. Full Text

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BACKGROUND: Early identification of alcohol use is crucial for informing recommendations of appropriate follow-up treatment pre-liver transplant and optimizing post-liver transplant outcomes. The purpose of the study was to investigate whether there are psychosocial factors associated with a positive PEth test. METHODS: All patients who underwent a routine pre-surgical psychological evaluation for liver transplant listing (all etiologies, including acute liver failure, dual organ, and re-transplantation) at a single health care system in 2020 were included in a retrospective chart review. Data extraction included results from PEth testing and information from the psychological evaluation (i.e., demographic, psychiatric symptoms, and cognitive functioning). RESULTS: There were 158 patients (73.8%) who had a PEth test, of whom 21.5% had a positive result (n = 34). Younger age was associated with a positive PEth ($p < .001$). ALD status and type of ALD (hepatitis vs. cirrhosis) were also associated with a positive PEth

test. Other demographic characteristics and psychiatric symptoms were not associated with a positive PEth result (p > .05). CONCLUSION: Younger age was the only significant demographic variable associated with a positive PEth test. Given the difficulty of predicting who may be using alcohol, it may be useful to use PEth testing for all patients during the pre-liver transplant evaluation and while patients are listed for liver transplant. Early identification of alcohol use through routine PEth testing will help identify patients who are using alcohol and need further treatment for alcohol use to optimize health and post-transplant outcomes.

Behavioral Health Services/Psychiatry/Neuropsychology

Xiao L, Liu S, Wu Y, Huang Y, Tao S, Liu Y, Tang Y, Xie M, Ma Q, Yin Y, Dai M, Zhang M, **Llamocca E**, **Gui H**, and Wang Q. The interactions between host genome and gut microbiome increase the risk of psychiatric disorders: Mendelian randomization and biological annotation. *Brain Behav Immun* 2023; 113:389-400. PMID: 37557965. Full Text

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BACKGROUND: The correlation between human gut microbiota and psychiatric diseases has long been recognized. Based on the heritability of the microbiome, genome-wide association studies on human genome and gut microbiome (mbGWAS) have revealed important host-microbiome interactions. However, establishing causal relationships between specific gut microbiome features and psychological conditions remains challenging due to insufficient sample sizes of previous studies of mbGWAS. METHODS: Cross-cohort meta-analysis (via METAL) and multi-trait analysis (via MTAG) were used to enhance the statistical power of mbGWAS for identifying genetic variants and genes. Using two large mbGWAS studies (7,738 and 5,959 participants respectively) and12 disease-specific studies from the Psychiatric Genomics Consortium (PGC), we performed bidirectional two-sample mendelian randomization (MR) analyses between microbial features and psychiatric diseases (up to 500,199 individuals). Additionally, we conducted downstream gene- and gene-set-based analyses to investigate the shared biology linking gut microbiota and psychiatric diseases. RESULTS: METAL and MTAG conducted in mbGWAS could boost power for gene prioritization and MR analysis. Increases in the number of lead SNPs and mapped genes were witnessed in 13/15 species and 5/10 genera after using METAL, and MTAG analysis gained an increase in sample size equivalent to expanding the original samples from 7% to 63%. Following METAL use, we identified a positive association between Bacteroides faecis and ADHD (OR, 1.09; 95 %CI, 1.02-1.16; P = 0.008). Bacteroides eggerthii and Bacteroides thetaiotaomicron were observed to be positively associated with PTSD (OR, 1.11; 95 %CI, 1.03-1.20; P = 0.007; OR, 1.11; 95 %CI, 1.01-1.23; P = 0.03). These findings remained stable across statistical models and sensitivity analyses. No genetic liabilities to psychiatric diseases may alter the abundance of gut microorganisms.Using biological annotation, we identified that those genes contributing to microbiomes (e.g., GRIN2A and RBFOX1) are expressed and enriched in human brain tissues. CONCLUSIONS: Our statistical genetics strategy helps to enhance the power of mbGWAS, and our genetic findings offer new insights into biological pleiotropy and causal relationship between microbiota and psychiatric diseases.

Behavioral Health Services/Psychiatry/Neuropsychology

Yeh HH, **Peltz-Rauchman C**, **Johnson CC**, Pawloski PA, Chesla D, Waring SC, Stevens AB, Epstein M, **Joseph C**, **Miller-Matero LR**, **Gui H**, **Tang A**, Boerwinkle E, Cicek M, Clark CR, Cohn E, Gebo K, Loperena R, Mayo K, Mockrin S, Ohno-Machado L, Schully S, Ramirez AH, Qian J, and **Ahmedani BK**. Examining sociodemographic correlates of opioid use, misuse, and use disorders in the All of Us Research Program. *PLoS One* 2023; 18(8):e0290416. PMID: 37594966. Full Text

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BACKGROUND: The All of Us Research Program enrolls diverse US participants which provide a unique opportunity to better understand the problem of opioid use. This study aims to estimate the prevalence of opioid use and its association with sociodemographic characteristics from survey data and electronic health record (EHR). METHODS: A total of 214,206 participants were included in this study who competed survey modules and shared EHR data. Adjusted logistic regressions were used to explore the associations between sociodemographic characteristics and opioid use. RESULTS: The lifetime prevalence of street opioids was 4%, and the nonmedical use of prescription opioids was 9%. Men had higher odds of lifetime opioid use (aOR: 1.4 to 3.1) but reduced odds of current nonmedical use of prescription opioids (aOR: 0.6). Participants from other racial and ethnic groups were at reduced odds of lifetime use (aOR: 0.2 to 0.9) but increased odds of current use (aOR: 1.9 to 9.9) compared with non-Hispanic White participants. Foreign-born participants were at reduced risks of opioid use and diagnosed with opioid use disorders (OUD) compared with US-born participants (aOR: 0.36 to 0.67). Men, Younger, White, and US-born participants are more likely to have OUD. CONCLUSIONS: All of Us research data can be used as an indicator of national trends for monitoring the prevalence of receiving prescription opioids, diagnosis of OUD, and non-medical use of opioids in the US. The program employs a longitudinal design for routinely collecting health-related data including EHR data, that will contribute to the literature by providing important clinical information related to opioids over time. Additionally, this data will enhance the estimates of the prevalence of OUD among diverse populations, including groups that are underrepresented in the national survey data.

Cardiology/Cardiovascular Research

Alexandrou M, Kostantinis S, Rempakos A, Simsek B, Karacsonyi J, Choi JW, Poommipanit P, **Alaswad K**, **Basir MB**, **Megaly M**, Davies R, Benton S, Jaffer FA, Karmpaliotis D, Azzalini L, Kearney KE, El Guindy AM, Rafeh NA, Goktekin O, Gorgulu S, Khatri JJ, Aygul N, Jaber W, Nicholson W, Rinfret S, Krestyaninov O, Khelimskii D, Rangan BV, Mastrodemos OC, Allana SS, Sandoval Y, Burke MN, and Brilakis ES. Outcomes of Chronic Total Occlusion Percutaneous Coronary Interventions in Patients With Previous Coronary Artery Bypass Graft Surgery. *Am J Cardiol* 2023; 205:40-49. PMID: 37586120. Full Text

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The outcomes of chronic total occlusion (CTO) percutaneous coronary interventions (PCIs) in patients with previous coronary artery bypass graft (CABG) surgery have received limited study. We examined the baseline characteristics and outcomes of CTO PCIs performed at 47 United States and non-United States centers between 2012 and 2023. Of the 12,164 patients who underwent CTO PCI during the study period, 3,475 (29%) had previous CABG. Previous CABG patients were older, more likely to be men, and had more comorbidities and lower left ventricular ejection fraction and estimated glomerular filtration rate. Their CTOs were more likely to have moderate/severe calcification and proximal tortuosity, proximal cap ambiguity, longer lesion length, and higher Japanese CTO scores. The first and final successful crossing strategy was more likely to be retrograde. Previous CABG patients had lower technical (82.1% vs 88.2%, p <0.001) and procedural (80.8% vs 86.8%, p <0.001) success, higher in-hospital mortality (0.8% vs 0.3%, p <0.001), acute myocardial infarction (0.9% vs 0.5%, p = 0.007) and perforation (7.0% vs 4.2%, p <0.001) but lower incidence of pericardial tamponade and pericardiocentesis (0.1% vs 1.3%, p <0.001). At 2-year follow-up, the incidence of major adverse cardiac events, repeat PCI and acute coronary syndrome was significantly higher in previous CABG patients, whereas all-cause mortality was similar. In conclusion, patients with previous CABG who underwent CTO PCI had more complex clinical and angiographic characteristics and lower success rate, higher perioperative mortality, and myocardial infarction but lower tamponade, and higher incidence of major adverse cardiac events with similar all-cause mortality during follow-up.

Cardiology/Cardiovascular Research

Almasri W, Haque MZ, Shaik M, Mannan A, **Rehman S**, and **Husain M**. Analyzing the Content Found on Fellowship Websites for Adult Congenital Heart Disease. *Cureus* 2023; 15(7):e42682. PMID: 37649934. Full Text

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The Adult Congenital Heart Disease (ACHD) fellowship is a two-year fellowship that can be done by physicians who have finished their internal medicine residency and cardiology fellowship. This study evaluated the accessibility and provided information on the websites of the ACHD fellowship programs to identify potential areas of improvement for future fellowship applicants. Analysis of 25 ACHD fellowship program websites was conducted based on 34 criteria under three main categories: recruitment information, education and research information, and incentive information. This study found that many evaluated ACHD program websites lacked information regarding recruitment. Specifically, information regarding mentorship opportunities, hospital statistics/number of beds, selection process, and interview dates, leaving out crucial details on what to expect during the matching process. Additionally, more information on education and research is beneficial for applicants to sufficiently compare ACHD fellowship programs and make more informed decisions about which programs they would like to apply to. Information on academic stipends, evaluation criteria, expected caseload, moonlighting opportunities, elective opportunities, rotation schedules, call requirements, and types of procedures were all limited across multiple websites. Lastly, incentive information was found to be insufficient across most ACHD fellowship websites. Incentive information included fellow wellness, harassment policies, parental leave, salary, benefits, and vacation/sick leave. This study shows that ACHD fellowship programs need to supply more information on their websites to provide applicants with details to help them choose the fellowship program that corresponds best with their career goals. Expanding upon information regarding recruitment, education, research, and incentives will provide applicants with a strong understanding of ACHD fellowship programs and what they can expect throughout their education. In return, this will help ACHD fellowship programs attract stronger applicants, ultimately improving the quality of their respective programs.

Cardiology/Cardiovascular Research

Balakrishna AM, Kalathil RAM, Pusapati S, Atreya A, Mehta A, Bansal M, Aggarwal V, **Basir MB**, Kochar A, Truesdell AG, and Vallabhajosyula S. Comparative Outcomes of Catheter-Directed Thrombolysis Plus Systemic Anticoagulation Versus Systemic Anticoagulation Alone in the Management of Intermediate-Risk Pulmonary Embolism in a Systematic Review and Meta-Analysis. *Am J Cardiol* 2023; 205:249-258. PMID: 37619491. Full Text

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There are limited and conflicting data on the initial management of intermediate-risk (or submassive) pulmonary embolism (PE). This study sought to compare the outcomes of catheter-directed thrombolysis (CDT) in combination with systemic anticoagulation (SA) to SA alone. A systematic search was conducted in MEDLINE, EMBASE, PubMed, and the Cochrane databases from inception to March 1, 2023 for studies comparing the outcomes of CDT + SA versus SA alone in intermediate-risk PE. The

outcomes were in-hospital, 30-day, 90-day, and 1-year mortality; bleeding; blood transfusion; right ventricular recovery; and length of stay. Random-effects models was used to calculate the pooled incidence and risk ratios (RRs) with 95% confidence intervals (CIs). A total of 15 (2 randomized and 13 observational) studies with 10,549 (2,310 CDT + SA and 8,239 SA alone) patients were included. Compared with SA, CDT + SA was associated with significantly lower in-hospital mortality (RR 0.41, 95% CI 0.30 to 0.56, p <0.001), 30-day mortality (RR 0.34, 95% CI 0.18 to 0.67, p = 0.002), 90-day mortality (RR 0.34, 95% CI 0.17 to 0.67, p = 0.002), and 1-year mortality (RR 0.58, 95% CI 0.34 to 0.97, p = 0.04). There were no significant differences between the 2 cohorts in the rates of major bleeding (RR 1.39, 95% CI 0.72 to 2.68, p = 0.56), minor bleeding (RR 1.83, 95% CI 0.97 to 3.46, p = 0.06), and blood transfusion (RR 0.34, 95% CI 0.10 to 1.15, p = 0.08). In conclusion, CDT + SA is associated with significantly lower short-term and long-term all-cause mortality, without any differences in major/minor bleeding, in patients with intermediate-risk PE.

Cardiology/Cardiovascular Research

Brawner CA, and **Lazar MH**. Cardiopulmonary exercise testing criteria for advanced therapies in patients with heart failure. *Heart Fail Rev* 2023; Epub ahead of print. PMID: 37644366. Full Text

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Many cardiology associations endorse the role of the cardiopulmonary exercise test (CPET) to define the severity of impairment of functional capacity in individuals with heart failure with reduced ejection fraction (HFrEF) and when evaluating the need for advanced therapies for these patients. The focus of the CPET within the cardiology community has been on peak volume of oxygen uptake (VO(2)). However, several CPET variables are associated with outcomes in individuals with and without chronic disease and can inform clinical decisions in individuals with HFrEF. In this manuscript, we will review the normal cardiopulmonary response to a graded exercise test and review current guideline recommendations relative to CPET in patients with HFrEF.

Cardiology/Cardiovascular Research

Colombo PC, Castagna F, Onat D, Wong KY, Harxhi A, Hayashi Y, Friedman RA, Pinsino A, Ladanyi A, Mebazaa A, Jelic S, Arrigo M, LeJemtel TH, Papapanou P, **Sabbah HN**, Schmidt AM, Yuzefpolskaya M, and Demmer RT. Experimentally-Induced Peripheral Venous Congestion Exacerbates Inflammation, Oxidative Stress, Neurohormonal and Endothelial Cell Activation in Systolic Heart Failure Patients. *J Card Fail* 2023; Epub ahead of print. PMID: 37625581. Full Text

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BACKGROUND: Venous congestion (VC) is a hallmark of symptomatic heart failure (HF) requiring hospitalization; however, its role in the pathogenesis of HF progression remains unclear. We investigated whether peripheral VC exacerbates inflammation, oxidative stress, neurohormonal and endothelial cell (EC) activation in HF with reduced ejection fraction (HFrEF) patients. METHODS AND RESULTS: Two matched groups of HFrEF patients with no peripheral VC, with vs. without recent HF hospitalization were studied. We modeled peripheral VC by inflating a cuff around the dominant arm, targeting ~30mmHg increase in venous pressure (venous stress test (VST)). Blood and ECs were sampled before and after 90 minutes of VST. Forty-four patients were studied (age 53±12 years, 32% female). Circulating endothelin-1, tumor necrosis factor-α, interleukin-6, isoprostane, angiotensin II, angiopoietin-2, vascular cell adhesion molecule-1 and CD146 significantly increased after VST. Enhanced endothelin-1 and angiopoietin-2 response to VST was present in patients with vs. without recent hospitalization, and prospectively associated with incident HF-related events. 6,698mRNA probe sets were differentially expressed in ECs after VST. CONCLUSIONS: Experimental VC exacerbates inflammation, oxidative stress, neurohormonal and EC activation, and promotes unfavorable transcriptome remodeling in ECs of HFrEF patients. A distinct biological sensitivity to VC appears associated with high-risk for HF progression.

Cardiology/Cardiovascular Research
Fadel RA, **Cerna Viacava R**, **Makki T**, Fadel CD, Malette K, Demertzis ZD, Ahluwalia G, **Miller J**, and **Russell C**. Compression wraps as adjuvant therapy in the management of acute systolic heart failure. *Heliyon* 2023; 9(8):e19008. PMID: 37600376. Full Text

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BACKGROUND: Guidelines recommend targeting decongestion in management of decompensated HF, with lower extremity edema often serving as the clinical target. LECW are seldom used in the acute setting, with a paucity of data on efficacy in HF, despite serving as a cornerstone of chronic lymphedema management. PRIMARY OBJECTIVE: Study the efficacy and safety of LECW in acute decompensated HF. METHODS: Open-label, randomized, parallel-group clinical trial. PRIMARY OUTCOMES: Days on intravenous (IV) diuretic therapy, total hospital length of stay (LOS), and 30-day all-cause readmission. RESULTS: 32 patients were enrolled, with 29 patients completing the study. Enrollment was suspended due to the COVID-19 pandemic. Overall LOS was shorter in the intervention group (3.5 vs 6 days, $p = 0.05$), with no significant difference in total days on IV diuresis or 30-day readmission rate with use of LECW. Fewer patients required continuous diuretic infusion after treatment with LECW (0 vs 7 patients, $p = 0.027$). The intervention group scored significantly better on the MLWHF (55.5 vs 65, $p = 0.021$), including both the physical and emotional dimension scores. No adverse events were reported with use of LECW, including a significantly lower incidence of AKI (1 vs 13 patients, $p = 0.005$). CONCLUSION: The use of LECW resulted in reduced hospital LOS compared to standard therapy, with no difference in days of IV diuresis administration or 30-day readmission. Treatment with LECW also resulted in less continuous IV diuretic therapy, fewer incidence of AKI, and improved quality of life. Trends toward less escalation of diuresis, and greater reduction in edema were also observed.

Cardiology/Cardiovascular Research
Grimshaw C, **Keteyian SJ**, Benzo R, Finkelstein J, Forman DE, Gaalema DE, Peterson PN, Einhorn PT, Punturieri A, Shero S, and Fleg JL. Baseline Characteristics and Barriers to Recruitment in Cardiac and Pulmonary Rehabilitation NIH-Funded Trials. *J Cardiopulm Rehabil Prev* 2023; Epub ahead of print. PMID: 37643249. Full Text

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Center (GRECC), VA Pittsburgh Healthcare System, Pittsburgh, Pennsylvania (Dr Forman); University of Vermont, Burlington (Dr Gaalema); Denver Health Medical Center and University of Colorado Anschutz Medical Center, Denver and Aurora (Dr Peterson); and National Heart, Lung, and Blood Institute, Bethesda, Maryland (Drs Einhorn, Punturieri, and Fleg and Ms Shero).

Cardiology/Cardiovascular Research
Grinstein J, **Cowger JA**, Belkin MN, Houston BA, and Tedford RJ. Hemodynamic Consequences of Long-Term Continuous Flow: The Importance of the Right Ventricular-Aortic Valve Interactions. *Circ Heart Fail* 2023; e010713. Epub ahead of print. PMID: 37577824. Full Text

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Cardiology/Cardiovascular Research
Henry TD, and **Basir MB**. Editorial: Studying the past to direct the future in cardiogenic shock. *Cardiovasc Revasc Med* 2023; Epub ahead of print. PMID: 37586998. Full Text

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Cardiology/Cardiovascular Research
Kostantinis S, Rempakos A, Simsek B, Karacsonyi J, Allana SS, **Alaswad K**, **Basir MB**, Krestyaninov O, Khelimskii D, Gorgulu S, Davies RE, Benton SM, Khatri JJ, Poommipanit P, Choi JW, Jaber WA, Rinfret S, Nicholson W, Al-Azizi KM, Potluri S, Aygul N, Altunkeser BB, Koutouzis M, Tsiafoutis I, Milkas A, ElGuindy AM, Abi Rafeh N, Goktekin O, Mastrodemos OC, Rangan BV, Sandoval Y, Burke MN, and Brilakis ES. Incidence, mechanisms, treatment, and outcomes of donor vessel injury during percutaneous coronary interventions for chronic total occlusion. *Catheter Cardiovasc Interv* 2023; Epub ahead of print. PMID: 37560823. Full Text

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BACKGROUND: Donor vessel injury is a potentially life-threatening complication of chronic total occlusion (CTO) percutaneous coronary intervention (PCI). AIMS: Our goal was to examine the incidence, mechanisms, treatment, and outcomes of patients with donor vessel injury in a large multicenter CTO PCI registry. METHODS: We analyzed the baseline clinical and angiographic characteristics, and procedural outcomes of 12,349 CTO PCIs performed between 2012 and 2022 at 44 centers. RESULTS: The

incidence of donor vessel injury was 0.35% (n = 43). The baseline clinical characteristics of patients with and without donor vessel injury were similar. Cases complicated by donor vessel injury were more complex with higher Japanese CTO score (2.9 ± 1.1 vs. 2.4 ± 1.3; p = 0.004) and lower procedural success rate (69.8% vs. 85.2%; p = 0.004). The retrograde approach was used more commonly in donor vessel injury cases (68.9% vs. 30.9%; p < 0.001). Most (53.5%) donor vessel injuries were guide catheter-induced, whereas 20.9% were due to donor vessel thrombosis. Of the 43 patients with donor vessel injury, 36 (83.7%) were treated with stenting and seven (16.3%) received a left ventricular assist device. The incidence of major adverse cardiovascular events (MACEs) was significantly higher in cases with donor vessel injury (23.3% vs. 2.0%; p < 0.001). Of the 43 patients with donor vessel injury, five patients (11.6%) experienced acute myocardial infarction and four patients (9.3%) died. CONCLUSIONS: Donor vessel injury, occurred in 0.35% of CTO PCIs performed by experienced operators, was mainly due to guide catheter-induced dissection or thrombosis and was associated with lower procedural success and higher MACE.

Cardiology/Cardiovascular Research

Kostantinis S, Rempakos A, Simsek B, Karacsonyi J, Allana SS, Alexandrou M, Gorgulu S, **Alaswad K**, **Basir MB**, Davies RE, Benton SM, Jr., Krestyaninov O, Khelimskii D, Frizzell J, Ybarra LF, Bagur R, Reddy N, Kerrigan JL, Haddad EV, Love M, Elbarouni B, Soylu K, Yildirim U, Dattilo P, Azzalini L, Kearney K, Sadek Y, ElGuindy AM, Abi Rafeh N, Goktekin O, Mastrodemos OC, Rangan BV, Sandoval Y, Burke MN, and Brilakis ES. Impact of calcium on the procedural techniques and outcomes of chronic total occlusion percutaneous coronary intervention. *Int J Cardiol* 2023;131254. Epub ahead of print. PMID: 37562751. Full Text

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BACKGROUND: Coronary calcification is common and increases the difficulty of chronic total occlusion (CTO) percutaneous coronary intervention (PCI). METHODS: We examined the impact of calcium on procedural outcomes of 13,079 CTO PCIs performed in 12,799 patients at 46 US and non-US centers between 2012 and 2023. RESULTS: Moderate or severe calcification was present in 46.6% of CTO lesions. Patients whose lesions were calcified were older and more likely to have had prior coronary artery bypass graft surgery. Calcified lesions were more complex with higher J-CTO score (3.0 ± 1.1 vs. 1.9 ± 1.2; p < 0.001) and lower technical (83.0% vs. 89.9%; p < 0.001) and procedural (81.0% vs. 89.1%; p < 0.001) success rates compared with mildly calcified or non-calcified CTO lesions. The retrograde approach was more commonly used among cases with moderate/severe calcification (40.3% vs. 23.5%; p < 0.001). Balloon angioplasty (76.6%) was the most common lesion preparation technique for calcified lesions, followed by rotational atherectomy (7.3%), laser atherectomy (3.4%) and, intravascular lithotripsy (3.4%). The incidence of major adverse cardiovascular events (MACE) was higher in cases with

moderate or severe calcification (3.0% vs. 1.2%; p < 0.001), as was the incidence of perforation (6.5% vs. 3.4%; p < 0.001). On multivariable analysis, the presence of moderate/severe calcification was independently associated with lower technical success (odds ratio, OR = 0.73, 95% CI: 0.63-0.84) and higher MACE (OR = 2.33, 95% CI: 1.66-3.27). CONCLUSIONS: Moderate/severe calcification was present in nearly half of CTO lesions, and was associated with higher utilization of the retrograde approach, lower technical and procedural success rates, and higher incidence of in-hospital MACE.

Cardiology/Cardiovascular Research
Mansour AI, Fu W, Fliegner M, Stewart JW, 2nd, **Keteyian SJ**, and Thompson MP. Assessing the Readability and Quality of Cardiac Rehabilitation Program Websites in Michigan. *J Cardiopulm Rehabil Prev* 2023; Epub ahead of print. PMID: 37643241. Full Text

University of Michigan Medical School, Ann Arbor (Dr Mansour); Department of Surgery, Michigan Medicine, Ann Arbor (Drs Fu and Stewart); Oakland University William Beaumont School of Medicine, Auburn Hills, Michigan (Mr Fliegner); Division of Cardiovascular Medicine, Henry Ford Health, Detroit (Dr Keteyian); and Institute of Healthcare Policy and Innovation, University of Michigan, Ann Arbor, and Section of Health Services Research and Quality, Department of Cardiac Surgery, Michigan Medicine, Ann Arbor (Dr Thompson).

Cardiology/Cardiovascular Research
Minhas AMK, **Gupta K**, Jain V, **Kakar TS**, Merchant AT, Shapiro MD, Abushamat LA, Nambi V, and Virani SS. Trends in Cardiovascular Mortality in the United States from 1968 to 2019: Analysis of the CDC Wonder Database. *Eur J Prev Cardiol* 2023; Epub ahead of print. PMID: 37619975. Full Text

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Section of Cardiology, Department of Medicine, The Aga Khan University, Karachi, Pakistan.

Cardiology/Cardiovascular Research
Nayak A, Hall SA, Uriel N, Goldstein DJ, Cleveland JC, Jr., **Cowger JA**, Salerno CT, Naka Y, Horstmanshof D, Crandall D, Wang A, and Mehra MR. Predictors of 5-Year Mortality in Patients Managed With a Magnetically Levitated Left Ventricular Assist Device. *J Am Coll Cardiol* 2023; 82(9):771-781. PMID: 37612008. Full Text

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BACKGROUND: In advanced heart failure patients implanted with a fully magnetically levitated HeartMate 3 (HM3, Abbott) left ventricular assist device (LVAD), it is unknown how preimplant factors and postimplant index hospitalization events influence 5-year mortality in those able to be discharged. OBJECTIVES: The goal was to identify risk predictors of mortality through 5 years among HM3 LVAD recipients conditional on discharge from index hospitalization in the MOMENTUM 3 pivotal trial. METHODS: This analysis evaluated 485 of 515 (94%) patients discharged after implantation of the HM3 LVAD. Preimplant (baseline), implant surgery, and index hospitalization characteristics were analyzed individually, and as multivariable predictors for mortality risk through 5 years. RESULTS: Cumulative 5-year mortality in the cohort (median age: 62 years, 80% male, 65% White, 61% destination therapy due to transplant ineligibility) was 38%. Two preimplant characteristics (elevated blood urea nitrogen and prior coronary artery bypass graft or valve procedure) and 3 postimplant characteristics (hemocompatibility-related adverse events, ventricular arrhythmias, and estimated glomerular filtration rate <60 mL/min/1.73 m(2) at discharge) were predictors of 5-year mortality. In 171 of 485 patients (35.3%) without any risk predictors, 5-year mortality was reduced to 22.6% (95% CI: 15.4%-32.7%). Even among those with 1 or more predictors, mortality was <50% at 5 years (45.7% [95% CI: 39.0%-52.8%]). CONCLUSIONS: Long-term survival in successfully discharged HM3 LVAD recipients is largely influenced by clinical events experienced during the index surgical hospitalization in tandem with baseline factors, with mortality of <50% at 5 years. In patients without identified predictors of risk, long-term 5-year mortality is low and rivals that achieved with heart transplantation, even though most were implanted with destination therapy intent. (MOMENTUM 3 IDE Clinical Study Protocol, NCT02224755; MOMENTUM 3 Pivotal Cohort Extended Follow-up PAS, NCT03982979).

Cardiology/Cardiovascular Research

Rawlley B, Bansal K, Dayal U, Julka D, Salooja I, Sanchez AC, **Gupta K**, Kumar S, and Chaudhuri D. Trends in Data Monitoring Committees, Randomization, and Blinding in Cardiovascular Disease Studies on ClinicalTrials.gov from 2012 to 2021. *Am J Cardiol* 2023; 205:10-11. PMID: 37579654. Full Text

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Cardiology/Cardiovascular Research

Sedhom R, Beshai R, Moussa P, **Megaly M**, Mohsen A, Abramov D, Stoletniy L, and Elgendy IY. Outcomes With Malignancy-Associated High-Risk Pulmonary Embolism: A Nationwide Analysis. *Mayo Clin Proc* 2023; Epub ahead of print. PMID: 37632484. Full Text

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OBJECTIVE: To examine the characteristics and outcomes among patients with high-risk pulmonary embolism (PE) and malignancy. PATIENTS AND METHODS: The Nationwide Readmissions Database was used to identify hospitalizations with high-risk PE from January 1, 2016, to December 31, 2019. The main outcome was the difference in all-cause in-hospital mortality. RESULTS: Among 28,547 weighted hospitalizations with high-risk PE, 4,825 (16.9%) had malignancy. Admissions with malignancy had a

lower prevalence of other comorbid conditions except for anemia and coagulopathy. The use of systemic thrombolysis, catheter-directed interventions, and surgical embolectomy was less common among admissions with malignancy, whereas the use of inferior vena cava filter was more common among those with malignancy. All-cause in-hospital mortality was higher among admissions with malignancy even after adjustment (adjusted odds ratio, 1.91; 95% CI, 1.72 to 2.11; P<.001). Metastatic genitourinary, gastrointestinal (other than colorectal), and lung malignancies were associated with the highest incidence of in-hospital mortality. The incidence of intracranial hemorrhage (3.9% vs 3.1%; P=.056) and the composite of non-intracranial hemorrhage bleeding (21.9% vs 20.6%; P=.185) was not different between admissions with and without malignancy. However, admissions with malignancy had higher incidence of gastrointestinal bleeding. CONCLUSION: In this nationwide analysis of patients admitted with high-risk PE, malignancy was independently associated with an increased risk of in-hospital mortality. The risk was highest among patients with metastatic genitourinary, gastrointestinal, and lung malignancies. Advanced therapies were less frequently used among patients with malignancy.

Cardiology/Cardiovascular Research

Wu B, Yee SW, **Xiao S**, Xu F, Sridhar SB, **Yang M**, **Hochstadt S**, **Cabral W**, **Lanfear DE**, Hedderson MM, Giacomini KM, and **Williams LK**. Genome-Wide Association Study Identifies Pharmacogenomic Variants Associated With Metformin Glycemic Response in African American Patients With Type 2 Diabetes. *Diabetes Care* 2023; Epub ahead of print. PMID: 37639712. Full Text

Center for Individualized and Genomic Medicine Research (CIGMA), Department of Internal Medicine, Henry Ford Health System, Detroit, MI.
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OBJECTIVE: Metformin is the most common treatment for type 2 diabetes (T2D). However, there have been no pharmacogenomic studies for T2D in which a population of color was used in the discovery analysis. This study sought to identify genomic variants associated with metformin response in African American patients with diabetes. RESEARCH DESIGN AND METHODS: Patients in the discovery set were adult, African American participants from the Diabetes Multi-omic Investigation of Drug Response (DIAMOND), a cohort study of patients with T2D from a health system serving southeast Michigan. DIAMOND participants had genome-wide genotype data and longitudinal electronic records of laboratory results and medication fills. The genome-wide discovery analysis identified polymorphisms correlated to changes in glycated hemoglobin (HbA1c) levels among individuals on metformin monotherapy. Lead associations were assessed for replication in an independent cohort of African American participants from Kaiser Permanente Northern California (KPNC) and in European American participants from DIAMOND. RESULTS: The discovery set consisted of 447 African American participants, whereas the replication sets included 353 African American KPNC participants and 466 European American DIAMOND participants. The primary analysis identified a variant, rs143276236, in the gene ARFGEF3, which met the threshold for genome-wide significance, replicated in KPNC African Americans, and was still significant in the meta-analysis (P = 1.17 × 10-9). None of the significant discovery variants replicated in European Americans DIAMOND participants. CONCLUSIONS: We identified a novel and biologically plausible genetic variant associated with a change in HbA1c levels among African American patients on metformin monotherapy. These results highlight the importance of diversity in pharmacogenomic studies.

Cardiology/Cardiovascular Research

Zghouzi M, Osman H, Erdem S, Ullah W, Patel N, Sattar Y, **Aronow H**, Paul T, Aggarwal V, Licha H, Gurm H, Fischman D, Mamas M, AlJaroudi W, and Alraies MC. In-Hospital Outcomes of Combined Coronary Revascularization and Transcatheter Aortic Valve Implantation in Inpatient Nationwide Analysis. *Curr Probl Cardiol* 2023; 101913. Epub ahead of print. PMID: 37557942. Full Text

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BACKGROUND: Transcatheter aortic valve implantation (TAVI) is accepted as an alternative to surgery, but data on combined percutaneous coronary interventions (PCI) and TAVI during the same in-hospital stay are still lacking. METHODS: Using the national inpatient sample (NIS) database, we identified all TAVI encounters and compared in-hospital outcomes of patients who had TAVI only to patients who had TAVI and PCI. We used multivariable logistic regression analysis to calculate the adjusted odds ratio (aOR). RESULTS: Of 291,810 patient encounters with TAVI, 13,114 (4.5%) had combined PCI during the same index admission. The average age was 79.61 ± 8.61 years in the TAVI-only vs. 80.25 ± 8.73 years in the combined TAVI-PCI group. Combined TAVI and PCI was associated with higher in-hospital mortality (4.5% vs. 1.8%, aOR: 2.3), stroke (4.7% vs. 2.9%, aOR: 1.4), net adverse events (NAE) (20.2% vs. 5.7%, aOR: 3.6), major bleeding (40.1% vs. 24.3%, aOR: 1.8), vascular complications (10.6% vs. 2.5%, aOR: 3.9), acute kidney injury (AKI) (23.3% vs. 11.7%, aOR: 2.1), hemodialysis (HD) (4.2% vs. 2.4%, aOR: 1.4), postoperative cardiogenic shock (1.2% vs. 0.4%, aOR: 2.8), need for mechanical circulatory support (MCS) (6.9% vs. 1%, aOR: 7); p-value <0.001 for all. The utilization of permanent pacemakers (PPM) was similar between the groups (9.8% vs. 9.2%, aOR: 1; p=0.6). CONCLUSION: Combining TAVI and PCI during the same index admission is associated with worse outcomes. The decision to do PCI for patients undergoing TAVI should be individualized and tailored based on the patient's clinical conditions.

Center for Health Policy and Health Services Research

Ferber M, **Hecht LM**, **Martens KM**, **Hamann A**, **Carlin AM**, and **Miller-Matero LR**. Examining differences in long-term weight loss outcomes after bariatric surgery: The role of romantic relationship status. *Fam Syst Health* 2023; Epub ahead of print. PMID: 37616105. Request Article

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INTRODUCTION: This study tested for differences based on relationship status at the time of surgery in baseline body mass index (BMI), weight loss outcomes (change in BMI [ΔBMI], percent total weight loss [%TWL], percent excess weight loss [%EWL]), and rates of successful weight loss (defined as ≥ 50%EWL) up to 4-year postbariatric surgery. METHOD: Data came from a secondary analysis of patients (N = 492) who were up to 4-year postsurgery and completed a presurgical psychological evaluation and postsurgical survey. RESULTS: Sixty-nine percent of participants were patients in committed relationships and 31% were single/divorced/widowed patients. Single patients had higher presurgical BMIs than those who were partnered (t = 2.28, p = .02). There were no differences between those who were partnered and singles regarding ΔBMI and %TWL, although singles had smaller %EWL (t = -2.08, p = .04), which became nonsignificant after controlling for covariates. Most participants had successful weight loss (76.8%); however, this was not related to romantic relationship status. DISCUSSION: The results suggest those who were partnered undergo surgery at better-starting weights than singles and maintain this advantage in the long term. Providers working with patients considering bariatric surgery could inquire about how their romantic and social relationships play a part in their decision-making process. (PsycInfo Database Record (c) 2023 APA, all rights reserved).

Center for Health Policy and Health Services Research

Miller-Matero LR, **Yeh HH**, **Maffett A**, **Mooney JT**, **Sala-Hamrick K**, **Frank CB**, Simon GE, Rossom R, Owen-Smith AA, Lynch FL, Beck A, Waring S, Daida YG, Lu CY, and **Ahmedani BK**. Racial-Ethnic Differences in Receipt of Past-Year Health Care Services Among Suicide Decedents: A Case-Control Study. *Psychiatr Serv* 2023; Epub ahead of print. PMID: 37554000. Full Text

Behavioral Health (Miller-Matero, Maffett, Mooney, Frank, Ahmedani) and Center for Health Policy and Health Services Research (Miller-Matero, Yeh, Sala-Hamrick, Ahmedani), Henry Ford Health, Detroit; Kaiser Permanente Washington Health Research Institute, Seattle (Simon); HealthPartners Institute, Minneapolis (Rossom); Department of Health Policy and Behavioral Sciences, School of Public Health, Georgia State University, and Center for Research and Evaluation, Kaiser Permanente Georgia, Atlanta (Owen-Smith); Center for Health Research, Kaiser Permanente Northwest, Portland, Oregon (Lynch); Institute for Health Research, Kaiser Permanente Colorado, Aurora (Beck); Essentia Institute of Rural Health, Duluth, Minnesota (Waring); Center for Integrated Health Care Research, Kaiser Permanente Hawaii, Honolulu (Daida); Department of Population Medicine, Harvard Medical School, and Harvard Pilgrim Health Care Institute, Boston (Lu).

OBJECTIVE: Suicide remains an urgent public health crisis. Although some sociodemographic characteristics are associated with greater suicide risk in the general population, it is unclear whether individuals utilizing health care in the United States have similar suicide incidence patterns. The authors examined whether race-ethnicity is associated with suicide death among patients seeking health care and investigated health care utilization patterns. METHODS: Data were collected from electronic health records and government mortality records for patients seeking health care across nine health care systems in the United States. Patients who died by suicide (N=1,935) were matched with patients in a control group (N=19,350) within each health care system. RESULTS: Patients who died by suicide were significantly more likely to be White, older, male, living in low-education areas, living in rural areas, or diagnosed as having mental health conditions or were significantly less likely to have commercial insurance ($p<0.05$). Among most racial-ethnic groups, those who died by suicide had a higher number of past-year mental health, primary care, and total health care visits; for American Indian/Alaska Native patients, the number of health care visits tended to be lower among suicide decedents. CONCLUSIONS: These findings suggest that higher past-year health care utilization was associated with increased likelihood of suicide death across several racial-ethnic groups. This observation underscores the need for identifying and managing suicide risk in health care settings, including outside of mental health visits, among most racial-ethnic groups.

Center for Health Policy and Health Services Research

Simon GE, Cruz M, Shortreed SM, Sterling SA, Coleman KJ, **Ahmedani BK**, Yaseen ZS, and Mosholder AD. Stability of Suicide Risk Prediction Models During Changes in Health Care Delivery. *Psychiatr Serv* 2023; Epub ahead of print. PMID: 37587793. Full Text

Washington Health Research Institute, Kaiser Permanente, Seattle (Simon, Cruz, Shortreed); Bernard J. Tyson School of Medicine (Simon, Coleman) and Southern California Department of Research and Evaluation (Coleman), Kaiser Permanente, Pasadena; Department of Biostatistics, University of Washington, Seattle (Cruz, Shortreed); Northern California Division of Research, Kaiser Permanente, Oakland (Sterling); Henry Ford Health Center for Health Services Research, Detroit (Ahmedani); U.S. Food and Drug Administration (FDA), Silver Spring, Maryland (Yaseen, Mosholder).

OBJECTIVE: The authors aimed to use health records data to examine how the accuracy of statistical models predicting self-harm or suicide changed between 2015 and 2019, as health systems implemented suicide prevention programs. METHODS: Data from four large health systems were used to identify specialty mental health visits by patients ages ≥11 years, assess 311 potential predictors of self-harm (including demographic characteristics, historical risk factors, and index visit characteristics), and ascertain fatal or nonfatal self-harm events over 90 days after each visit. New prediction models were developed with logistic regression with LASSO (least absolute shrinkage and selection operator) in random samples of visits (65%) from each calendar year and were validated in the remaining portion of the sample (35%). RESULTS: A model developed for visits from 2009 to mid-2015 showed similar

classification performance and calibration accuracy in a new sample of about 13.1 million visits from late 2015 to 2019. Area under the receiver operating characteristic curve (AUC) ranged from 0.840 to 0.849 in the new sample, compared with 0.851 in the original sample. New models developed for each year for 2015-2019 had classification performance (AUC range 0.790-0.853), sensitivity, and positive predictive value similar to those of the previously developed model. Models selected similar predictors from 2015 to 2019, except for more frequent selection of depression questionnaire data in later years, when questionnaires were more frequently recorded. CONCLUSIONS: A self-harm prediction model developed with 2009-2015 visit data performed similarly when applied to 2015-2019 visits. New models did not yield superior performance or identify different predictors.

Center for Health Policy and Health Services Research
Tabb KM, Beck DC, Tilea A, Bell S, Sugg GA, **Vance A**, Schroeder A, Admon L, and Zivin K. The relationship between diagnosed antenatal depression and anxiety and adverse birth outcomes between 2009 and 2020. *Gen Hosp Psychiatry* 2023; Epub ahead of print. PMID: 37567852. Full Text

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Center for Health Policy and Health Services Research
Xiao L, Liu S, Wu Y, Huang Y, Tao S, Liu Y, Tang Y, Xie M, Ma Q, Yin Y, Dai M, Zhang M, **Llamocca E**, **Gui H**, and Wang Q. The interactions between host genome and gut microbiome increase the risk of psychiatric disorders: Mendelian randomization and biological annotation. *Brain Behav Immun* 2023; 113:389-400. PMID: 37557965. Full Text

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BACKGROUND: The correlation between human gut microbiota and psychiatric diseases has long been recognized. Based on the heritability of the microbiome, genome-wide association studies on human genome and gut microbiome (mbGWAS) have revealed important host-microbiome interactions. However, establishing causal relationships between specific gut microbiome features and psychological conditions remains challenging due to insufficient sample sizes of previous studies of mbGWAS.

METHODS: Cross-cohort meta-analysis (via METAL) and multi-trait analysis (via MTAG) were used to enhance the statistical power of mbGWAS for identifying genetic variants and genes. Using two large mbGWAS studies (7,738 and 5,959 participants respectively) and12 disease-specific studies from the Psychiatric Genomics Consortium (PGC), we performed bidirectional two-sample mendelian randomization (MR) analyses between microbial features and psychiatric diseases (up to 500,199 individuals). Additionally, we conducted downstream gene- and gene-set-based analyses to investigate the shared biology linking gut microbiota and psychiatric diseases. RESULTS: METAL and MTAG conducted in mbGWAS could boost power for gene prioritization and MR analysis. Increases in the number of lead SNPs and mapped genes were witnessed in 13/15 species and 5/10 genera after using METAL, and MTAG analysis gained an increase in sample size equivalent to expanding the original samples from 7% to 63%. Following METAL use, we identified a positive association between Bacteroides faecis and ADHD (OR, 1.09; 95 %CI, 1.02-1.16; P = 0.008). Bacteroides eggerthii and Bacteroides thetaiotaomicron were observed to be positively associated with PTSD (OR, 1.11; 95 %CI, 1.03-1.20; P = 0.007; OR, 1.11; 95 %CI, 1.01-1.23; P = 0.03). These findings remained stable across statistical models and sensitivity analyses. No genetic liabilities to psychiatric diseases may alter the abundance of gut microorganisms.Using biological annotation, we identified that those genes contributing to microbiomes (e.g., GRIN2A and RBFOX1) are expressed and enriched in human brain tissues. CONCLUSIONS: Our statistical genetics strategy helps to enhance the power of mbGWAS, and our genetic findings offer new insights into biological pleiotropy and causal relationship between microbiota and psychiatric diseases.

Center for Health Policy and Health Services Research

Yeh HH, **Peltz-Rauchman C**, **Johnson CC**, Pawloski PA, Chesla D, Waring SC, Stevens AB, Epstein M, **Joseph C**, **Miller-Matero LR**, **Gui H**, **Tang A**, Boerwinkle E, Cicek M, Clark CR, Cohn E, Gebo K, Loperena R, Mayo K, Mockrin S, Ohno-Machado L, Schully S, Ramirez AH, Qian J, and **Ahmedani BK**. Examining sociodemographic correlates of opioid use, misuse, and use disorders in the All of Us Research Program. *PLoS One* 2023; 18(8):e0290416. PMID: 37594966. Full Text

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BACKGROUND: The All of Us Research Program enrolls diverse US participants which provide a unique opportunity to better understand the problem of opioid use. This study aims to estimate the prevalence of opioid use and its association with sociodemographic characteristics from survey data and electronic health record (EHR). METHODS: A total of 214,206 participants were included in this study who competed survey modules and shared EHR data. Adjusted logistic regressions were used to explore the associations between sociodemographic characteristics and opioid use. RESULTS: The lifetime prevalence of street opioids was 4%, and the nonmedical use of prescription opioids was 9%. Men had higher odds of lifetime opioid use (aOR: 1.4 to 3.1) but reduced odds of current nonmedical use of prescription opioids (aOR: 0.6). Participants from other racial and ethnic groups were at reduced odds of lifetime use (aOR: 0.2 to 0.9) but increased odds of current use (aOR: 1.9 to 9.9) compared with non-Hispanic White participants. Foreign-born participants were at reduced risks of opioid use and diagnosed with opioid use disorders (OUD) compared with US-born participants (aOR: 0.36 to 0.67). Men, Younger, White, and US-born participants are more likely to have OUD. CONCLUSIONS: All of Us research data can be used as an indicator of national trends for monitoring the prevalence of receiving prescription opioids, diagnosis of OUD, and non-medical use of opioids in the US. The program employs a longitudinal design for routinely collecting health-related data including EHR data, that will contribute to the literature by providing important clinical information related to opioids over time. Additionally, this data will enhance the estimates of the prevalence of OUD among diverse populations, including groups that are underrepresented in the national survey data.

Center for Individualized and Genomic Medicine Research

Li JH, Perry JA, Jablonski KA, Srinivasan S, Chen L, Todd JN, Harden M, Mercader JM, Pan Q, Dawed AY, Yee SW, Pearson ER, Giacomini KM, Giri A, Hung AM, **Xiao S**, **Williams LK**, Franks PW, Hanson RL, Kahn SE, Knowler WC, Pollin TI, and Florez JC. Identification of Genetic Variation Influencing Metformin Response in a Multiancestry Genome-Wide Association Study in the Diabetes Prevention Program (DPP). *Diabetes* 2023; 72(8):1161-1172. PMID: 36525397. Full Text

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Genome-wide significant loci for metformin response in type 2 diabetes reported elsewhere have not been replicated in the Diabetes Prevention Program (DPP). To assess pharmacogenetic interactions in prediabetes, we conducted a genome-wide association study (GWAS) in the DPP. Cox proportional hazards models tested associations with diabetes incidence in the metformin (MET; n = 876) and placebo (PBO; n = 887) arms. Multiple linear regression assessed association with 1-year change in metformin-related quantitative traits, adjusted for baseline trait, age, sex, and 10 ancestry principal components. We tested for gene-by-treatment interaction. No significant associations emerged for diabetes incidence. We identified four genome-wide significant variants after correcting for correlated traits ($P < 9 \times 10\text{-}9$). In the MET arm, rs144322333 near ENOSF1 (minor allele frequency [MAF]AFR = 0.07; MAFEUR = 0.002) was associated with an increase in percentage of glycated hemoglobin (per minor allele, $\beta = 0.39$ [95% CI 0.28, 0.50]; $P = 2.8 \times 10\text{-}12$). rs145591055 near OMSR (MAF = 0.10 in American Indians) was associated with weight loss (kilograms) (per G allele, $\beta = -7.55$ [95% CI -9.88, -5.22]; $P = 3.2 \times 10\text{-}10$) in the MET arm. Neither variant was significant in PBO; gene-by-treatment interaction was significant for both variants [$P(G \times T) < 1.0 \times 10\text{-}4$]. Replication in individuals with diabetes did not yield significant findings. A GWAS for metformin response in prediabetes revealed novel ethnic-specific associations that require further investigation but may have implications for tailored therapy.

Center for Individualized and Genomic Medicine Research

Wu B, Yee SW, **Xiao S**, Xu F, Sridhar SB, **Yang M**, **Hochstadt S**, **Cabral W**, **Lanfear DE**, Hedderson MM, Giacomini KM, and **Williams LK**. Genome-Wide Association Study Identifies Pharmacogenomic Variants Associated With Metformin Glycemic Response in African American Patients With Type 2 Diabetes. *Diabetes Care* 2023; Epub ahead of print. PMID: 37639712. Full Text

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OBJECTIVE: Metformin is the most common treatment for type 2 diabetes (T2D). However, there have been no pharmacogenomic studies for T2D in which a population of color was used in the discovery analysis. This study sought to identify genomic variants associated with metformin response in African American patients with diabetes. RESEARCH DESIGN AND METHODS: Patients in the discovery set were adult, African American participants from the Diabetes Multi-omic Investigation of Drug Response (DIAMOND), a cohort study of patients with T2D from a health system serving southeast Michigan. DIAMOND participants had genome-wide genotype data and longitudinal electronic records of laboratory results and medication fills. The genome-wide discovery analysis identified polymorphisms correlated to changes in glycated hemoglobin (HbA1c) levels among individuals on metformin monotherapy. Lead associations were assessed for replication in an independent cohort of African American participants from Kaiser Permanente Northern California (KPNC) and in European American participants from DIAMOND. RESULTS: The discovery set consisted of 447 African American participants, whereas the replication sets included 353 African American KPNC participants and 466 European American DIAMOND participants. The primary analysis identified a variant, rs143276236, in the gene ARFGEF3, which met the threshold for genome-wide significance, replicated in KPNC African Americans, and was still significant in the meta-analysis ($P = 1.17 \times 10\text{-}9$). None of the significant discovery variants replicated in European Americans DIAMOND participants. CONCLUSIONS: We identified a novel and biologically plausible genetic variant associated with a change in HbA1c levels among African American patients on metformin monotherapy. These results highlight the importance of diversity in pharmacogenomic studies.

Dermatology

Bhatia ND, Werschler WP, Baldwin H, Sugarman J, Green LJ, Levy-Hacham O, Nov O, Ram V, and **Stein Gold L**. Efficacy and Safety of Microencapsulated Benzoyl Peroxide Cream, 5%, in Rosacea: Results From Two Phase III, Randomized, Vehicle-Controlled Trials. *J Clin Aesthet Dermatol* 2023; 16(8):34-40. PMID: 37636253. Full Text

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OBJECTIVE: A new formulation of benzoyl peroxide (E-BPO cream, 5%) entraps benzoyl peroxide (BPO) in silica microcapsules. This study assesses the efficacy, safety, and tolerability of E-BPO cream, 5%, in rosacea in two Phase III clinical trials. METHODS: In two 12-week, randomized, double-blind, vehicle cream-controlled Phase III trials, 733 subjects at least 18 years old with moderate to severe rosacea were randomized (2:1) to once-daily E-BPO cream, 5%, or vehicle. RESULTS: In Study 1, the proportion of subjects achieving IGA clear/almost clear at Week 12 was 43.5 percent for E-BPO cream, 5%, and 16.1 percent for vehicle. In Study 2, the respective values were 50.1 percent and 25.9 percent. In Study 1, the decrease in lesion count from baseline to Week 12 was -17.4 for E-BPO cream, 5%, versus -9.5 for vehicle. In Study 2, the respective values were -20.3 and -13.3 (all P<0.001). The difference was also significant at Week 2. There were no treatment-related serious adverse events; 1.4 percent of subjects (1.8% E-BPO cream, 5%, 0.4% vehicle) discontinued due to adverse events. Assessed local tolerability was found to be similar among subjects in both E-BPO and vehicle. E-BPO was not compared with unencapsulated BPO. CONCLUSION: E-BPO is an effective and well tolerated treatment for rosacea. Clinicaltrials.gov Identifiers: NCT03564119, NCT03448939.

Dermatology
Bibeau K, Ezzedine K, Harris JE, van Geel N, Grimes P, Parsad D, Tulpule M, Gardner J, Valle Y, Tlhong Matewa G, LaFiura C, Lindley A, Ren H, and **Hamzavi IH**. Mental Health and Psychosocial Quality-of-Life Burden Among Patients With Vitiligo: Findings From the Global VALIANT Study. *JAMA Dermatol* 2023; Epub ahead of print. PMID: 37647073. Full Text

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IMPORTANCE: Patients with vitiligo often have impaired quality of life (QOL) and experience substantial psychosocial burden. OBJECTIVE: To explore the global association of vitiligo with QOL and mental health from the patient perspective. DESIGN, SETTING, AND PARTICIPANTS: This qualitative study of the cross-sectional population-based Vitiligo and Life Impact Among International Communities (VALIANT) study was conducted from May 6, 2021, to June 21, 2021. Potential participants for this qualitative study were recruited from an online panel in 17 countries. Of 5859 surveyed adults (aged ≥18 years) who reported a vitiligo diagnosis, 3919 (66.9%) completed the survey, and 3541 (60.4%) were included in the analysis. EXPOSURES: Patients were asked questions regarding their emotional well-being, including QOL and mental health. MAIN OUTCOMES AND MEASURES: Reported analyses are descriptive and hypothesis generating. Vitiligo Impact Patient scale (VIPs) scores ranged from 0 to 60, with higher scores indicating more psychosocial burden. RESULTS: The median age of the 3541 patients

was 38 years (range, 18-95 years), and 1933 (54.6%) were male; 1602 patients (45.2%) had more than 5% affected body surface area (BSA; Self-Assessment Vitiligo Extent Score assessed), and 1445 patients (40.8%) had Fitzpatrick skin types IV to VI (ie, darker skin). The mean (SD) global short-form VIPs score was 27.3 (15.6) overall; patients from India (mean [SD], 40.2 [14.1]) reported the highest scores (ie, most burden). The QOL burden according to the scale was profound for patients with more than 5% affected BSA (mean [SD] score, 32.6 [14.2]), darker skin (mean [SD] score, 31.2 [15.6]), and lesions on the face (mean [SD] score, 30.0 [14.9]) or hands (mean [SD], 29.2 [15.2]). At least 40% of patients globally reported that vitiligo frequently affected aspects of their daily lives, including choosing clothes to wear (1956 of 3541 [55.2%]). Most patients (2103 of 3541 [59.4%]) reported concealing their vitiligo frequently. More than half of patients (2078 of 3541 [58.7%]) reported diagnosed mental health conditions, including anxiety (1019 of 3541 [28.8%]) and depression (866 of 3541 [24.5%]). The Patient Health Questionnaire-9 depression screener showed that 55.0% of patients (1948 of 3541) had moderate to severe depressive symptoms; the highest rates were in India (271 of 303 [89.4%]) and among patients with more than 5% affected BSA (1154 of 1602 [72.0%]) and darker skin (987 of 1445 [68.3%]). CONCLUSIONS AND RELEVANCE: This qualitative study found that, globally, patients with vitiligo reported being substantially affected in their emotional well-being, daily lives, and psychosocial health; the burden was typically greatest among patients with more than 5% affected BSA, darker skin types, and lesions on the face or hands. Survey findings suggest that patients reported having altered their behavior, expressed clear discontent, and have symptoms consistent with depression, which may be underdiagnosed.

Dermatology

Ceresnie MS, Mohney L, **Seale L**, Fahs F, and **Mohammad TF**. The development of non-scarring alopecia in women who wear the hijab. *Arch Dermatol Res* 2023; Epub ahead of print. PMID: 37610623. Full Text

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Little is known about hair loss associated with wearing the hijab, a religious head covering worn by Muslim women. We performed a single-center analysis to investigate the association between various forms of non-scarring alopecia and wearing the hijab. This study included 125 patients who wore the hijab and 40 race/ethnicity-matched women who did not wear the hijab. Among the 165 total patients diagnosed between January 2015 and March 2022, 71 had telogen effluvium, 78 had female pattern hair loss, and 16 had traction alopecia. We found patients who wore the hijab had a younger mean age of alopecia onset than patients who did not wear the hijab (31.5 vs. 37.3 years; P = 0.02). Our study suggests that vitamin D deficiency (OR 4.1; 95% CI 1.2-14.1; P = 0.02) and seborrheic dermatitis (OR 2.9; 95% CI 1.1-8.1; P = 0.03) may significantly impact the development of telogen effluvium in patients who wear the hijab. Targeting these risk factors among patients who wear the hijab may be considered to prevent hair loss.

Dermatology

Ezzedine K, Bergqvist C, Baissac C, Cullell NP, Saint Aroman M, Taïeb C, and **Lim HW**. Use of Multiple Correspondence Analysis to Explore Associations Between Caregivers and Sun Protective Habits During Summer Vacations. *Clin Exp Dermatol* 2023; Epub ahead of print. PMID: 37539734. Full Text

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BACKGROUND: Childhood exposure to ultraviolet radiation (UVR) plays an important role in the development of keratinocyte carcinomas and melanomas. Therefore, sun-protective measures ought to be implemented during early childhood. Young children are largely dependent upon adult care providers' in achieving proper sun protection. OBJECTIVES: To develop effective photoprotection in children, it is necessary to understand caregivers' attitudes and knowledge about UVR exposure. This study aimed to explore the variables associated with sun protective behavior in parents and grandparents during summer vacations. METHODS: Multinational, cross-sectional study was conducted using a web-based online survey on a representative sample of parents and grandparents of children aged 12 or under, who cared for their children/grandchildren for at least 2 weeks during the summer of 2021, in five countries (France, Germany, Spain, Italy and the United States). Multiple correspondence analysis (MCA) was used to explore in an unbiased way the possible relationships among all the variables and to identify specific profiles. RESULTS: A total of 6,190 adult participants responded to the questionnaire: 5,104 parents (average age 42.01 years (y), 54,3% women) and 1,086 grandparents (average age 64,21y, 55,5% women).Grandparents adopted more cautious behaviors than parents. "Parents" fell in closer proximity to the "unprotected sun exposure habits", and "sunburn reported in youngest child". "Grandparents" fell in proximity to "having exposed the grandchild to the sun between 11am and 5pm", "not using an umbrella" and "not using sunglasses". CONCLUSIONS: While grandparents appear to adopt more cautious behaviors than parents, many gaps in proper sun protection behavior were observed in both groups of guardians.

Dermatology
Kumar N, **Pourang A**, **Ezekwe N**, **Parks-Miller A**, **Mohammad TF**, **Huggins RH**, Deal LS, Lukic T, Zhang F, **Lim HW**, **Hamzavi I**, and **Kohli I**. A method for assessing rater reliability in applying the Vitiligo Area Scoring Index (VASI). *Br J Dermatol* 2023; Epub ahead of print. PMID: 37555429. Full Text

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Dermatology
Kwa MC, Kang R, Cherupally M, Aikman C, and Ackermann R. Initiation patterns among novel systemic agents for US adults with psoriasis and psoriatic arthritis: a retrospective cohort study. *Arch Dermatol Res* 2023; Epub ahead of print. PMID: 37584693. Full Text

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Dermatology
Lim SS, **Mohammad TF**, **Kohli I**, **Hamzavi I**, and Rodrigues M. Optimisation of skin phototype classification. *Pigment Cell Melanoma Res* 2023; Epub ahead of print. PMID: 37550876. Full Text

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Understanding individuals' skin pigmentation and photosensitivity is important in judging risk of skin cancer and response to certain treatment modalities. However, individuals with darkly pigmented skin are poorly represented in the widely used Fitzpatrick skin phototype (FST) system. Moreover, the FST system is prone to misuse, as it relies on subjective patient and clinician assessment of skin type, and does not clearly differentiate pigmentation from photosensitivity. By evaluating the key literature surrounding the FST system, its criticisms and proposed alternatives, this review serves to understand how skin phototype classification can be optimised.

Dermatology

Maghfour J, **Shoukfeh R**, **Hamzavi IH**, Ezzedine K, and **Mohammad TF**. Assessing the trends of outcome measures and quality of life instruments in vitiligo: A systematic review. *J Eur Acad Dermatol Venereol* 2023; Epub ahead of print. PMID: 37566732. Full Text

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Dermatology

Passeron T, **Lim HW**, Goh CL, Kang HY, Ly F, Morita A, Ocampo-Candiani J, Puig S, Schalka S, Liu W, Demessant-Flavigny AL, Le Floc'h C, Kerob D, Dreno B, and Krutmann J. Sun exposure behaviours as a compromise to paradoxical injunctions: Insight from a worldwide survey. *J Eur Acad Dermatol Venereol* 2023; Epub ahead of print. PMID: 37590528. Full Text

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BACKGROUND: Behavioural interventions can improve attitudes towards sun protection but the impact remains inconsistent worldwide. OBJECTIVE: To assess awareness of and attitudes towards the multiple facets of sun exposure and suggest ways to improve prevention from overexposure to the sun in all geographical zones and multiple skin types. METHODS: Online survey was conducted from 28 September to 18 October 2021. Study population was selected from the Ipsos online Panel (3,540,000 panellists), aged ≥18 years, from 17 countries around the five continents. Demographics, sun-exposure habits and practices, understanding of risks and information on phototypes were documented and analysed using descriptive statistics. RESULTS: Eighty-eight per cent of participants knew that sunlight can cause skin health problems (90% phototypes I-II, 82% phototypes V-VI, >90% in American and

European countries, 72% in Asia and 85% in Africa). Eighty-five per cent used some form of protection against sunlight, predominantly: Seeking shade (77%), avoiding the midday sun (66%), facial application of sunscreen (60%) and wearing protective clothing (44%). The perception of sunlight itself is positive ('it gives energy' for 82%; 'tanned skin looks attractive' for 72%), although less in Asian countries and among individuals with dark skin phototypes. Eighty-three per cent reported having experienced sunburn, mainly in Australia, Canada, USA, Germany, France and Russia, and among individuals with dark skin phototypes. Only 12% systematically/often used all types of protection during exposure to the sun and 23% believed it is safe to go out in the sun with no protection when their skin is already tanned. From 13% (skin phototype I) to 26% (phototype VI) reported not using any form of protection against the sun. Knowledge and habits were significantly superior among people who are accustomed to seeing a dermatologist for a complete skin exam. CONCLUSIONS: Dermatologists could play a crucial role in relaying novel prevention messages, more finely tailored to specific risks, populations and areas of the world.

Dermatology

Stein Gold L, Lain E, Del Rosso JQ, Gold M, Draelos ZD, Eichenfield LF, Sadick N, Werschler WP, Gooderham MJ, and Lupo M. Clindamycin phosphate 1.2%/adapalene 0.15%/benzoyl peroxide 3.1% gel for moderate-to-severe acne: Efficacy and safety results from two randomized phase 3 trials. *J Am Acad Dermatol* 2023; Epub ahead of print. PMID: 37656094. Full Text

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BACKGROUND: A three-pronged acne treatment approach-combining an antibiotic, antibacterial agent, and retinoid-may provide greater efficacy than single/double treatments. Topical clindamycin phosphate 1.2%/adapalene 0.15%/benzoyl peroxide (BPO) 3.1% gel (IDP-126) is the first fixed-dose triple-combination in development for acne. OBJECTIVE: To confirm efficacy, safety, and tolerability of IDP-126 gel in acne treatment. METHODS: Two phase 3, double-blind, 12-week studies randomized participants aged ≥9 years with moderate-to-severe acne (N = 183; N = 180) 2:1 to once-daily IDP-126 or vehicle gel. Co-primary endpoints comprised participants achieving ≥2-grade reduction from baseline in Evaluator's Global Severity Score (EGSS) and clear/almost clear skin (treatment success) and change from baseline in inflammatory/noninflammatory lesion counts. Treatment-emergent adverse events (TEAEs) were assessed. RESULTS: At week 12, 49.6% and 50.5% of participants achieved treatment success with IDP-126 versus 24.9% and 20.5% with vehicle ($P < .01$, both). IDP-126 also provided significantly greater reductions in inflammatory/noninflammatory lesions versus vehicle (least-squares mean percent range: 72.7% to 80.1% vs 47.6% to 59.6%; $P < .001$, all). Most TEAEs were of mild-moderate severity. LIMITATIONS: Inter-observer bias/variation in acne severity ratings, limited treatment duration, and population differences that may not generalize to real-world populations. CONCLUSION: The innovative fixed-dose, triple-combination IDP-126 gel was efficacious and well tolerated in 2 clinical studies of participants with moderate-to-severe acne.

Dermatology

van Geel N, Duponselle J, Delbaere L, Herbelet S, Eleftheriadou V, Ezzedine K, Forman M, Garg A, **Hamzavi IH**, Seneschal J, Spuls P, Terwee CB, Wolkerstorfer A, Speeckaert R, and Pandya AG. Clinician-Reported OUTCOME MEASURES FOR THE ASSESSMENT OF VITILIGO: A SCOPING REVIEW. *J Eur Acad Dermatol Venereol* 2023; Epub ahead of print. PMID: 37602494. Full Text

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Clinician-reported outcome measures (ClinROMs) are essential for assessment of vitiligo in clinical trials and daily practice. Several instruments have been developed and tested to measure e.g., vitiligo extent, repigmentation and activity. The goal of this review was to identify all introductory publications of ClinROMs for vitiligo that include at least some aspects of validation and to describe the instruments' characteristics, intention for use, and practical strengths and limitations. A search strategy was conducted in Pubmed, Embase and Cochrane Library (CENTRAL) from inception to July 2022. Based on the literature search (n=2860), 10 articles were identified, describing 14 different ClinROMs. 6 ClinRoms measured disease extent and/or repigmentation, 7 evaluated disease activity and 1 was a composite score. The Vitiligo Area Scoring Index (VASI), and Vitiligo Extent Score [VES and VESplus] measure overall disease extent and/or repigmentation. The VASI relies on hand units (1% body surface are) whereas the VES and VESplus uses a picture-based scoring technique. The Vitiligo Extent Score for a Target Area (VESTA) measures repigmentation percentage for target lesions. One global assessment score for extent has been validated. Vitiligo disease activity scores included a static measure of clinical activity signs [Vitiligo Signs of Activity Score (VSAS)] and two measures assessing dynamic evolution [(Vitiligo Disease Activity Score (VDAS), Vitiligo Disease Improvement Score (VDIS)]. The Vitiligo European Task Force assessment tool (VETFa) is a composite score. Depending on the practical strength and limitations as well as the research question and setting (clinical trials versus daily practice) the choice of an appropriate ClinROM may differ. Fourteen ClinROMs in vitiligo were identified to measure vitiligo extent, repigmentation and activity. Further research evaluating the validity, reliability and responsiveness of each instrument and worldwide consensus on which instrument to use for a specific outcome (domain) is greatly needed.

Dermatology

Werschler WP, Sugarman J, Bhatia N, Baldwin H, Green LJ, Nov O, Ram V, Levy-Hacham O, and **Stein Gold L**. Long-term Efficacy and Safety of Microencapsulated Benzoyl Peroxide Cream, 5%, in Rosacea: Results From an Extension of Two Phase III, Vehicle-controlled Trials. *J Clin Aesthet Dermatol* 2023; 16(8):27-33. PMID: 37636251. Request Article

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Dr. Green is with the George Washington University School of Medicine in Washington, DC.
Dr. Nov, Mr. Ram, and Dr. Levy-Hacham are with Sol-Gel Technologies Ltd in Ness Ziona, Israel.
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OBJECTIVE: We sought to assess the long-term safety and tolerability of microencapsulated benzoyl peroxide cream, 5% (E-BPO cream, 5%), in subjects with rosacea. Efficacy and tolerability have been previously demonstrated in two 12-week, randomized, double-blind, vehicle-controlled Phase III trials. METHODS: In this open-label extension study (NCT03564145; clinicaltrials.gov), all subjects from the initial placebo-controlled Phase III trials could receive E-BPO cream, 5%, for up to an additional 40 weeks, up to a total of 52 weeks of E-BPO cream, 5%, exposure. If a subject was assessed at study visits as "clear" or "almost clear" using the 5-point Investigator Global Assessment (IGA) scale (IGA 0 or 1), E-BPO cream, 5%, was not dispensed. If a subject was assessed as "mild to severe" (IGA 2+), E-BPO cream, 5%, was applied daily until they reached "clear" or "almost clear." RESULTS: The safety and tolerability profile for E-BPO cream, 5%, was similar to that reported in the Phase III studies. Five subjects (0.9%) discontinued study drug due to treatment-related adverse events, and 17 subjects (3.2%) experienced an adverse event considered related to study drug. IGA success after 40 weeks of active treatment was 66.5 percent for subjects continuing from the Phase III vehicle group (n=172) and 67.6 percent for subjects who continued Phase III E-BPO cream, 5% (n=363). The study ended early in accordance with the protocol. LIMITATIONS: Safety and tolerability of E-BPO were not compared with those of unencapsulated BPO. CONCLUSION: E-BPO cream, 5%, showed a favorable safety and tolerability profile during this 40-week, open-label extension study.

Diagnostic Radiology
Poyiadji N, **Beauchamp N**, **Myers D**, **Krupp S**, and **Griffith B**. Diagnostic Imaging Utilization in the Emergency Department: Recent Trends in Volume and Radiology Work Relative Value Units. *J Am Coll Radiol* 2023; Epub ahead of print. PMID: 37543154. Full Text

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PURPOSE: The aim of this study was to quantify and characterize the recent trend in emergency department (ED) imaging volumes and radiology work relative value units (wRVUs) at level I and level III trauma centers. METHODS: Total annual diagnostic radiology imaging volumes and wRVUs were obtained from level I and level III trauma centers from January 2014 to December 2021. Imaging volumes were analyzed by modality type, examination code, and location. Total annual patient ED encounters (EDEs), annual weighted Emergency Severity Index, and patient admissions from the ED were obtained. Data were analyzed using annual imaging volume or wRVUs per EDE, and percentage change was calculated. RESULTS: At the level I trauma center, imaging volumes per EDE increased for chest radiography (5.5%), CT (35.5%), and MRI (56.3%) and decreased for ultrasound (-5.9%) from 2014 to 2021. Imaging volumes per EDE increased for ultrasound (10.4%), CT (74.6%), and MRI (2.0%) and decreased for chest radiography (-4.4%) at the level III trauma center over the same 8-year period. Total wRVUs per EDE increased at both the level I (34.9%) and level III (76.6%) trauma centers over the study period. CONCLUSIONS: ED imaging utilization increased over the 8-year study period at both level I and level III trauma centers, with an increase in total wRVUs per EDE. There was a disproportionate increased utilization of advanced imaging, such as CT, over time. ED utilization trends suggest that there

will be a continued increase in demand for advanced imaging interpretation, including at lower acuity hospitals, so radiology departments should prepare for this increased work demand.

Diagnostic Radiology

Zhang R, Griner D, Garrett JW, **Qi Z**, and Chen GH. Training certified detectives to track down the intrinsic shortcuts in COVID-19 chest x-ray data sets. *Sci Rep* 2023; 13(1):12690. PMID: 37542078. Full Text

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Deep learning faces a significant challenge wherein the trained models often underperform when used with external test data sets. This issue has been attributed to spurious correlations between irrelevant features in the input data and corresponding labels. This study uses the classification of COVID-19 from chest x-ray radiographs as an example to demonstrate that the image contrast and sharpness, which are characteristics of a chest radiograph dependent on data acquisition systems and imaging parameters, can be intrinsic shortcuts that impair the model's generalizability. The study proposes training certified shortcut detective models that meet a set of qualification criteria which can then identify these intrinsic shortcuts in a curated data set.

Emergency Medicine

Fadel RA, **Cerna Viacava R**, **Makki T**, Fadel CD, Malette K, Demertzis ZD, Ahluwalia G, **Miller J**, and **Russell C**. Compression wraps as adjuvant therapy in the management of acute systolic heart failure. *Heliyon* 2023; 9(8):e19008. PMID: 37600376. Full Text

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BACKGROUND: Guidelines recommend targeting decongestion in management of decompensated HF, with lower extremity edema often serving as the clinical target. LECW are seldom used in the acute setting, with a paucity of data on efficacy in HF, despite serving as a cornerstone of chronic lymphedema management. PRIMARY OBJECTIVE: Study the efficacy and safety of LECW in acute decompensated HF. METHODS: Open-label, randomized, parallel-group clinical trial. PRIMARY OUTCOMES: Days on intravenous (IV) diuretic therapy, total hospital length of stay (LOS), and 30-day all-cause readmission. RESULTS: 32 patients were enrolled, with 29 patients completing the study. Enrollment was suspended due to the COVID-19 pandemic. Overall LOS was shorter in the intervention group (3.5 vs 6 days, $p = 0.05$), with no significant difference in total days on IV diuresis or 30-day readmission rate with use of LECW. Fewer patients required continuous diuretic infusion after treatment with LECW (0 vs 7 patients, $p = 0.027$). The intervention group scored significantly better on the MLWHF (55.5 vs 65, $p = 0.021$), including both the physical and emotional dimension scores. No adverse events were reported with use of LECW, including a significantly lower incidence of AKI (1 vs 13 patients, $p = 0.005$). CONCLUSION: The use of LECW resulted in reduced hospital LOS compared to standard therapy, with no difference in days of IV diuresis administration or 30-day readmission. Treatment with LECW also resulted in less continuous IV diuretic therapy, fewer incidence of AKI, and improved quality of life. Trends toward less escalation of diuresis, and greater reduction in edema were also observed.

Emergency Medicine

Hanson CG, **Stewart C**, and **Cronovich K**. Intracranial Hemorrhage and Facial Fractures After Nose Blowing and Sternutation: A Case Report. *Clin Pract Cases Emerg Med* 2023; 7(3):185-188. PMID: 37595299. Full Text

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INTRODUCTION: Blowing the nose and sneezing are ubiquitous physiologic processes. While exceedingly rare, traumatic injuries have been described. We detail a case of spontaneous intracranial hemorrhage and orbital fractures sustained as a result of these two phenomena in an otherwise healthy adult without known risk factors for bleeding or intracranial hemorrhage. CASE REPORT: A 79-year-old female presented to the emergency department after blowing her nose with an episode of sneezing following mild epistaxis. She denied any history of trauma, anticoagulation use, bleeding disorders, or pain associated with her symptoms. On examination, she had notable right periorbital swelling. Computed tomography revealed multiple areas of intracranial hemorrhage along with right-sided orbital and zygomatic fractures. After consulting trauma surgery and neurosurgery, we elected to pursue conservative management with repeat imaging. The patient had an uneventful course and was discharged with outpatient follow-up two days later. CONCLUSION: To our knowledge, this is the first case described of this constellation of injuries after a relatively benign process. Despite not having increased risk factors for intracranial hemorrhage (anticoagulation use, history of trauma, history of coagulopathy), this patient had severe injuries that presented with few external symptoms. This case serves as a reminder that while physiologic processes are almost always benign, serious traumatic injuries can result. Clinicians should have a low threshold for advanced imaging when there is a high clinical suspicion of facial fractures or more ominous processes.

Emergency Medicine

Poyiadji N, **Beauchamp N**, **Myers D**, **Krupp S**, and **Griffith B**. Diagnostic Imaging Utilization in the Emergency Department: Recent Trends in Volume and Radiology Work Relative Value Units. *J Am Coll Radiol* 2023; Epub ahead of print. PMID: 37543154. Full Text

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PURPOSE: The aim of this study was to quantify and characterize the recent trend in emergency department (ED) imaging volumes and radiology work relative value units (wRVUs) at level I and level III trauma centers. METHODS: Total annual diagnostic radiology imaging volumes and wRVUs were obtained from level I and level III trauma centers from January 2014 to December 2021. Imaging volumes were analyzed by modality type, examination code, and location. Total annual patient ED encounters (EDEs), annual weighted Emergency Severity Index, and patient admissions from the ED were obtained. Data were analyzed using annual imaging volume or wRVUs per EDE, and percentage change was calculated. RESULTS: At the level I trauma center, imaging volumes per EDE increased for chest radiography (5.5%), CT (35.5%), and MRI (56.3%) and decreased for ultrasound (-5.9%) from 2014 to 2021. Imaging volumes per EDE increased for ultrasound (10.4%), CT (74.6%), and MRI (2.0%) and decreased for chest radiography (-4.4%) at the level III trauma center over the same 8-year period. Total wRVUs per EDE increased at both the level I (34.9%) and level III (76.6%) trauma centers over the study period. CONCLUSIONS: ED imaging utilization increased over the 8-year study period at both level I and level III trauma centers, with an increase in total wRVUs per EDE. There was a disproportionate

increased utilization of advanced imaging, such as CT, over time. ED utilization trends suggest that there will be a continued increase in demand for advanced imaging interpretation, including at lower acuity hospitals, so radiology departments should prepare for this increased work demand.

Endocrinology and Metabolism

Dogra P, Šambula L, Saini J, Thangamuthu K, **Athimulam S**, Delivanis DA, Baikousi DA, Nathani R, Zhang CD, Genere N, Salman Z, Turcu AF, Ambroziak U, Garcia RG, Achenbach SJ, Atkinson EJ, Singh S, LeBrasseur NK, Kastelan D, and Bancos I. High Prevalence of Frailty in Patients with Adrenal Adenomas and Adrenocortical Hormone Excess - a cross-sectional multi-centre study with prospective enrolment. *Eur J Endocrinol* 2023; Epub ahead of print. PMID: 37590964. Full Text

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OBJECTIVE: Frailty, characterized by multisystem decline, increases vulnerability to adverse health outcomes and can be measured using Frailty Index (FI). We aimed to assess the prevalence of frailty in patients with adrenal disorders (based on hormonal subtype) and examine association between FI and performance-based measures of physical function. DESIGN: Multicenter, cross-sectional study (03/2019-08/2022). METHODS: Adult patients with adrenal disorders (nonfunctioning adrenal adenomas [NFA], mild autonomous cortisol secretion [MACS], Cushing syndrome [CS], primary aldosteronism [PA]) and referent subjects without adrenal disorders completed a questionnaire encompassing 47 health variables (comorbidities, symptoms, daily living activities). FI was calculated as the average score of all variables and frailty defined as FI > 0.25. Physical function was assessed with hand grip, timed up-and-go test, chair rising test, 6-minute walk test, and gait speed. RESULTS: Compared to referent subjects (n=89), patients with adrenal disorders (n=520) showed increased age, sex, and BMI-adjusted prevalence of frailty (CS [OR 19.2, 95% CI 6.7-70], MACS [OR 12.5, 95% CI 4.8-42.9], PA [OR 8.4, 95% CI 2.9-30.4], NFA [OR 4.5, 95% CI 1.7-15.9]). Prevalence of frailty was similar to referent subjects when post-dexamethasone cortisol was <28 nmol/L and was higher when post-dexamethasone cortisol was 28-50 nmol/L (OR 4.6, 95% CI 1.7-16.5). FI correlated with all measures of physical function (p<0.001). CONCLUSION: While frailty prevalence was highest in patients with adrenocortical hormone excess, even patients with NFA demonstrated an increased prevalence compared to the referent population. Future longitudinal studies are needed to evaluate the impact of various management strategies on frailty.

Gastroenterology

Kaafarani M, **Shamma O**, and **Jafri SM**. Transcatheter Aortic Valve Replacement Restoring Candidacy for Liver Transplant in Patients With Cirrhosis. *ACG Case Rep J* 2023; 10(8):e01102. PMID: 37601302. Full Text

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Guidelines for preoperative workup for an orthotopic liver transplant often rule out patients with severe aortic stenosis as transplant candidates. This case illustrates the potential of transcatheter aortic valve replacement (TAVR) as a bridge for liver transplants in cirrhotic patients with severe aortic stenosis. The 1-year and 2-year post-liver transplant follow-ups showed no complications in the patient's prosthetic aortic valves, and graft survival was 100% with no evidence of rejection. Notable post-transplant recovery involved medical complications that were not related to the liver function or surgical procedure.

Gastroenterology
Obri MS, **Nimri F**, **Kamran W**, Nimri R, **Pompa R**, and **Zuchelli T**. Gastrointestinal Stromal Tumor Presenting as Food Impaction and Pseudo-Achalasia. *ACG Case Rep J* 2023; 10(8):e01116. PMID: 37583506. Full Text

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Gastrointestinal stromal tumors (GISTs) are one of the most common mesenchymal tumors of the gastrointestinal tract. Studies report the incidence of GIST to be 14.5 per million, with 18% being diagnosed incidentally. The most common location is the stomach while the esophagus is the rarest, representing only 0.7% of cases. The clinical manifestations of GISTs vary. Most patients present with bleeding and gastric discomfort. Some may present with life-threatening hematemesis or melena. We present a unique case of a GIST presenting as pseudo-achalasia and food impaction.

Gastroenterology
Segal A, **Pearl E**, **Fatabhoy M**, **Zohr SJ**, **Bryce K**, **Gonzalez HC**, and **Miller-Matero LR**. Factors associated with a positive phosphatidylethanol test during liver transplantation evaluation. *Clin Transplant* 2023; e15100. Epub ahead of print. PMID: 37577900. Full Text

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BACKGROUND: Early identification of alcohol use is crucial for informing recommendations of appropriate follow-up treatment pre-liver transplant and optimizing post-liver transplant outcomes. The purpose of the study was to investigate whether there are psychosocial factors associated with a positive PEth test. METHODS: All patients who underwent a routine pre-surgical psychological evaluation for liver transplant listing (all etiologies, including acute liver failure, dual organ, and re-transplantation) at a single health care system in 2020 were included in a retrospective chart review. Data extraction included results from PEth testing and information from the psychological evaluation (i.e., demographic, psychiatric symptoms, and cognitive functioning). RESULTS: There were 158 patients (73.8%) who had a PEth test, of whom 21.5% had a positive result (n = 34). Younger age was associated with a positive PEth ($p < .001$). ALD status and type of ALD (hepatitis vs. cirrhosis) were also associated with a positive PEth test. Other demographic characteristics and psychiatric symptoms were not associated with a positive PEth result ($p > .05$). CONCLUSION: Younger age was the only significant demographic variable associated with a positive PEth test. Given the difficulty of predicting who may be using alcohol, it may be useful to use PEth testing for all patients during the pre-liver transplant evaluation and while patients are listed for liver transplant. Early identification of alcohol use through routine PEth testing will help identify patients who are using alcohol and need further treatment for alcohol use to optimize health and post-transplant outcomes.

Gastroenterology

Weiner J, Llore N, Ormsby D, Fujiki M, Segovia MC, **Obri M**, **Jafri SM**, Liggett J, Kroemer AHK, Matsumoto C, Moon J, Di Cocco P, Selvaggi G, Garcia J, Ganoza A, Khanna A, Mazariegos G, Wendel D, and Reyes J. The First Collective Examination of Immunosuppressive Practices Among American Intestinal Transplant Centers. *Transplant Direct* 2023; 9(9):e1512. PMID: 37636483. Full Text

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BACKGROUND: Unlike other solid organs, no standardized treatment algorithms exist for intestinal transplantation (ITx). We established a consortium of American ITx centers to evaluate current practices. METHODS: All American centers performing ITx during the past 3 y were invited to participate. As a consortium, we generated questions to evaluate and collect data from each institution. The data were compiled and analyzed. RESULTS: Ten centers participated, performing 211 ITx during the past 3 y (range, 3-46; mean 21.1). Induction regimens varied widely. Thymoglobulin was the most common, used in the plurality of patients (85/211; 40.3%), but there was no consensus regimen. Similarly, regimens for the treatment of acute cellular rejection, antibody-mediated rejection, and graft-versus-host disease varied significantly between centers. We also evaluated differences in maintenance immunosuppression protocols, desensitization regimens, mammalian target of rapamycin use, antimetabolite use, and posttransplantation surveillance practices. Maintenance tacrolimus levels, stoma presence, and scoping frequency were not associated with differences in rejection events. Definitive association between treatments and outcomes, including graft and patient survival, was not the intention of this initial collaboration and is prevented by the lack of patient-level data and the presence of confounders. However, we identified trends regarding rejection episodes after various induction strategies that require further investigation in our subsequent collaborations. CONCLUSIONS: This initial collaboration reveals the extreme heterogeneity of practices among American ITx centers. Future collaboration will explore patient-level data, stratified by age and transplant type (isolated intestine versus multivisceral), to explore the association between treatment regimens and outcomes.

Hematology-Oncology

Carducci MA, **Wang D**, Habermehl C, Bödding M, Rohdich F, Lignet F, Duecker K, Karpenko O, Pudelko L, Gimmi C, and LoRusso P. A First-in-human, Dose-escalation Study of the Methionine Aminopeptidase 2 Inhibitor M8891 in Patients with Advanced Solid Tumors. *Cancer Res Commun* 2023; 3(8):1638-1647. PMID: 37637935. Full Text

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Methionine aminopeptidase 2 (MetAP2) is essential to endothelial cell growth and proliferation during tumor angiogenesis. M8891 is a novel orally bioavailable, potent, selective, reversible MetAP2 inhibitor

with antiangiogenic and antitumor activity in preclinical studies. The safety, tolerability, pharmacokinetics, and pharmacodynamics of M8891 monotherapy were assessed in a phase I, first-in-human, multicenter, open-label, single-arm, dose-escalation study (NCT03138538). Patients with advanced solid tumors received 7-80 mg M8891 once daily in 21-day cycles. The primary endpoint was dose-limiting toxicity (DLT) during cycle 1, with the aim to determine the maximum tolerated dose (MTD). Twenty-seven patients were enrolled across six dose levels. Two DLTs (platelet count decrease) were reported, one each at 60 and 80 mg/once daily M8891, resolving after treatment discontinuation. MTD was not determined. The most common treatment-emergent adverse event was platelet count decrease. M8891 plasma concentration showed dose-linear increase up to 35 mg and low-to-moderate variability; dose-dependent tumor accumulation of methionylated elongation factor 1α, a MetAP2 substrate, was observed, demonstrating MetAP2 inhibition. Pharmacokinetic/pharmacodynamic response data showed that preclinically defined target levels required for in vivo efficacy were achieved at safe, tolerated doses. Seven patients (25.9%) had stable disease for 42-123 days. We conclude that M8891 demonstrates a manageable safety profile, with dose-proportional exposure and low-to-moderate interpatient variability at target pharmacokinetic/pharmacodynamic levels at ≤35 mg M8891 once daily. On the basis of the data, 35 mg M8891 once daily is the recommended phase II dose for M8891 monotherapy. This study forms the basis for future development of M8891 in monotherapy and combination studies. SIGNIFICANCE: M8891 represents a novel class of reversible MetAP2 inhibitors and has demonstrated preclinical antitumor activity. This dose-escalation study assessed M8891 treatment for patients with advanced solid tumors. M8891 demonstrated favorable pharmacokinetics, tumoral target engagement, and a manageable safety profile, and thus represents a novel antitumor strategy warranting further clinical studies.

Hematology-Oncology

Cornwell AC, Tisdale AA, Venkat S, Maraszek KE, Alahmari AA, George A, Attwood K, **George M**, **Rempinski D**, Franco-Barraza J, Seshadri M, Parker MD, Cortes Gomez E, Fountzilas C, Cukierman E, Steele NG, and Feigin ME. Lorazepam Stimulates IL6 Production and Is Associated with Poor Survival Outcomes in Pancreatic Cancer. *Clin Cancer Res* 2023; 1-20. Epub ahead of print. PMID: 37587561. Full Text

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PURPOSE: This research investigates the association between benzodiazepines (BZD) and cancer patient survival outcomes, the pancreatic cancer tumor microenvironment, and cancer-associated fibroblast (CAF) signaling. EXPERIMENTAL DESIGN: Multivariate Cox regression modeling was used to retrospectively measure associations between Roswell Park cancer patient survival outcomes and BZD prescription records. IHC, H&E, Masson's trichrome, RNAscope, and RNA sequencing were used to evaluate the impact of lorazepam (LOR) on the murine PDAC tumor microenvironment. ELISA and qPCR were used to determine the impact of BZDs on IL6 expression or secretion by human-immortalized

pancreatic CAFs. PRESTO-Tango assays, reanalysis of PDAC single-cell sequencing/TCGA data sets, and GPR68 CRISPRi knockdown CAFs were used to determine the impact of BZDs on GPR68 signaling. RESULTS: LOR is associated with worse progression-free survival (PFS), whereas alprazolam (ALP) is associated with improved PFS, in pancreatic cancer patients receiving chemotherapy. LOR promotes desmoplasia (fibrosis and extracellular matrix protein deposition), inflammatory signaling, and ischemic necrosis. GPR68 is preferentially expressed on human PDAC CAFs, and n-unsubstituted BZDs, such as LOR, significantly increase IL6 expression and secretion in CAFs in a pH and GPR68-dependent manner. Conversely, ALP and other GPR68 n-substituted BZDs decrease IL6 in human CAFs in a pH and GPR68-independent manner. Across many cancer types, LOR is associated with worse survival outcomes relative to ALP and patients not receiving BZDs. CONCLUSIONS: We demonstrate that LOR stimulates fibrosis and inflammatory signaling, promotes desmoplasia and ischemic necrosis, and is associated with decreased pancreatic cancer patient survival.

Hematology-Oncology

Farhan S, and Holtan SG. Graft-versus-host disease: teaching old drugs new tricks at less cost. *Front Immunol* 2023; 14:1225748. PMID: 37600820. Full Text

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Graft-versus-host disease (GVHD) remains a major cause of morbidity and mortality after allogeneic stem cell transplantation (SCT). Currently, more patients can receive SCT. This is attributed to the use of reduced intensity regimens and the use of different GVHD prophylaxis that breaks the barrier of human leukocyte antigen, allowing an increase in the donor pool. Once an area with relatively few clinical trial options, there has been an increase in interest in GVHD prophylaxis and treatment, which has led to many US Food and Drug Administration (FDA) approvals. Although there is considerable excitement over novel therapies, many patients may not have access to them due to geographical or other resource constraints. In this review article, we summarize the latest evidence on how we can continue to repurpose drugs for GVHD prophylaxis and treatment. Drugs covered by our review include those that have been FDA approved for other uses for at least 15 years (since 2008); thus, they are likely to have generic equivalents available now or in the near future.

Hematology-Oncology

Ferber M, **Hecht LM**, **Martens KM**, **Hamann A**, **Carlin AM**, and **Miller-Matero LR**. Examining differences in long-term weight loss outcomes after bariatric surgery: The role of romantic relationship status. *Fam Syst Health* 2023; Epub ahead of print. PMID: 37616105. Request Article

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INTRODUCTION: This study tested for differences based on relationship status at the time of surgery in baseline body mass index (BMI), weight loss outcomes (change in BMI [ΔBMI], percent total weight loss [%TWL], percent excess weight loss [%EWL]), and rates of successful weight loss (defined as ≥ 50%EWL) up to 4-year postbariatric surgery. METHOD: Data came from a secondary analysis of patients (N = 492) who were up to 4-year postsurgery and completed a presurgical psychological evaluation and postsurgical survey. RESULTS: Sixty-nine percent of participants were patients in committed relationships and 31% were single/divorced/widowed patients. Single patients had higher presurgical BMIs than those who were partnered ($t = 2.28$, $p = .02$). There were no differences between those who were partnered and singles regarding ΔBMI and %TWL, although singles had smaller %EWL ($t = -2.08$, $p = .04$), which became nonsignificant after controlling for covariates. Most participants had successful weight loss (76.8%); however, this was not related to romantic relationship status. DISCUSSION: The results suggest those who were partnered undergo surgery at better-starting weights than singles and

maintain this advantage in the long term. Providers working with patients considering bariatric surgery could inquire about how their romantic and social relationships play a part in their decision-making process. (PsycInfo Database Record (c) 2023 APA, all rights reserved).

Hematology-Oncology

Gulati S, Hsu CY, Shah S, Shah PK, Zon R, Alsamarai S, Awosika J, El-Bakouny Z, Bashir B, Beeghly A, Berg S, de-la-Rosa-Martinez D, Doroshow DB, Egan PC, Fein J, Flora DB, Friese CR, Fromowitz A, Griffiths EA, **Hwang C**, Jani C, Joshi M, Khan H, Klein EJ, Heater NK, Koshkin VS, Kwon DH, Labaki C, Latif T, McKay RR, Nagaraj G, Nakasone ES, Nonato T, Polimera HV, Puc M, Razavi P, Ruiz-Garcia E, Saliby RM, Shastri A, Singh SRK, Tagalakis V, Vilar-Compte D, Weissmann LB, Wilkins CR, Wise-Draper TM, Wotman MT, Yoon JJ, Mishra S, Grivas P, Shyr Y, Warner JL, Connors JM, Shah DP, and Rosovsky RP. Systemic Anticancer Therapy and Thromboembolic Outcomes in Hospitalized Patients With Cancer and COVID-19. *JAMA Oncol* 2023; Epub ahead of print. PMID: 37589970. Full Text

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Henry Ford Cancer Institute, Henry Ford Hospital, Detroit, Michigan.
Mount Auburn Hospital, Boston, Massachusetts.
Penn State Cancer Institute, Hershey, Pennsylvania.
UCSF Helen Diller Family Comprehensive Cancer Center at the University of California San Francisco.
Moores Cancer Center, University of California San Diego.
Loma Linda University Cancer Center, Loma Linda, California.
Seattle Cancer Care Alliance, Fred Hutchinson Cancer Research Center, University of Washington, Seattle.
Virtua Health, Marlton, New Jersey.
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IMPORTANCE: Systematic data on the association between anticancer therapies and thromboembolic events (TEEs) in patients with COVID-19 are lacking. OBJECTIVE: To assess the association between anticancer therapy exposure within 3 months prior to COVID-19 and TEEs following COVID-19 diagnosis in patients with cancer. DESIGN, SETTING, AND PARTICIPANTS: This registry-based retrospective cohort study included patients who were hospitalized and had active cancer and laboratory-confirmed

SARS-CoV-2 infection. Data were accrued from March 2020 to December 2021 and analyzed from December 2021 to October 2022. EXPOSURE: Treatments of interest (TOIs) (endocrine therapy, vascular endothelial growth factor inhibitors/tyrosine kinase inhibitors [VEGFis/TKIs], immunomodulators [IMiDs], immune checkpoint inhibitors [ICIs], chemotherapy) vs reference (no systemic therapy) in 3 months prior to COVID-19. MAIN OUTCOMES AND MEASURES: Main outcomes were (1) venous thromboembolism (VTE) and (2) arterial thromboembolism (ATE). Secondary outcome was severity of COVID-19 (rates of intensive care unit admission, mechanical ventilation, 30-day all-cause mortality following TEEs in TOI vs reference group) at 30-day follow-up. RESULTS: Of 4988 hospitalized patients with cancer (median [IQR] age, 69 [59-78] years; 2608 [52%] male), 1869 had received 1 or more TOIs. Incidence of VTE was higher in all TOI groups: endocrine therapy, 7%; VEGFis/TKIs, 10%; IMiDs, 8%; ICIs, 12%; and chemotherapy, 10%, compared with patients not receiving systemic therapies (6%). In multivariable log-binomial regression analyses, relative risk of VTE (adjusted risk ratio [aRR], 1.33; 95% CI, 1.04-1.69) but not ATE (aRR, 0.81; 95% CI, 0.56-1.16) was significantly higher in those exposed to all TOIs pooled together vs those with no exposure. Among individual drugs, ICIs were significantly associated with VTE (aRR, 1.45; 95% CI, 1.01-2.07). Also noted were significant associations between VTE and active and progressing cancer (aRR, 1.43; 95% CI, 1.01-2.03), history of VTE (aRR, 3.10; 95% CI, 2.38-4.04), and high-risk site of cancer (aRR, 1.42; 95% CI, 1.14-1.75). Black patients had a higher risk of TEEs (aRR, 1.24; 95% CI, 1.03-1.50) than White patients. Patients with TEEs had high intensive care unit admission (46%) and mechanical ventilation (31%) rates. Relative risk of death in patients with TEEs was higher in those exposed to TOIs vs not (aRR, 1.12; 95% CI, 0.91-1.38) and was significantly associated with poor performance status (aRR, 1.77; 95% CI, 1.30-2.40) and active/progressing cancer (aRR, 1.55; 95% CI, 1.13-2.13). CONCLUSIONS AND RELEVANCE: In this cohort study, relative risk of developing VTE was high among patients receiving TOIs and varied by the type of therapy, underlying risk factors, and demographics, such as race and ethnicity. These findings highlight the need for close monitoring and perhaps personalized thromboprophylaxis to prevent morbidity and mortality associated with COVID-19-related thromboembolism in patients with cancer.

Hematology-Oncology

Li P, Kane K, Wolf FM, Berry AB, **Gadgeel S**, and **Pilling A**. Race-Associated Genomic Correlates of Therapeutic Response in African American Patients With Non-Small-Cell Lung Cancer. *JCO Precis Oncol* 2023; 7:e2300155. PMID: 37625101. Full Text

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PURPOSE: African American individuals are disproportionately affected by lung cancer in terms of incidence and mortality. In oncogene-driven non-small-cell lung cancer (NSCLC), emerging evidence indicates that underlying molecular heterogeneity, which can be affected by ancestry, contributes to variable drug sensitivity and therapeutic responses. The purpose of this study was to evaluate race-associated differences in reported treatment decisions, therapeutic outcomes, and molecular features in KRAS- and EGFR-mutant NSCLC. MATERIALS AND METHODS: This is a retrospective study using real-world clinical-genomic data from health systems in the United States to evaluate race-associated outcomes in advanced-stage KRAS- or EGFR-driven NSCLC. Our overall objectives were to evaluate race-associated therapeutic outcomes and to describe molecular features in non-Hispanic Black (NHB) and non-Hispanic White (NHW) patients with NSCLC. RESULTS: A total of 723 NSCLC patients with KRAS and 315 patients with EGFR oncogenic mutations were evaluated. In KRAS-mutant patients, variable outcomes were observed in NHB and NHW patients on the basis of receiving chemotherapy alone or in combination with immune checkpoint inhibitors. NHB patients received treatment at significantly lower rates compared with NHW patients. In the EGFR-mutant cohort, NHB and NHW patients received EGFR-targeted agents at similar rates, and overall survival was not significantly different. Race-associated differences in molecular features included a higher frequency of TP53 comutation in KRAS-mutant NHB patients and higher prevalence of EGFR G719S subtype in NHB patients. CONCLUSION: In a real-world cohort of patients with NSCLC, we identified race-associated differences in therapeutic outcomes and described molecular characteristics in NHB and NHW patients

with NSCLC. To proactively identify patients most likely to respond to systemic therapies, a more comprehensive approach is needed to help guide therapy selection in individualized patient populations.

Hematology-Oncology
Trendowski MR, Lusk CM, Wenzlaff AS, **Neslund-Dudas C**, **Gadgeel SM**, Soubani AO, and Schwartz AG. Assessing a Polygenic Risk Score for Lung Cancer Susceptibility in Non-Hispanic White and Black Populations. *Cancer Epidemiol Biomarkers Prev* 2023; Epub ahead of print. PMID: 37578347. Request Article

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BACKGROUND: Polygenic risk scores (PRS) have become an increasingly popular approach to evaluate cancer susceptibility, but have not adequately represented Black populations in model development. METHODS: We used a previously published lung cancer PRS based on 80 SNPs associated with lung cancer risk in the OncoArray cohort and validated in UK Biobank. The PRS was evaluated for association with lung cancer risk adjusting for age, sex, total pack-years, family history of lung cancer, history of COPD, and the top five principal components for genetic ancestry. RESULTS: Among the 80 PRS SNPs included in the score, 14 were significantly associated with lung cancer risk ($p<0.05$) in INHALE White participants, while there were no significant SNPs among INHALE Black participants. After adjusting for covariates, the PRS was significantly associated with risk in Whites (continuous score $p=0.007$), but not in Blacks (continuous score $p=0.88$). The PRS remained a statistically significant predictor of lung cancer risk in Whites ineligible for lung cancer screening under current USPSTF guidelines ($p=0.02$). CONCLUSIONS: Using a previously validated PRS, we did find some predictive ability for lung cancer in INHALE White participants beyond traditional risk factors. However, this effect was not observed in Black participants, indicating the need to develop and validate ancestry-specific lung cancer risk models. IMPACT: While a previously published lung cancer PRS was able to stratify White participants into different levels of risk, the model was not predictive in Blacks. Our findings highlight the need to develop and validate ancestry-specific lung cancer risk models.

Hospital Medicine
Minhas AMK, **Gupta K**, Jain V, **Kakar TS**, Merchant AT, Shapiro MD, Abushamat LA, Nambi V, and Virani SS. Trends in Cardiovascular Mortality in the United States from 1968 to 2019: Analysis of the CDC Wonder Database. *Eur J Prev Cardiol* 2023; Epub ahead of print. PMID: 37619975. Full Text

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Hospital Medicine
Nelson AJ, Young R, **Tarrar IH**, Wojdyla D, Wang TY, and Mehta RH. Temporal Trends in Risk Factors of Periprocedural Stroke in Patients Undergoing Percutaneous Coronary Intervention: Insights from the ACC NCDR CathPCI Registry. *Am J Cardiol* 2023; 204:284-286. PMID: 37562194. Full Text

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Hypertension and Vascular Research
Monu SR, **Potter DL**, **Liao TD**, **King KN**, and **Ortiz PA**. Role of Alström syndrome 1 in the regulation of glomerular hemodynamics. *Am J Physiol Renal Physiol* 2023; 325(4):F418-f425. PMID: 37560774. Full Text

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Inactivating mutations in the ALMS1 gene in humans cause Alström syndrome, characterized by the early onset of obesity, insulin resistance, and renal dysfunction. However, the role of ALMS1 in renal function and hemodynamics is unclear. We previously found that ALMS1 is expressed in thick ascending limbs, where it binds and decreases Na(+)-K(+)-2Cl(-) cotransporter activity. We hypothesized that ALMS1 is expressed in macula densa cells and that its deletion enhances tubuloglomerular feedback (TGF) and reduces glomerular filtration rate (GFR) in rats. To test this, homozygous ALMS1 knockout (KO) and littermate wild-type Dahl salt-sensitive rats were studied. TGF sensitivity was higher in ALMS1 KO rats as measured by in vivo renal micropuncture. Using confocal microscopy, we confirmed immunolabeling of ALMS1 in macula densa cells (nitric oxide synthase 1 positive), supporting a role for ALMS1 in TGF regulation. Baseline glomerular capillary pressure was higher in ALMS1 KO rats, as was mean arterial pressure. Renal interstitial hydrostatic pressure was lower in ALMS1 KO rats, which is linked to increased Na(+) reabsorption and hypertension. GFR was reduced in ALMS1 KO rats. Seven-week-old ALMS1 KO rats were not proteinuric, but proteinuria was present in 18- to 22-wk-old ALMS1 KO rats. The glomerulosclerosis index was higher in 18-wk-old ALMS1 KO rats. In conclusion, ALMS1 is involved in the control of glomerular hemodynamics in part by enhancing TGF sensitivity, and this may contribute to decreased GFR. Increased TGF sensitivity, enhanced glomerular capillary pressure, and hypertension may lead to glomerular damage in ALMS1 KO rats. These are the first data supporting the role of ALMS1 in TGF and glomerular hemodynamics.NEW & NOTEWORTHY ALMS1 is a novel protein involved in regulating tubuloglomerular feedback (TGF) sensitivity, glomerular capillary pressure, and blood pressure, and its dysfunction may reduce renal function and cause glomerular damage.

Infectious Diseases
Jamil M, Salam A, Joseph Benher BM, **Rehman S**, Jamil J, and **Suleyman G**. A Case of Alcohol Withdrawal-Induced Central and Extrapontine Myelinolysis. *Cureus* 2023; 15(7):e41640. PMID: 37565130. Full Text

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A 40-year-old female with a history of chronic alcohol use disorder presented with an acute intractable left-sided headache for three days and progressively worsening unsteady gait requiring a wheelchair to ambulate. The patient had a history of chronic alcoholism since 2019 but reported abstinence since September 2021. One month after quitting alcohol, she experienced a sudden deterioration in bilateral extremity neuropathy, forgetfulness, difficulty writing, and severe mood swings, which continued to worsen until her presentation in July 2022. Laboratory tests, including complete blood count and electrolyte levels, were within normal ranges. A previous MRI performed during the investigation for alcoholic neuropathy a few months before she quit drinking showed no abnormalities. However, a subsequent MRI during work-up for the current acute symptoms revealed significant signal abnormalities involving the central pons, bilateral cerebral peduncles, and medullary pyramids, consistent with chronic

central pontine myelinolysis (CPM) with extrapontine myelinolysis (EPM) extending into the peduncles. The patient received treatment with folate and multivitamins and was scheduled for outpatient follow-up with physical therapy for rehabilitation. This case highlights CPM as a consequence of alcohol withdrawal and emphasizes the importance of timely diagnosis and appropriate management in such patients.

Infectious Diseases
Koneru S, **Thiruvadi V**, and **Ramesh M**. Gut microbiome and its clinical implications: exploring the key players in human health. *Curr Opin Infect Dis* 2023; Epub ahead of print. PMID: 37593952. Full Text

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PURPOSE OF REVIEW: The human gut harbors a diverse community of microorganisms known as the gut microbiota. Extensive research in recent years has shed light on the profound influence of the gut microbiome on human health and disease. This review aims to explore the role of the gut microbiome in various clinical conditions and highlight the emerging therapeutic potential of targeting the gut microbiota for disease management. RECENT FINDINGS: Knowledge of the influence of gut microbiota on human physiology led to the development of various therapeutic possibilities such as fecal microbiota transplant (FMT), phage therapy, prebiotics, and probiotics. Recently, the U.S. FDA approved two FMT products for the treatment of recurrent Clostridioides difficile infection with ongoing research for the treatment of various disease conditions. SUMMARY: Advancement in the knowledge of the association between gut microbiota and various disease processes has paved the way for novel therapeutics.

Infectious Diseases
Robinson C, **Maraj D**, Minhas JS, **Bhatia M**, and **Kak V**. Gradenigo's Syndrome and Vernet Syndrome as Presenting Signs of Nasopharyngeal Carcinoma. *Cureus* 2023; 15(7):e41636. PMID: 37565094. Full Text

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Both Gradenigo's syndrome and Vernet syndrome are rare pathologies of the intracranial space; both involve compression of a particular anatomic location in the skull, thus affecting structures nearby or within that space. A patient presenting with one or both of these syndromes should raise concern for malignancy, head trauma, or an intracranial infection. We present a case of a 39-year-old female with three weeks of left-sided ear, face, and neck pain along with difficulty swallowing and reduced vision in the left eye. Magnetic resonance imaging of the brain revealed fullness in the left nasopharyngeal region, raising concern for malignancy or infection. Biopsy of the mass ultimately revealed Epstein-Barr virus positive nasopharyngeal carcinoma, nonkeratinizing undifferentiated type, along with culture data revealing methicillin-resistant Staphylococcus aureus positive left otomastoiditis. She received chemoradiation therapy along with six weeks of antibiotic therapy. A patient presenting with symptoms reflective of a sinus infection unrelieved by antibiotics with concomitant cranial nerve deficits should raise clinical concern for an intracranial pathology rather than a simple case of sinusitis.

Internal Medicine
Almasri W, Haque MZ, Shaik M, Mannan A, **Rehman S**, and **Husain M**. Analyzing the Content Found on Fellowship Websites for Adult Congenital Heart Disease. *Cureus* 2023; 15(7):e42682. PMID: 37649934. Full Text

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The Adult Congenital Heart Disease (ACHD) fellowship is a two-year fellowship that can be done by physicians who have finished their internal medicine residency and cardiology fellowship. This study evaluated the accessibility and provided information on the websites of the ACHD fellowship programs to identify potential areas of improvement for future fellowship applicants. Analysis of 25 ACHD fellowship program websites was conducted based on 34 criteria under three main categories: recruitment information, education and research information, and incentive information. This study found that many evaluated ACHD program websites lacked information regarding recruitment. Specifically, information regarding mentorship opportunities, hospital statistics/number of beds, selection process, and interview dates, leaving out crucial details on what to expect during the matching process. Additionally, more information on education and research is beneficial for applicants to sufficiently compare ACHD fellowship programs and make more informed decisions about which programs they would like to apply to. Information on academic stipends, evaluation criteria, expected caseload, moonlighting opportunities, elective opportunities, rotation schedules, call requirements, and types of procedures were all limited across multiple websites. Lastly, incentive information was found to be insufficient across most ACHD fellowship websites. Incentive information included fellow wellness, harassment policies, parental leave, salary, benefits, and vacation/sick leave. This study shows that ACHD fellowship programs need to supply more information on their websites to provide applicants with details to help them choose the fellowship program that corresponds best with their career goals. Expanding upon information regarding recruitment, education, research, and incentives will provide applicants with a strong understanding of ACHD fellowship programs and what they can expect throughout their education. In return, this will help ACHD fellowship programs attract stronger applicants, ultimately improving the quality of their respective programs.

Internal Medicine

Arriola-Montenegro J, Beas R, **Cerna-Viacava R**, Chaponan-Lavalle A, Hernandez Randich K, Chambergo-Michilot D, Flores Sanga H, and Mutirangura P. Therapies for patients with coexisting heart failure with reduced ejection fraction and non-alcoholic fatty liver disease. *World J Cardiol* 2023; 15(7):328-341. PMID: 37576545. Full Text

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Heart failure with reduced ejection fraction (HFrEF) and nonalcoholic fatty liver disease (NAFLD) are two common comorbidities that share similar pathophysiological mechanisms. There is a growing interest in the potential of targeted therapies to improve outcomes in patients with coexisting HFrEF and NAFLD. This manuscript reviews current and potential therapies for patients with coexisting HFrEF and NAFLD. Pharmacological therapies, including angiotensin-converting enzyme inhibitors/angiotensin receptor blockers, mineralocorticoids receptor antagonist, and sodium-glucose cotransporter-2 inhibitors, have been shown to reduce fibrosis and fat deposits in the liver. However, there are currently no data showing the beneficial effects of sacubitril/valsartan, ivabradine, hydralazine, isosorbide nitrates, digoxin, or beta blockers on NAFLD in patients with HFrEF. This study highlights the importance of considering HFrEF and NAFLD when developing treatment plans for patients with these comorbidities. Further research is needed in patients with coexisting HFrEF and NAFLD, with an emphasis on novel therapies and the importance of a multidisciplinary approach for managing these complex comorbidities.

Internal Medicine

Fadel RA, **Cerna Viacava R**, **Makki T**, Fadel CD, Malette K, Demertzis ZD, Ahluwalia G, **Miller J**, and **Russell C**. Compression wraps as adjuvant therapy in the management of acute systolic heart failure. *Heliyon* 2023; 9(8):e19008. PMID: 37600376. Full Text

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BACKGROUND: Guidelines recommend targeting decongestion in management of decompensated HF, with lower extremity edema often serving as the clinical target. LECW are seldom used in the acute setting, with a paucity of data on efficacy in HF, despite serving as a cornerstone of chronic lymphedema management. PRIMARY OBJECTIVE: Study the efficacy and safety of LECW in acute decompensated HF. METHODS: Open-label, randomized, parallel-group clinical trial. PRIMARY OUTCOMES: Days on intravenous (IV) diuretic therapy, total hospital length of stay (LOS), and 30-day all-cause readmission. RESULTS: 32 patients were enrolled, with 29 patients completing the study. Enrollment was suspended due to the COVID-19 pandemic. Overall LOS was shorter in the intervention group (3.5 vs 6 days, $p = 0.05$), with no significant difference in total days on IV diuresis or 30-day readmission rate with use of LECW. Fewer patients required continuous diuretic infusion after treatment with LECW (0 vs 7 patients, $p = 0.027$). The intervention group scored significantly better on the MLWHF (55.5 vs 65, $p = 0.021$), including both the physical and emotional dimension scores. No adverse events were reported with use of LECW, including a significantly lower incidence of AKI (1 vs 13 patients, $p = 0.005$). CONCLUSION: The use of LECW resulted in reduced hospital LOS compared to standard therapy, with no difference in days of IV diuresis administration or 30-day readmission. Treatment with LECW also resulted in less continuous IV diuretic therapy, fewer incidence of AKI, and improved quality of life. Trends toward less escalation of diuresis, and greater reduction in edema were also observed.

Internal Medicine

Hedderich P, **Sueng LN**, and **Shaban H**. Geriatric Medicine Principles in Conservative Kidney Management: Frailty, Functional Assessments, and Selective Deprescribing. *Semin Nephrol* 2023; 43(1):151400. PMID: 37536079. Full Text

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Conservative kidney management is a nondialytic treatment option for advanced chronic kidney disease that involves interventions to delay kidney function loss, medications to treat symptoms, and psychosocial support for patients and their loved ones. Several geriatric medicine principles are applicable to patients who are considering or receiving conservative kidney management, including the integration of physical, psychological, and social factors into medical care and medical decisions; careful review of medication lists with selective deprescribing; and screening for geriatric syndromes such as frailty and functional impairment. In this review, we discuss how functional and frailty assessments as well as selective deprescribing can be useful for patients considering or receiving conservative kidney management.

Internal Medicine

Jaiswal V, Agrawal V, Ang SP, Saleeb M, **Ishak A**, Hameed M, Rajak K, Kalra K, and Jaiswal A. Post-Diagnostic Statin Use and its Association with Cancer Recurrence and Mortality in Breast Cancer Patients: A Systematic Review and Meta-analysis. *Eur Heart J Cardiovasc Pharmacother* 2023; Epub ahead of print. PMID: 37562940. Full Text

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BACKGROUND: Statins are widely acknowledged for their application in patients with hypercholesterolemia to reduce cardiovascular morbidity and mortality. More recently, their potential to exert pleiotropic effects, particularly in impeding the proliferation of neoplastic cells, has attracted considerable attention. Prior studies have demonstrated that statins may mitigate cancer progression and micrometastasis. However, the benefits of statins in breast cancer have been inconclusive. OBJECTIVE: The aim of this meta-analysis was to evaluate the impact of statin use following a breast cancer diagnosis on breast cancer recurrence and mortality. METHODS: We performed a systematic literature search using PubMed, Embase, and Scopus for relevant articles from inception until 30th May 2023. Hazard ratios (HR) were pooled using a random-effect model. The primary outcome of interest was the risk of breast cancer recurrence. The secondary outcomes included breast cancer-specific mortality and all-cause mortality. RESULTS: A total of 15 studies with 156,448 patients were included in the final analysis. The mean age of patients between statin users and non-users was 64.59 and 59.15 years, respectively. Statin use was associated with a reduction in the recurrence of breast cancer (HR 0.76, 95%CI: 0.67-0.87) compared with non-statin users. This trend was similar among lipophilic statin users (HR 0.73, 95%CI: 0.63-0.85) but not for hydrophilic statin users (HR 1.17, 95%CI: 0.82-1.68). Furthermore, all-cause mortality (HR 0.82, 95%CI: 0.66-1.02) and breast cancer mortality (HR 0.87, 95% CI: 0.69-1.10) were comparable between statin and non-statin users. However, lipophilic statins demonstrated a reduction in both all-cause mortality (HR 0.84, 95%CI: 0.75-0.93) and breast cancer mortality (HR 0.85, 95%CI: 0.74-0.99) compared to non-statin users. CONCLUSION: Among patients with breast cancer, statin use post-diagnosis decreases the risk of breast cancer recurrence. Furthermore, lipophilic statins exhibit an additional advantage of reducing both all-cause and breast cancer-specific mortality.

Internal Medicine
Jamil M, **Daneshvar A**, **Nachawati D**, El Sharu H, and **Meysami A**. A Rare Presentation of Zoledronate-Induced Systemic Inflammatory Response. *Cureus* 2023; 15(7):e41524. PMID: 37551226. Full Text

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Zoledronic acid is a bisphosphonate commonly used to treat various conditions involving bone loss. While it is generally well-tolerated, the occurrence of severe inflammatory reactions is rare. We present the case of an 82-year-old female who developed a severe immune reaction, including weakness and tenderness in her upper and lower extremities, following a single dose of zoledronic acid infusion for the treatment of osteoporosis. The onset of symptoms occurred one week after the infusion and persisted, progressively worsening over time, leading to functional impairment and the need for a walker for ambulation. Laboratory studies revealed an elevated erythrocyte sedimentation rate while other autoimmune markers were within normal limits. Differential diagnosis included an adverse reaction to zoledronic acid or underlying polymyalgia rheumatica. The patient showed significant improvement with a prednisone taper, suggesting an immune-mediated response. This case highlights the importance of considering severe immune reactions as a potential side effect of zoledronic acid and emphasizes the need for further research to better understand the underlying mechanisms and optimize patient management.

Internal Medicine
Jamil M, Salam A, Joseph Benher BM, **Rehman S**, Jamil J, and **Suleyman G**. A Case of Alcohol Withdrawal-Induced Central and Extrapontine Myelinolysis. *Cureus* 2023; 15(7):e41640. PMID: 37565130. Full Text

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A 40-year-old female with a history of chronic alcohol use disorder presented with an acute intractable left-sided headache for three days and progressively worsening unsteady gait requiring a wheelchair to ambulate. The patient had a history of chronic alcoholism since 2019 but reported abstinence since September 2021. One month after quitting alcohol, she experienced a sudden deterioration in bilateral extremity neuropathy, forgetfulness, difficulty writing, and severe mood swings, which continued to worsen until her presentation in July 2022. Laboratory tests, including complete blood count and electrolyte levels, were within normal ranges. A previous MRI performed during the investigation for alcoholic neuropathy a few months before she quit drinking showed no abnormalities. However, a subsequent MRI during work-up for the current acute symptoms revealed significant signal abnormalities involving the central pons, bilateral cerebral peduncles, and medullary pyramids, consistent with chronic central pontine myelinolysis (CPM) with extrapontine myelinolysis (EPM) extending into the peduncles. The patient received treatment with folate and multivitamins and was scheduled for outpatient follow-up with physical therapy for rehabilitation. This case highlights CPM as a consequence of alcohol withdrawal and emphasizes the importance of timely diagnosis and appropriate management in such patients.

Internal Medicine
Mangal R, **Hasso MF**, **Obri MS**, **Almajed MR**, and **Entz A**. A Case of a Large and Rare Incidental Pleural Tumor in an Elderly Female. *Cureus* 2023; 15(7):e42198. PMID: 37601997. Full Text

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

Solitary fibrous tumors are very rare in the pleura, and they are generally found incidentally. Even though they can potentially become malignant and metastasize, they have minimal clinical symptoms and can still be benign. Due to the low incidence of these tumors, there is no standard of therapy beyond surgical resection. We present an asymptomatic case of a large, rapidly expanding solitary fibrous tumor of the pleura in an elderly female.

Internal Medicine
Obri MS, **Nimri F**, **Kamran W**, Nimri R, **Pompa R**, and **Zuchelli T**. Gastrointestinal Stromal Tumor Presenting as Food Impaction and Pseudo-Achalasia. *ACG Case Rep J* 2023; 10(8):e01116. PMID: 37583506. Full Text

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Gastrointestinal stromal tumors (GISTs) are one of the most common mesenchymal tumors of the gastrointestinal tract. Studies report the incidence of GIST to be 14.5 per million, with 18% being diagnosed incidentally. The most common location is the stomach while the esophagus is the rarest, representing only 0.7% of cases. The clinical manifestations of GISTs vary. Most patients present with bleeding and gastric discomfort. Some may present with life-threatening hematemesis or melena. We present a unique case of a GIST presenting as pseudo-achalasia and food impaction.

Internal Medicine
Riasat M, Hanumanthu BKJ, Khan A, Haseeb Riaz A, Anjum Z, Ehtesham M, Ur Rehman S, Javed A, **Muhammad A**, and Misra D. Outcomes and survival of patients undergoing percutaneous vegetectomy for right heart endocarditis. *Int J Cardiol Heart Vasc* 2023; 47:101231. PMID: 37576075. Full Text

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BACKGROUNDS: AngioVac is used for the percutaneous removal of vegetations and for debulking of large vegetations in patients who are not surgical candidates.This study aims to identify the demographics, echocardiographic features, indications, improvement of the tricuspid valve regurgitation, and survival outcomes of patients who have undergone AngioVac vegetectomy reported in the literature. METHODS: A systematic review was performed to identify articles reporting suction thromectomy or vegetation removal using the AngioVac system for RSIE (right sided infective endocarditis). Survival on discharge was our primary outcome. Additionally, we evaluated indications for suction thrombectomy and TR improvement. Categorical variables were expressed as percentages and ratios. RESULTS: A total of 49 studies were identified. The most common risk factor was intravenous drug abuse seen in 45% (20/49) and cardiovascular implantable electronic device (CIED) in 45% (20/49). Circulatory shock was seen in 35% of patients. The causative organism was gram positive cocci (86%). Moderate to severe TR was present in 74% of cases with documented echocardiograms. Indications for AngioVac were poor surgical candidacy (81%) or to reduce septic emboli risk (19%). Survival at discharge was 93%. TR improvement was reported only in 16% cases and remained unchanged/worsened in 84%. CONCLUSION: AngioVac procedure is an alternative treatment for critically ill patients who cannot undergo surgery. To understand the survival, safety and candidacy of patients undergoing this procedure, further randomized control studies and literature reviews are needed. The improvement or worsening of tricuspid regurgitation in patients with TR valve involvement is another factor to be investigated.

Internal Medicine
Robinson C, **Maraj D**, Minhas JS, **Bhatia M**, and **Kak V**. Gradenigo's Syndrome and Vernet Syndrome as Presenting Signs of Nasopharyngeal Carcinoma. *Cureus* 2023; 15(7):e41636. PMID: 37565094. Full Text

Internal Medicine, Henry Ford Health System, Jackson, USA.
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Both Gradenigo's syndrome and Vernet syndrome are rare pathologies of the intracranial space; both involve compression of a particular anatomic location in the skull, thus affecting structures nearby or within that space. A patient presenting with one or both of these syndromes should raise concern for malignancy, head trauma, or an intracranial infection. We present a case of a 39-year-old female with three weeks of left-sided ear, face, and neck pain along with difficulty swallowing and reduced vision in the left eye. Magnetic resonance imaging of the brain revealed fullness in the left nasopharyngeal region, raising concern for malignancy or infection. Biopsy of the mass ultimately revealed Epstein-Barr virus positive nasopharyngeal carcinoma, nonkeratinizing undifferentiated type, along with culture data revealing methicillin-resistant Staphylococcus aureus positive left otomastoiditis. She received chemoradiation therapy along with six weeks of antibiotic therapy. A patient presenting with symptoms reflective of a sinus infection unrelieved by antibiotics with concomitant cranial nerve deficits should raise clinical concern for an intracranial pathology rather than a simple case of sinusitis.

Internal Medicine
Weiner J, Llore N, Ormsby D, Fujiki M, Segovia MC, **Obri M**, **Jafri SM**, Liggett J, Kroemer AHK, Matsumoto C, Moon J, Di Cocco P, Selvaggi G, Garcia J, Ganoza A, Khanna A, Mazariegos G, Wendel D, and Reyes J. The First Collective Examination of Immunosuppressive Practices Among American Intestinal Transplant Centers. *Transplant Direct* 2023; 9(9):e1512. PMID: 37636483. Full Text

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BACKGROUND: Unlike other solid organs, no standardized treatment algorithms exist for intestinal transplantation (ITx). We established a consortium of American ITx centers to evaluate current practices. METHODS: All American centers performing ITx during the past 3 y were invited to participate. As a consortium, we generated questions to evaluate and collect data from each institution. The data were compiled and analyzed. RESULTS: Ten centers participated, performing 211 ITx during the past 3 y (range, 3-46; mean 21.1). Induction regimens varied widely. Thymoglobulin was the most common, used in the plurality of patients (85/211; 40.3%), but there was no consensus regimen. Similarly, regimens for the treatment of acute cellular rejection, antibody-mediated rejection, and graft-versus-host disease varied significantly between centers. We also evaluated differences in maintenance immunosuppression protocols, desensitization regimens, mammalian target of rapamycin use, antimetabolite use, and posttransplantation surveillance practices. Maintenance tacrolimus levels, stoma presence, and scoping frequency were not associated with differences in rejection events. Definitive association between treatments and outcomes, including graft and patient survival, was not the intention of this initial collaboration and is prevented by the lack of patient-level data and the presence of confounders. However, we identified trends regarding rejection episodes after various induction strategies that require further investigation in our subsequent collaborations. CONCLUSIONS: This initial collaboration reveals the extreme heterogeneity of practices among American ITx centers. Future collaboration will explore patient-level data, stratified by age and transplant type (isolated intestine versus multivisceral), to explore the association between treatment regimens and outcomes.

Nephrology

Hedderich P, **Sueng LN**, and **Shaban H**. Geriatric Medicine Principles in Conservative Kidney Management: Frailty, Functional Assessments, and Selective Deprescribing. *Semin Nephrol* 2023; 43(1):151400. PMID: 37536079. Full Text

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Conservative kidney management is a nondialytic treatment option for advanced chronic kidney disease that involves interventions to delay kidney function loss, medications to treat symptoms, and psychosocial support for patients and their loved ones. Several geriatric medicine principles are applicable to patients who are considering or receiving conservative kidney management, including the integration of physical, psychological, and social factors into medical care and medical decisions; careful review of medication lists with selective deprescribing; and screening for geriatric syndromes such as frailty and functional impairment. In this review, we discuss how functional and frailty assessments as well as selective deprescribing can be useful for patients considering or receiving conservative kidney management.

Neurology

Hauser RA, Espay AJ, Ellenbogen AL, Fernandez HH, Isaacson SH, **LeWitt PA**, Ondo WG, Pahwa R, Schwarz J, Stocchi F, Zeitlin L, Banisadr G, Fisher S, Visser H, and D'Souza R. IPX203 vs Immediate-Release Carbidopa-Levodopa for the Treatment of Motor Fluctuations in Parkinson Disease: The RISE-PD Randomized Clinical Trial. *JAMA Neurol* 2023; Epub ahead of print. PMID: 37578800. Full Text

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IMPORTANCE: Levodopa has a short half-life and a limited window of opportunity for absorption in the proximal small intestine. IPX203 is an oral, extended-release formulation of carbidopa-levodopa developed to address these limitations. OBJECTIVE: To assess the efficacy and safety of IPX203 vs immediate-release carbidopa-levodopa in patients with Parkinson disease who are experiencing motor fluctuations. DESIGN, SETTING, AND PARTICIPANTS: RISE-PD was a 20-week, randomized, double-blind, double-dummy, active-controlled, phase 3 clinical trial. The study was conducted between November 6, 2018, and June 15, 2021, at 105 academic and clinical centers in the US and Europe. Patients with Parkinson disease taking a total daily dose of 400 mg or more of levodopa and experiencing an average of 2.5 hours or more daily off-time were included in the study. A total of 770 patients were screened, 140 were excluded (those taking controlled-release carbidopa-levodopa apart from a single daily bedtime dose, Rytary (Amneal Pharmaceuticals), additional carbidopa or benserazide, or catechol O-methyl transferase inhibitors or who had a history of psychosis within the past 10 years), and 630 were enrolled in the trial. INTERVENTIONS: Following open-label immediate-release carbidopa-levodopa dose adjustment (3 weeks) and conversion to IPX203 (4 weeks), patients were randomized in a 1:1 ratio to double-blind, double-dummy treatment with immediate-release carbidopa-levodopa or IPX203 for 13 weeks. MAIN OUTCOME AND MEASURES: The primary end point was mean change in daily good on-time (ie, on-time without troublesome dyskinesia) from baseline to the end of the double-blind treatment period. RESULTS: A total of 630 patients (mean [SD] age, 66.5 [8.95] years; 396 [62.9%] men) were enrolled, and 506 patients were randomly assigned to receive IPX203 (n = 256) or immediate-release carbidopa-levodopa (n = 250). The study met its primary end point, demonstrating statistically significant improvement in daily good on-time for IPX203 compared to immediate-release carbidopa-levodopa (least squares mean, 0.53 hours; 95% CI, 0.09-0.97; P = .02), with IPX203 dosed a mean 3 times per day vs 5 times per day for immediate-release carbidopa-levodopa. Good on-time per dose increased by 1.55 hours with IPX203 compared to immediate-release carbidopa-levodopa (95% CI, 1.37-1.73; P < .001). IPX203 was well tolerated. The most common adverse events in the double-blind phase (IPX203 vs immediate-release carbidopa-levodopa) were nausea (4.3% vs 0.8%) and anxiety (2.7% vs 0.0%). CONCLUSIONS AND RELEVANCE: In this study, IPX203 provided more hours of good on-time per day than immediate-release carbidopa-levodopa, even as IPX203 was dosed less frequently. TRIAL REGISTRATION: ClinicalTrials.gov Identifier: NCT03670953.

Neurology

Li L, **Ding G**, **Zhang L**, **Luo H**, **Davoodi-Bojd E**, **Li Q**, **Chopp M**, **Zhang ZG**, and **Jiang Q**. Glymphatic transport is reduced in rats with spontaneous pituitary tumor. *Front Med (Lausanne)* 2023; 10:1189614. PMID: 37601793. Full Text

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BACKGROUND AND OBJECTIVE: Pituitary tumor in patients induces adverse alterations in the brain, accompanied by cognitive deficits. Dysfunction of glymphatic waste clearance results in accumulation of

neurotoxic products within the brain, leading to cognitive impairment. However, the status of glymphatic function in the brain with pituitary tumor is unknown. Using magnetic resonance imaging (MRI) and an advanced mathematical modeling, we investigated the changes of glymphatic transport in the rats carrying spontaneous pituitary tumor. METHODS: Rats (22-24 months, female, Wistar) with and without pituitary tumor (n = 7/per group) underwent the identical experimental protocol. MRI measurements, including T2-weighted imaging and dynamic 3D T1-weighted imaging with intracisternal administration of contrast agent, were performed on each animal. The contrast-induced enhancement in the circle of Willis and in the glymphatic influx nodes were observed on the dynamic images and verified with time-signal-curves (TSCs). Model-derived parameters of infusion rate and clearance rate that characterize the kinetics of glymphatic tracer transport were evaluated in multiple representative brain regions. RESULTS: Our imaging data demonstrated a higher incidence of partially enhanced circle of Willis (86 vs. 14%; $p < 0.033$) and a lower incidence of enhancement in glymphatic influx nodes of pituitary (71 vs. 100%) and pineal (57 vs. 86%) recesses in the rats with pituitary tumor than in the rats with normal appearance of pituitary gland, indicating an intensification of impaired peri-vascular pathway and impeded glymphatic transport due to the presence of pituitary tumor. Consistently, our kinetic modeling and regional cerebral tissue quantification revealed significantly lower infusion and clearance rates in all examined regions in rats with spontaneous pituitary tumor than in non-tumor rats, representing a suppressed glymphatic transport in the brain with pituitary tumor. CONCLUSION: Our study demonstrates the compromised glymphatic transport in the rat brain with spontaneous pituitary tumor. The reduced efficiency in cerebral waste clearance increases the risk for neurodegeneration in the brain that may underlie the cognitive impairment commonly seen in patients with pituitary tumors.

Neurology

Martinez-Nunez AE, **Soltanian-Zadeh H**, **Latack K**, Ghazi N, and Mahajan A. Hyposmia and apathy in early, de novo Parkinson's disease: Lessons from structural brain connectivity. *J Neurol Sci* 2023; 452:120767. PMID: 37619327. Full Text

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INTRODUCTION: The neuroanatomical structures implicated in olfactory and emotional processing overlap significantly. Our understanding of the relationship between hyposmia and apathy, common manifestations of early Parkinson's disease (PD), is inadequate. MATERIALS AND METHODS: We analyzed data on 40 patients with early de-novo idiopathic PD enrolled within 2 years of motor symptom onset in the Parkinson's Progression Markers Initiative (PPMI) study. To be included in the analysis, patients must have smell dysfunction but no apathy at the baseline visit and had completed a diffusion MRI (dMRI) at the baseline visit and at the 48-month follow-up visit. We used the FMRIB Software Library's diffusion tool kit to measure fractional anisotropy (FA) in six regions of interest on dMRI: bilateral anterior corona radiata, left cingulum, left superior corona radiata, genu and body of the corpus callosum. We compared the FA in each region from the dMRI done at the beginning of the study with the follow up studies at 4 years. RESULTS: We found a significant decrease of FA at the bilateral anterior corona radiata, and the genu and body of the corpus callosum comparing baseline scans with follow up images at 4-years after starting the study. CONCLUSION: Structural connectivity changes associated with apathy can be seen early in PD patients with smell dysfunction.

Neurology

Sajad M, **Zahoor I**, **Rashid F**, **Cerghet M**, **Rattan R**, and **Giri S**. Pyruvate Dehydrogenase-Dependent Metabolic Programming Affects the Oligodendrocyte Maturation and Remyelination. *Mol Neurobiol* 2023; Epub ahead of print. PMID: 37620688. Full Text

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The metabolic needs of the premature/premyelinating oligodendrocytes (pre-OLs) and mature oligodendrocytes (OLs) are distinct. The metabolic control of oligodendrocyte maturation from the pre-OLs to the OLs is not fully understood. Here, we show that the terminal maturation and higher mitochondrial respiration in the OLs is an integrated process controlled through pyruvate dehydrogenase complex (Pdh). Combined bioenergetics and metabolic studies show that OLs show elevated mitochondrial respiration than the pre-OLs. Our signaling studies show that the increased mitochondrial respiration activity in the OLs is mediated by the activation of Pdh due to inhibition of the pyruvate dehydrogenase kinase-1 (Pdhk1) that phosphorylates and inhibits Pdh activity. Accordingly, when Pdhk1 is directly expressed in the pre-OLs, they fail to mature into the OLs. While Pdh converts pyruvate into the acetyl-CoA by its oxidative decarboxylation, our study shows that Pdh-dependent acetyl-CoA generation from pyruvate contributes to the acetylation of the bHLH family transcription factor, oligodendrocyte transcription factor 1 (Olig1) which is known to be involved in the OL maturation. Pdh inhibition via direct expression of Pdhk1 in the pre-OLs blocks the Olig1-acetylation and OL maturation. Using the cuprizone model of demyelination, we show that Pdh is deactivated during the demyelination phase, which is however reversed in the remyelination phase upon cuprizone withdrawal. In addition, Pdh activity status correlates with the Olig1-acetylation status in the cuprizone model. Hence, the Pdh metabolic node activation allows a robust mitochondrial respiration and activation of a molecular program necessary for the terminal maturation of oligodendrocytes. Our findings open a new dialogue in the developmental biology that links cellular development and metabolism. These findings have far-reaching implications in the development of therapies for a variety of demyelinating disorders including multiple sclerosis.

Neurology

Wang L, **Lu X**, **Chopp M**, **Li C**, **Zhang Y**, **Szalad A**, **Liu XS**, and **Zhang ZG**. Comparative proteomic analysis of exosomes derived from endothelial cells and Schwann cells. *PLoS One* 2023; 18(8):e0290155. PMID: 37594969. Full Text

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Exosomes derived from endothelial cells and Schwann cells have been employed as novel treatments of neurological diseases, including peripheral neuropathy. Exosomal cargo plays a critical role in mediating recipient cell function. In this study, we thus performed a comprehensive proteomic analysis of exosomes derived from healthy mouse dermal microvascular endothelial cells (EC-Exo) and healthy mouse Schwann cells (SC-Exo). We detected 1,817and 1,579 proteins in EC-Exo and SC-Exo, respectively. Among them, 1506 proteins were present in both EC-Exo and SC-Exo, while 311 and 73 proteins were detected only in EC-Exo and SC-Exo, respectively. Bioinformatic analysis revealed that EC-Exo enriched proteins were involved in neurovascular function, while SC-Exo enriched proteins were related to lipid metabolism. Western blot analysis of 14 enriched proteins revealed that EC-Exo contained proteins involved in mediating endothelial function such as delta-like 4 (DLL4) and endothelial NOS (NOS3), whereas SC-Exo had proteins involved in mediating glial function such as apolipoprotein A-I (APOA1) and phospholipid transfer protein (PLTP). Collectively, the present study identifies differences in the cargo protein profiles of EC-Exo and SC-Exo, thus providing new molecular insights into their biological functions for the treatment of peripheral neuropathy.

Neurology

Wen Q, Wang H, Haacke EM, **Jiang Q**, and Hu J. Contribution of Direct Cerebral Vascular Transport in Brain Substance Clearance. *Aging Dis* 2023; Epub ahead of print. PMID: 37611901. Full Text

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The accumulation of harmful substances has long been recognized as a likely cause of many neurodegenerative diseases. The two classic brain clearance pathways are cerebrospinal fluid (CSF) and vascular circulation systems. Since the discovery of the glymphatic system, research on the CSF pathway has gained momentum, and impaired CSF clearance has been implicated in virtually all neurodegenerative animal models. However, the contribution of the direct participation of vascular transport across the blood-brain barrier in clearing substances is often ignored in glymphatic papers. Supportive evidence for the direct involvement of parenchymal vasculature in substance clearance is accumulated. First, multiple mechanisms have been proposed for the vascular drainage of exogenous and endogenous substances across the blood-brain barriers. Second, the "traditional" role of arachnoid villi and granulations as the main site for CSF draining into the vasculature system has been questioned. Third, MRI studies using different CSF tracers indicate that parenchymal vasculature directly participates in tracer efflux, consistent with immunohistochemical findings. Here we will review evidence in the literature that supports the direct participation of the parenchymal vascular system in substance clearance, in addition to the CSF clearance pathways.

Neurosurgery

Irfan M, Malik KM, Ahmad J, and **Malik G**. StrokeNet: An automated approach for segmentation and rupture risk prediction of intracranial aneurysm. *Comput Med Imaging Graph* 2023; 108:102271. PMID: 37556901. Full Text

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Intracranial Aneurysms (IA) present a complex challenge for neurosurgeons as the risks associated with surgical intervention, such as Subarachnoid Hemorrhage (SAH) mortality and morbidity, may outweigh the benefits of aneurysmal occlusion in some cases. Hence, there is a critical need for developing techniques that assist physicians in assessing the risk of aneurysm rupture to determine which aneurysms require treatment. However, a reliable IA rupture risk prediction technique is currently unavailable. To address this issue, this study proposes a novel approach for aneurysm segmentation and multidisciplinary rupture prediction using 2D Digital Subtraction Angiography (DSA) images. The proposed method involves training a fully connected convolutional neural network (CNN) to segment aneurysm regions in DSA images, followed by extracting and fusing different features using a multidisciplinary approach, including deep features, geometrical features, Fourier descriptor, and shear pressure on the aneurysm wall. The proposed method also adopts a fast correlation-based filter approach to drop highly correlated features from the set of fused features. Finally, the selected fused features are passed through a Decision Tree classifier to predict the rupture severity of the associated aneurysm into four classes: Mild, Moderate, Severe, and Critical. The proposed method is evaluated on a newly developed DSA image dataset and on public datasets to assess its generalizability. The system's performance is also evaluated on DSA images annotated by expert neurosurgeons for the rupture risk assessment of the segmented aneurysm. The proposed system outperforms existing state-of-the-art segmentation methods, achieving an 85 % accuracy against annotated DSA images for the risk assessment of aneurysmal rupture.

Neurosurgery

Nizar R, **Cazacu S**, **Xiang C**, Krasner M, Barbiro-Michaely E, Gerber D, Schwartz J, Fried I, Yuval S, Brodie A, Kazimirsky G, Amos N, Unger R, **Brown S**, **Rogers L**, **Penning DH**, and **Brodie C**. Propofol Inhibits Glioma Stem Cell Growth and Migration and Their Interaction with Microglia via BDNF-AS and Extracellular Vesicles. *Cells* 2023; 12(15). PMID: 37566001. Full Text

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Glioblastoma (GBM) is the most common and aggressive primary brain tumor. GBM contains a small subpopulation of glioma stem cells (GSCs) that are implicated in treatment resistance, tumor infiltration, and recurrence, and are thereby considered important therapeutic targets. Recent clinical studies have suggested that the choice of general anesthetic (GA), particularly propofol, during tumor resection, affects subsequent tumor response to treatments and patient prognosis. In this study, we investigated the molecular mechanisms underlying propofol's anti-tumor effects on GSCs and their interaction with microglia cells. Propofol exerted a dose-dependent inhibitory effect on the self-renewal, expression of mesenchymal markers, and migration of GSCs and sensitized them to both temozolomide (TMZ) and radiation. At higher concentrations, propofol induced a large degree of cell death, as demonstrated using microfluid chip technology. Propofol increased the expression of the lncRNA BDNF-AS, which acts as a tumor suppressor in GBM, and silencing of this lncRNA partially abrogated propofol's effects. Propofol also inhibited the pro-tumorigenic GSC-microglia crosstalk via extracellular vesicles (EVs) and delivery of BDNF-AS. In conclusion, propofol exerted anti-tumor effects on GSCs, sensitized these cells to radiation and TMZ, and inhibited their pro-tumorigenic interactions with microglia via transfer of BDNF-AS by EVs.

Obstetrics, Gynecology and Women's Health Services

Al Khatib S, **Bhatnagar A**, **Elshaikh N**, **Ghanem AI**, **Burmeister C**, **Allo G**, **Alkamachi B**, **Paridon A**, and **Elshaikh MA**. The Prognostic Significance of the Depth of Cervical Stromal Invasion in Women With FIGO Stage II Uterine Endometrioid Carcinoma. *Am J Clin Oncol* 2023; Epub ahead of print. PMID: 37525355. Full Text

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OBJECTIVE: The objective of this study was to investigate the prognostic significance of the depth of cervical stromal invasion (CSI) in women with FIGO stage II uterine endometrioid adenocarcinoma (EC). METHODS: Our database of women with EC was quired for patients with stage II EC. Pathologic slides were retrieved and reviewed by gynecologic pathologists to determine cervical stromal thickness and depth of CSI as a percentage of stromal thickness (%CSI). Kaplan-Meier, univariate, and multivariate analyses were used to compare recurrence-free, disease-specific (DSS), and overall survival (OS) between women who had<50% versus ≥50% CSI. Univariate and multivariate analyses were used to assess other prognostic variables associated with survival endpoints. RESULTS: A total of 117 patients were included in our study who had hysterectomy between 1/1990 and 8/2021. Seventy-nine patients (68%) with <50% and 38 (32w%) with ≥50% CSI. After a median follow-up of 131 months, 5-year DSS was significantly worse for women with ≥50% CSI (78% vs. 91%; P=0.04). However, %CSI was not an independent predictor for any of the studied survival endpoints. Independent predictors of worse 5-year recurrence-free survival and DSS included FIGO grade 3 tumors (P=0.02) and the presence of

lymphovascular space invasion (P=0.03). Grade 3 tumors were the only independent predictor of worse 5-year OS (P=0.02). CONCLUSIONS: Our results suggest that deep CSI is not an independent prognostic factor for survival endpoints in women with stage II uterine endometroid adenocarcinoma. The lack of independent prognostic significance of the depth CSI needs to be validated in a multi-institutional analysis.

Obstetrics, Gynecology and Women's Health Services
Kalmbach DA, **Cheng P**, **Reffi AN**, Ong JC, Swanson LM, Espie CA, **Seymour GM**, **Hirata M**, Walch O, **Pitts DS**, **Roth T**, and **Drake CL**. Reducing cognitive arousal and sleep effort alleviates insomnia and depression in pregnant women with DSM-5 insomnia disorder treated with a mindfulness sleep program. *Sleep Adv* 2023; 4(1). PMID: 37645455. Full Text

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OBJECTIVES: Combining mindfulness with behavioral sleep strategies has been found to alleviate symptoms of insomnia and depression during pregnancy, but mechanisms for this treatment approach remain unclear. The present study examined nocturnal cognitive arousal and sleep effort as potential treatment mechanisms for alleviating insomnia and depression via a mindfulness sleep program for pregnant women. METHODS: Secondary analysis from a proof-of-concept trial of 12 pregnant women with DSM-5 insomnia disorder who were treated with Perinatal Understanding of Mindful Awareness for Sleep (PUMAS), which places behavioral sleep strategies within a mindfulness framework. Data were collected across eight weekly assessments: pretreatment, six sessions, and posttreatment. Measures included the insomnia severity index (ISI), Edinburgh postnatal depression scale (EPDS), pre-sleep arousal scale's cognitive factor (PSASC), and the Glasgow sleep effort scale (GSES). We used linear mixed modeling to test cognitive arousal and sleep effort as concurrent and prospective predictors of insomnia and depression. RESULTS: Most patients reported high cognitive arousal before PUMAS (75.0%), which decreased to 8.3% after treatment. All insomnia remitters reported low cognitive arousal after treatment, whereas half of nonremitters continued reporting high cognitive arousal. Both nocturnal cognitive arousal and sleep effort were associated with same-week changes in insomnia throughout treatment, and sleep effort yielded a prospective effect on insomnia. Lower levels of nocturnal cognitive arousal and sleep effort prospectively predicted reductions in depression. CONCLUSIONS: The present study offers preliminary evidence that reducing sleep effort and nocturnal cognitive arousal may serve as key mechanisms for alleviating insomnia and depression via mindfulness-based insomnia therapy. ClinicalTrials.gov ID: NCT04443959.

Obstetrics, Gynecology and Women's Health Services
Redding A, **Santarossa S**, **Murphy D**, **Udumula MP**, **Munkarah A**, **Hijaz M**, and **Rattan R**. A patient perspective on applying intermittent fasting in gynecologic cancer. *BMC Res Notes* 2023; 16(1):190. PMID: 37644560. Full Text

Public Health Sciences, Henry Ford Health, Detroit, MI, USA.
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OBJECTIVE: Researchers sought patient feedback on a proposed randomized controlled trial (RCT) in which gynecological cancer patients would modify their diets with intermittent fasting to gain insight into patients' perspectives, receptivity, and potential obstacles. A convenience sample of 47 patients who met the inclusion criteria of the proposed RCT provided their feedback on the feasibility and protocols of the RCT using a multi-method approach consisting of focus groups (n = 8 patients) and surveys (n = 36 patients). RESULTS: Patients were generally receptive to the concept of intermittent fasting, and many expressed an interest in attempting it themselves. Patients agreed that the study design was feasible in terms of study assessments, clinic visits, and biospecimen collection. Feedback on what could facilitate adherence included convenient appointment scheduling times and the availability of the research team to answer questions. Regarding recruitment, patients offered suggestions for study advertisements, with the majority concurring that a medical professional approaching them would increase their likelihood of participation.

Obstetrics, Gynecology and Women's Health Services

Sajad M, **Zahoor I**, **Rashid F**, **Cerghet M**, **Rattan R**, and **Giri S**. Pyruvate Dehydrogenase-Dependent Metabolic Programming Affects the Oligodendrocyte Maturation and Remyelination. *Mol Neurobiol* 2023; Epub ahead of print. PMID: 37620688. Full Text

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The metabolic needs of the premature/premyelinating oligodendrocytes (pre-OLs) and mature oligodendrocytes (OLs) are distinct. The metabolic control of oligodendrocyte maturation from the pre-OLs to the OLs is not fully understood. Here, we show that the terminal maturation and higher mitochondrial respiration in the OLs is an integrated process controlled through pyruvate dehydrogenase complex (Pdh). Combined bioenergetics and metabolic studies show that OLs show elevated mitochondrial respiration than the pre-OLs. Our signaling studies show that the increased mitochondrial respiration activity in the OLs is mediated by the activation of Pdh due to inhibition of the pyruvate dehydrogenase kinase-1 (Pdhk1) that phosphorylates and inhibits Pdh activity. Accordingly, when Pdhk1 is directly expressed in the pre-OLs, they fail to mature into the OLs. While Pdh converts pyruvate into the acetyl-CoA by its oxidative decarboxylation, our study shows that Pdh-dependent acetyl-CoA generation from pyruvate contributes to the acetylation of the bHLH family transcription factor, oligodendrocyte transcription factor 1 (Olig1) which is known to be involved in the OL maturation. Pdh inhibition via direct expression of Pdhk1 in the pre-OLs blocks the Olig1-acetylation and OL maturation. Using the cuprizone model of demyelination, we show that Pdh is deactivated during the demyelination phase, which is however reversed in the remyelination phase upon cuprizone withdrawal. In addition, Pdh activity status correlates with the Olig1-acetylation status in the cuprizone model. Hence, the Pdh metabolic node activation allows a robust mitochondrial respiration and activation of a molecular program necessary for the terminal maturation of oligodendrocytes. Our findings open a new dialogue in the developmental biology that links cellular development and metabolism. These findings have far-reaching implications in the development of therapies for a variety of demyelinating disorders including multiple sclerosis.

Ophthalmology and Eye Care Services

Rezaei S, **Steen D**, and **Amin S**. Successful treatment of an extensively drug-resistant pseudomonal ulcer associated with contaminated artificial tears. *Am J Ophthalmol Case Rep* 2023; 32:101909. PMID: 37560556. Full Text

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PURPOSE: To report a case of bacterial keratitis caused by an extensively drug-resistant (XDR) Pseudomonas aeruginosa strain linked to contaminated artificial tears in the United States. The ulcer was successfully treated without perforation or extracorneal spread. OBSERVATIONS: An 81-year-old patient presented with a corneal ulcer of the right eye. The patient had a notable complex ocular history including glaucoma and corneal edema from corneal decompensation after prolonged retained lens fragment. Despite starting hourly fortified tobramycin and vancomycin eye drops, the infiltrate grew significantly by the next day. Bacterial culture grew Pseudomonas aeruginosa that was resistant to all tested antibiotics except for intermediate susceptibility to colistin and susceptibility to cefiderocol. Tobramycin-soaked collagen shields were applied daily for three days, and the patient was started on fortified colistin eye drops. The ulcer improved and, after seven weeks of therapy, the infiltrate resolved and resulted in a large central corneal scar. CONCLUSIONS AND IMPORTANCE: A combination of fortified colistin and tobramycin (administered via a combination of fortified eye drops and tobramycin-soaked collagen shields) appears to be an effective treatment option for extensively drug-resistant Pseudomonas aeruginosa corneal ulcers.

Orthopedics/Bone and Joint Center

Alizadeh AH, Lively S, Lepage SIM, Potla P, Russell S, **Ali SA**, Kapoor M, and Koch TG. MicroRNAs as prognostic markers for chondrogenic differentiation potential of equine mesenchymal stromal cells. *Stem Cells Dev* 2023; Epub ahead of print. PMID: 37578107. Request Article

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Mesenchymal stromal cells (MSCs) are a promising cell source for cartilage tissue regeneration in animals and humans but with large inter-donor variation in their in vitro chondrogenic differentiation potential. Underlying molecular mechanisms responsible for culture-expanded MSC heterogeneity remains poorly understood. In this study, we sought to identify variations in miRNA signatures associated with cultured equine MSC chondrogenic differentiation potential from different donors. Neocartilage tissue generated from equine cord blood-derived MSCs (CB-MSCs) was categorized as having either high or low chondrogenic potential based on their histological appearance and quantification of glycosaminoglycan deposition. Using next-generation sequencing, we identified 30 differentially

expressed miRNAs amongst undifferentiated MSC cultures that corresponded with their chondrogenic potential. Of note, MSCs with low chondrogenic potential upregulated miR-146a and miR-487b-3p, which was also observed by qRT-PCR. Our findings suggest that miRNA profiling of equine MSC cultures may have prognostic value in selecting MSC donors with regards to their chondrogenic differentiation potential.

Orthopedics/Bone and Joint Center
Bryant SA, Jardaly AH, Ponce BA, **Guthrie ST**, Slone H, and Bruce JR. Reimagining the Path of an Unmatched Orthopaedic Residency Application: A Survey of Program Directors. *JB JS Open Access* 2023; 8(3). PMID: 37608919. Full Text

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BACKGROUND: Few evidence-based suggestions are available to help applicants and mentors improve reapplication outcomes. We sought to provide program directors' (PDs) perspectives on actionable steps to improve reapplicants' chances for a match. METHODS: The PDs were asked to rank positions unmatched applicants can pursue, steps these applicants can take for the next application cycle, and reasons why reapplicants do not match. RESULTS: Responses from 66 of 123 PDs were received (53.6% response rate). Obtaining new recommendation letters and rotating with orthopaedics were the highest 20 ranked steps unmatched applicants can take. No curriculum vitae (CV) improvement, poor interview, and poor letters of recommendation were the most important reasons hindering applicants from matching when reapplying. CONCLUSIONS: Steps reapplicants could prioritize include obtaining new recommendation letters, rotating in orthopaedics, and producing new research items. CV strengthening and improving interview skills address the 2 main reasons why unmatched applicants failed in subsequent attempts. LEVEL OF EVIDENCE: Level IV.

Orthopedics/Bone and Joint Center
Jildeh TR, **Buckley P**, **Abbas MJ**, Akioyamen NO, Abbas L, Montgomery JC, and Okoroha KR. Availability of Consumer Prices for Arthroscopic Meniscus Surgery. *J Surg Orthop Adv* 2023; 32(2):83-87. PMID: 37668642. Request Article

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The purpose is to examine the availability of consumer pricing information for arthroscopic meniscal surgery in the United States. Secondary objectives were comparing the price of meniscal repair to meniscectomy and regional pricing differences. Orthopaedic sports medicine clinics were sorted by state and randomly selected from American Orthopaedic Society for Sports Medicine's online directory. Following standardized script, each clinic was called a maximum of three times to obtain pricing information for meniscal surgery. A total of 1,008 distinct orthopaedic sport medicine practices were contacted. Six (6%) clinics were able to provide complete bundle pricing, and 183 (18.2%) clinics were able to provide physician-only fees for either meniscectomy or meniscal repair. Physician-only fees and bundle pricing were significantly less for meniscal repairs as compared to meniscectomies. There were no geographic regional differences in pricing for physician-only fees. There is a paucity of information regarding price transparency for arthroscopic meniscal surgery. (Journal of Surgical Orthopaedic Advances 32(2):083-087, 2023).

Orthopedics/Bone and Joint Center

Livingston N, Lindahl A, McConnell J, Chouman A, and **Day CS**. Do Orthopaedic Virtual Clinic Visits Demonstrate Cost and Time Efficiencies Compared With In-person Visits? *Clin Orthop Relat Res* 2023; Epub ahead of print. PMID: 37624757. Full Text

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BACKGROUND: There are numerous reasons for the increased use of telemedicine in orthopaedic surgery, one of which is the perception that virtual visits are more cost-effective than in-person visits. However, to our knowledge, no studies have compared the cost and time investment of virtual versus in-person visits using the time-driven activity-based costing (TDABC) method. Unlike methods that estimate cost based on charges for services rendered, TDABC provides a more precise measurement of costs, which is essential for assessing cost-effective innovations and moving to value-based healthcare. QUESTIONS/PURPOSES: (1) Are virtual visits less costly than analogous in-person visits, as measured by TDABC? (2) Does TDABC yield cost estimates that are lower or higher than the ratio of costs to charges (RCC), which is a simple, frequently used costing method? (3) Do the total time commitments of healthcare personnel, and that of the surgeon specifically, vary between the virtual and in-person settings? METHODS: Patients for this prospective, observational study were recruited from the practices of the highest-volume virtual-visit surgeons of three subspecialties (joints, hand, and sports) in a multihospital, tertiary-care academic institution in a metropolitan area in the Midwestern United States. Each surgeon had at least 10 years of clinical practice. Between June 2021 and September 2021, we analyzed both in-person and virtual return visits with patients who had an established relationship with the surgeon, because this represented the most frequent type of virtual visits and enabled a direct comparison between the two settings. New patients were not included in the study because of the limited availability of new-patient virtual visits; such patients often benefit from in-person physical examinations and on-site imaging. Additionally, patients seen for routine postoperative care were excluded because they were primarily seen in person by a physician assistant. Data were acquired during this period until 90 in-person and 90 virtual visits were collected according to selection criteria; no patients were lost to follow-up. Distinct process maps, which represent the steps involved in a clinic visit used to measure healthcare personnel time invested, were constructed for in-person and virtual clinic visits and used to compare total personnel and surgeon time spent. To calculate TDABC-derived costs, time allocated by personnel to complete each step was measured and used to calculate cost based on each personnel member's yearly salary. From the accounting department of our hospital, we acquired RCC cost data according to the level of service for a return visit. RESULTS: The total median cost, as measured by TDABC, was USD 127 (IQR USD 111 to 163) for an in-person visit and USD 140 (IQR USD 113 to 205) for a virtual visit (median difference USD 13; $p = 0.16$). RCC overestimated TDABC-calculated direct variable cost in five of six service levels (in-person levels 3, 4, and 5 and virtual levels 3 and 5) by a range of USD 25 to 88. Additionally, we found that virtual visits consumed 4 minutes less of total personnel time (in-person: 17 minutes [IQR 13.5 to 23.5 minutes], virtual: 13 minutes [IQR 11 to 19 minutes]; $p < 0.001$); however, this difference in personnel time did not equate to cost savings because surgeons spent 2 minutes longer on virtual visit activities than they did on in-person activities (in-person: 6 minutes [IQR 4.5 to 9.5 minutes], virtual: 8 minutes [IQR 5.5 to 13 minutes]; $p = 0.003$). CONCLUSION: Orthopaedic virtual visits did not deliver cost savings compared with in-person visits because surgeons spent more time on virtual visits and participated in virtual visits at the clinical site. Additionally, as anticipated, RCC overestimated costs as calculated by TDABC. These findings suggest that cost is not a primary advantage of transitioning to virtual visits, and that factors such as patient preference and satisfaction should be considered instead. LEVEL OF EVIDENCE: Level II, economic and decision analysis.

Orthopedics/Bone and Joint Center

McDonald M, **Timoteo TM**, and Schoch N. Contralateral preoperative templating for fracture reverse total shoulder arthroplasty: technique article and case series. *JSES Rev Rep Tech* 2023; 3(3):362-369. PMID: 37588500. Full Text

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Orthopedics/Bone and Joint Center
Rahman A, Jacobson A, Tetreault T, **Goodrich E**, Rogerson A, Samora J, and Bellamy J. Letter to the Editor: Equity360: Gender, Race, and Ethnicity: Sex and Fairness in Sports. *Clin Orthop Relat Res* 2023; 481(9):1839-1842. PMID: 37527335. Full Text

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Orthopedics/Bone and Joint Center
Stoddard JM, and **Moeller JL**. Sources of Information Utilized by Active Duty Service Members for Nutritional Supplement Safety and Efficacy. *Mil Med* 2023; Epub ahead of print. PMID: 37610323. Full Text

Division of Sports Medicine, Department of Orthopedic Surgery, Henry Ford Health, Detroit, MI 48202, USA.
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INTRODUCTION: The increasing prevalence of nutritional supplement use in the United States, combined with the risk of adverse effects from these largely unregulated products, poses a significant challenge to health care professionals. The purpose of our study is to evaluate the use of nutritional supplements in an active duty military population, particularly those supplements with increased adverse effect profiles, and the sources of information that service members use to make decisions regarding the safety and efficacy of supplements. MATERIALS AND METHODS: The investigators distributed a voluntary, anonymous, self-report survey to a battalion of active duty service members to collect demographic data and information pertaining to the use of, adverse effects from, and sources of information utilized regarding the safety and efficacy of nutritional supplements. Statistical analysis utilized Fisher's exact test for categorical variables and Kruskal-Wallis test for numeric variables via SAS 9.4 (SAS Institute Inc., Cary, NC, USA). The Henry Ford Health System Institutional Review Board evaluated and approved the study. The battalion commander approved the study protocol before the distribution of the survey. RESULTS: Over 50% of respondents reported using high-risk nutritional supplements. Males were more likely to use high-risk supplements than females (54.3% vs. 28.1%; P = .0017). Non-Commissioned Officers were more likely to use high-risk supplements than Junior Enlisted soldiers (67.2% vs. 40.2%, P = .0037). Only 27% of respondents who used high-risk supplements utilized medical professionals as their source of knowledge regarding the safety and efficacy of supplements. Females were more likely than males to seek supplement information from medical professionals (28.1% vs. 10.6%; P = .0202). Company-Grade Officers were more likely to seek supplement information from medical professionals than Junior Enlisted soldiers (40.9% vs. 8.3%; P = .0018). There was no statistically significant difference found for the rate of high-risk supplement use

and obtaining information from a medical professional (P = .6982). About 3% of respondents reported adverse or unintended effects of supplement use. CONCLUSIONS: The results of our study suggest that a minority of service members seek advice from medical professionals regarding nutritional supplements, women are more likely to do so than men, men may be more likely to use high-risk supplements than women, and Non-Commissioned Officers use high-risk supplements more often than Junior Enlisted. Limitations of this study include the voluntary self-report survey design, relatively small sample size, and single location. A larger, multicenter study would aid to alleviate these limitations in future studies. Numerous studies investigating nutritional supplement use and associated risks are present in the literature; however, the data comparing supplement use with sources of information regarding safety and efficacy are lacking.

Otolaryngology – Head and Neck Surgery
Chen AY, and **Singer MC**. Thyroid and Parathyroid Surgery: No Longer "Horrid Butchery". *Otolaryngol Clin North Am* 2023; Epub ahead of print. PMID: 37640561. Full Text

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Otolaryngology – Head and Neck Surgery
Donaldson L, **Okifo F**, and **Garcia-Rodriguez L**. Preparing for Facial Feminization Surgery. *Facial Plast Surg Clin North Am* 2023; 31(3):349-354. PMID: 37348976. Full Text

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Preparing for facial feminization surgery (FFS) or gender-affirming facial surgery is a daunting task. Patients do extensive research online to see what FFS means. Oftentimes it is the patients who are educating their physicians when discussing medical clearance or the esteemed "therapy letter." The therapy letter is a letter that details the support for surgery in a stable patient and reaffirms the need to have FFS in a person diagnosed with gender dysphoria. This typically follows the World Professional Association for Transgender Health standards-of-care guidelines. Besides having the therapy letter, patients must be counseled on concurrent mental health illnesses.

Otolaryngology – Head and Neck Surgery
Okifo O, Brown T, and Boyd C. Clinical Trials in Facial Plastic and Reconstructive Surgery. *Facial Plast Surg* 2023; Epub ahead of print. PMID: 37567564. Request Article

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Many facial plastic and reconstructive surgery providers are interested in incorporating clinical trials into their own practice. Clinical trials in facial plastics have made key contributions to current practices. Clinical trials range from investigating the safety and efficacy of Juvederm filler to reducing pain associated with injecting Juvederm. This article summarizes landmark clinical trials in facial plastic and reconstructive surgery and provides a framework for providers to get involved in clinical trials.

Palliative Medicine
Hedderich P, **Sueng LN**, and **Shaban H**. Geriatric Medicine Principles in Conservative Kidney Management: Frailty, Functional Assessments, and Selective Deprescribing. *Semin Nephrol* 2023; 43(1):151400. PMID: 37536079. Full Text

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Conservative kidney management is a nondialytic treatment option for advanced chronic kidney disease that involves interventions to delay kidney function loss, medications to treat symptoms, and psychosocial support for patients and their loved ones. Several geriatric medicine principles are applicable to patients who are considering or receiving conservative kidney management, including the integration of physical, psychological, and social factors into medical care and medical decisions; careful review of medication lists with selective deprescribing; and screening for geriatric syndromes such as frailty and functional impairment. In this review, we discuss how functional and frailty assessments as well as selective deprescribing can be useful for patients considering or receiving conservative kidney management.

Pathology and Laboratory Medicine

Al Khatib S, **Bhatnagar A**, **Elshaikh N**, **Ghanem AI**, **Burmeister C**, **Allo G**, **Alkamachi B**, **Paridon A**, and **Elshaikh MA**. The Prognostic Significance of the Depth of Cervical Stromal Invasion in Women With FIGO Stage II Uterine Endometrioid Carcinoma. *Am J Clin Oncol* 2023; Epub ahead of print. PMID: 37525355. Full Text

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OBJECTIVE: The objective of this study was to investigate the prognostic significance of the depth of cervical stromal invasion (CSI) in women with FIGO stage II uterine endometrioid adenocarcinoma (EC). METHODS: Our database of women with EC was quired for patients with stage II EC. Pathologic slides were retrieved and reviewed by gynecologic pathologists to determine cervical stromal thickness and depth of CSI as a percentage of stromal thickness (%CSI). Kaplan-Meier, univariate, and multivariate analyses were used to compare recurrence-free, disease-specific (DSS), and overall survival (OS) between women who had<50% versus ≥50% CSI. Univariate and multivariate analyses were used to assess other prognostic variables associated with survival endpoints. RESULTS: A total of 117 patients were included in our study who had hysterectomy between 1/1990 and 8/2021. Seventy-nine patients (68%) with <50% and 38 (32w%) with ≥50% CSI. After a median follow-up of 131 months, 5-year DSS was significantly worse for women with ≥50% CSI (78% vs. 91%; P=0.04). However, %CSI was not an independent predictor for any of the studied survival endpoints. Independent predictors of worse 5-year recurrence-free survival and DSS included FIGO grade 3 tumors (P=0.02) and the presence of lymphovascular space invasion (P=0.03). Grade 3 tumors were the only independent predictor of worse 5-year OS (P=0.02). CONCLUSIONS: Our results suggest that deep CSI is not an independent prognostic factor for survival endpoints in women with stage II uterine endometroid adenocarcinoma. The lack of independent prognostic significance of the depth CSI needs to be validated in a multi-institutional analysis.

Pharmacy

Gangat N, McCullough K, Abdelmagid M, Karrar O, **Powell M**, Al-Kali A, Alkhateeb H, Begna K, Mangaonkar A, Saliba A, Torghabeh MH, Litzow M, Hogan W, Shah M, Patnaik M, Pardanani A, Badar T, Foran J, Palmer J, Sproat L, Yi CA, and Tefferi A. Molecular predictors of response and survival following IDH1/2 inhibitor monotherapy in acute myeloid leukemia. *Haematologica* 2023; Epub ahead of print. PMID: 37534525. Full Text

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Pharmacy

Gutenschwager DW, **Patel A**, Soyad AT, Patel S, Szandzik EG, **Kelly B**, and **Smith ZR**. Provision of ambrisentan from a health-system specialty pharmacy affiliated with a pulmonary hypertension Center of Comprehensive Care. *Am J Health Syst Pharm* 2023; Epub ahead of print. PMID: 37611180. Full Text

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DISCLAIMER: In an effort to expedite the publication of articles, AJHP is posting manuscripts online as soon as possible after acceptance. Accepted manuscripts have been peer-reviewed and copyedited, but are posted online before technical formatting and author proofing. These manuscripts are not the final version of record and will be replaced with the final article (formatted per AJHP style and proofed by the authors) at a later time. PURPOSE: This descriptive report describes the process used to obtain access to providing ambrisentan from a health-system specialty pharmacy (HSSP) affiliated with a pulmonary hypertension Center of Comprehensive Care, develop a pulmonary arterial hypertension (PAH) care team at the HSSP, and characterize medication adherence and access metrics. SUMMARY: PAH is a rare disease treated with several specialty medications requiring intensive monitoring. Historically, specialty medications used to treat PAH have been provided by only select specialty pharmacies due to restricted drug distribution channels. It is recommended that patients with PAH receive their care at centers with expertise in the diagnosis and management of this disorder, but the HSSPs at these expert centers are unable to provide specialty PAH medications. The current care model for PAH leads to patients receiving their medical and pharmaceutical care from separate entities. This descriptive report describes a multidisciplinary team's approach to gaining access to providing ambrisentan and developing a disease state care team within an established HSSP. After implementing this service, specialty pharmacy metrics were assessed, including proportion of days covered (PDC), time to first fill, patient contact rate, Risk Evaluation and Mitigation Strategy (REMS) program compliance, time to prior authorization (PA) approval, rate of optimal adherence (PDC of >80%), and PA renewal rate, to demonstrate a proof-of-concept HSSP model for PAH. In this model, the HSSP was able to demonstrate high-quality specialty pharmacy metrics with regard to medication adherence, medication access, and REMS program compliance. CONCLUSION: The development of a PAH care team to provide ambrisentan at an existing HSSP was associated with high adherence rates, efficient and reliable medication access, and REMS program compliance.

Public Health Sciences

Al Khatib S, **Bhatnagar A**, **Elshaikh N**, **Ghanem AI**, **Burmeister C**, **Allo G**, **Alkamachi B**, **Paridon A**, and **Elshaikh MA**. The Prognostic Significance of the Depth of Cervical Stromal Invasion in Women With FIGO Stage II Uterine Endometrioid Carcinoma. *Am J Clin Oncol* 2023; Epub ahead of print. PMID: 37525355. Full Text

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OBJECTIVE: The objective of this study was to investigate the prognostic significance of the depth of cervical stromal invasion (CSI) in women with FIGO stage II uterine endometrioid adenocarcinoma (EC). METHODS: Our database of women with EC was quired for patients with stage II EC. Pathologic slides were retrieved and reviewed by gynecologic pathologists to determine cervical stromal thickness and depth of CSI as a percentage of stromal thickness (%CSI). Kaplan-Meier, univariate, and multivariate analyses were used to compare recurrence-free, disease-specific (DSS), and overall survival (OS) between women who had<50% versus ≥50% CSI. Univariate and multivariate analyses were used to assess other prognostic variables associated with survival endpoints. RESULTS: A total of 117 patients

were included in our study who had hysterectomy between 1/1990 and 8/2021. Seventy-nine patients (68%) with <50% and 38 (32w%) with ≥50% CSI. After a median follow-up of 131 months, 5-year DSS was significantly worse for women with ≥50% CSI (78% vs. 91%; P=0.04). However, %CSI was not an independent predictor for any of the studied survival endpoints. Independent predictors of worse 5-year recurrence-free survival and DSS included FIGO grade 3 tumors (P=0.02) and the presence of lymphovascular space invasion (P=0.03). Grade 3 tumors were the only independent predictor of worse 5-year OS (P=0.02). CONCLUSIONS: Our results suggest that deep CSI is not an independent prognostic factor for survival endpoints in women with stage II uterine endometroid adenocarcinoma. The lack of independent prognostic significance of the depth CSI needs to be validated in a multi-institutional analysis.

Public Health Sciences

Aris IM, Perng W, Dabelea D, Padula AM, Alshawabkeh A, Vélez-Vega CM, Aschner JL, Camargo CA, Jr., Sussman TJ, Dunlop AL, Elliott AJ, Ferrara A, **Joseph CLM**, Singh AM, Breton CV, Hartert T, Cacho F, Karagas MR, Lester BM, Kelly NR, Ganiban JM, Chu SH, O'Connor TG, Fry RC, Norman G, Trasande L, Restrepo B, Gold DR, James P, and Oken E. Neighborhood Opportunity and Vulnerability and Incident Asthma Among Children. *JAMA Pediatr* 2023; Epub ahead of print. PMID: 37639269. Full Text

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BACKGROUND: The extent to which physical and social attributes of neighborhoods play a role in childhood asthma remains understudied. OBJECTIVE: To examine associations of neighborhood-level opportunity and social vulnerability measures with childhood asthma incidence. DESIGN, SETTING, AND PARTICIPANTS: This cohort study used data from children in 46 cohorts participating in the Environmental Influences on Child Health Outcomes (ECHO) Program between January 1, 1995, and August 31, 2022. Participant inclusion required at least 1 geocoded residential address from birth and parent or caregiver report of a physician's diagnosis of asthma. Participants were followed up to the date of asthma diagnosis, date of last visit or loss to follow-up, or age 20 years. EXPOSURES: Census tract-level Child Opportunity Index (COI) and Social Vulnerability Index (SVI) at birth, infancy, or early childhood, grouped into very low (<20th percentile), low (20th to <40th percentile), moderate (40th to <60th percentile), high (60th to <80th percentile), or very high (≥80th percentile) COI or SVI. MAIN OUTCOMES AND MEASURES: The main outcome was parent or caregiver report of a physician's diagnosis of childhood asthma (yes or no). Poisson regression models estimated asthma incidence rate ratios (IRRs) associated with COI and SVI scores at each life stage. RESULTS: The study included 10 516 children (median age at follow-up, 9.1 years [IQR, 7.0-11.6 years]; 52.2% male), of whom 20.6% lived in neighborhoods with very high COI and very low SVI. The overall asthma incidence rate was 23.3 cases per 1000 child-years (median age at asthma diagnosis, 6.6 years [IQR, 4.1-9.9 years]). High and very high (vs very low) COI at birth, infancy, or early childhood were associated with lower subsequent asthma incidence independent of sociodemographic characteristics, parental asthma history, and parity. For example, compared with very low COI, the adjusted IRR for asthma was 0.87 (95% CI, 0.75-1.00) for high COI at birth and 0.83 (95% CI, 0.71-0.98) for very high COI at birth. These associations appeared to be attributable to the health and environmental and the social and economic domains of the COI. The SVI during early life was not significantly associated with asthma incidence. For example, compared with a very high SVI, the adjusted IRR for asthma was 0.88 (95% CI, 0.75-1.02) for low SVI at birth and 0.89 (95% CI, 0.76-1.03) for very low SVI at birth. CONCLUSIONS: In this cohort study, high and very high neighborhood opportunity during early life compared with very low neighborhood opportunity were associated with lower childhood asthma incidence. These findings suggest the need for future studies examining whether investing in health and environmental or social and economic resources in early life would promote health equity in pediatric asthma.

Public Health Sciences

Cheng P, **Santarossa S**, **Kalmbach D**, **Sagong C**, **Hu K**, and **Drake C**. Patient perspectives on facilitators and barriers to equitable engagement with digital CBT-I. *Sleep Health* 2023; Epub ahead of print. PMID: 37625947. Full Text

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STUDY OBJECTIVES: Digital cognitive behavioral therapy for insomnia has significant advantages for dissemination and scalability vs. in-person cognitive behavioral therapy for insomnia and is, therefore, well-positioned to be the first-line intervention for insomnia. However, only about half of patients remit following digital cognitive behavioral therapy for insomnia. Evidence suggests that treatment engagement is a critical driver of digital cognitive behavioral therapy for insomnia effectiveness, and barriers to engagement disproportionately impact people from under-resourced communities. For digital cognitive behavioral therapy for insomnia to be effective and scalable, we need to identify facilitators and barriers to digital cognitive behavioral therapy for insomnia engagement. METHODS: Responses from an exit survey about participant experiences with digital cognitive behavioral therapy for insomnia were analyzed using mixed methods. The survey included quantitative measures of treatment engagement and a free-

response item, which was coded and analyzed for themes using both inductive and deductive approaches. RESULTS: Analyses revealed five themes that were relevant for engagement: (1) digital person-to-person components, (2) type and extent of information, (3) user's sense of autonomy, (4) app functionality, and (5) importance of tailored content. Facilitators included enjoyment of digital cognitive behavioral therapy for insomnia elements, particularly those that enhanced a sense of connection (eg, a digital therapist avatar); content presented clearly and at an appropriate pace; and smooth app functionality. Barriers included desire for additional human support, perception that digital cognitive behavioral therapy for insomnia did not account for clinical complexities, and factors that interfered with implementation of key treatment recommendations. CONCLUSION: Many barriers and facilitators are influenced by health literacy and technological literacy. Those with access to health and technological literacy are better equipped to engage with digital cognitive behavioral therapy for insomnia. Recommendations for adaptations and enhancements are discussed.

Public Health Sciences

Davis M, **Stephens A**, **Butaney M**, **Morrison C**, **Corsi N**, Sood A, **Levin AM**, Cole A, Trinh QD, **Rogers C**, and **Abdollah F**. Trends in prostate cancer screening in the pre- and peri-COVID-19 Pandemic period. *Urol Pract* 2023; Epub ahead of print. PMID: 37647197. Full Text

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PURPOSE: This study sought to examine prostate-specific antigen testing rates before, early in, and later in the COVID-19 Pandemic. MATERIALS AND METHODS: Our cohort included test results from men >45 years who received prostate-specific antigen testing at least once at our institution from November 2018-September 2021 and were alive at the end of that period. Monthly trends were evaluated for three periods: Pre-COVID (November 2018-February 2020), early-COVID (March-May 2020), and late-COVID (June 2020-September 2021). Univariable and multivariable analysis tested the impact of these periods on prostate-specific antigen testing rate, after accounting for available confounders. All analyses were stratified by prostate cancer diagnosis status. RESULTS: A total of 141,777 prostate-specific antigen tests met inclusion criteria. The monthly number of tests in men without prostate cancer declined from 3,669 pre-COVID to 1,760 early-COVID (52% decrease; P=0.0086) before increasing to 4,171 (14% increase from pre-COVID; P<0.0001) late-COVID. The monthly average of first-time tests declined from 805 pre-COVID to 315 early-COVID (61% decrease; P=0.008) before rebounding to 795 (1% decrease from pre-COVID; P=0.7) late-COVID. The monthly number of tests in prostate cancer patients declined from 343 pre-COVID to 195 early-COVID (43% decrease; P=0.008) before partially rebounding to 313 (9% decrease; P=0.03) late-COVID. These differences remained within multivariable models. CONCLUSIONS: A number of men have forgone first-time prostate-specific antigen testing opportunities following the COVID-19 outbreak; thus, early cancer diagnoses in some individuals might have been missed. Likewise, many prostate cancer patients have forgone follow-up in the late-COVID period, which might compromise their oncologic outcomes.

Public Health Sciences

Li P, Kane K, Wolf FM, Berry AB, **Gadgeel S**, and **Pilling A**. Race-Associated Genomic Correlates of Therapeutic Response in African American Patients With Non-Small-Cell Lung Cancer. *JCO Precis Oncol* 2023; 7:e2300155. PMID: 37625101. Full Text

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PURPOSE: African American individuals are disproportionately affected by lung cancer in terms of incidence and mortality. In oncogene-driven non-small-cell lung cancer (NSCLC), emerging evidence

indicates that underlying molecular heterogeneity, which can be affected by ancestry, contributes to variable drug sensitivity and therapeutic responses. The purpose of this study was to evaluate race-associated differences in reported treatment decisions, therapeutic outcomes, and molecular features in KRAS- and EGFR-mutant NSCLC. MATERIALS AND METHODS: This is a retrospective study using real-world clinical-genomic data from health systems in the United States to evaluate race-associated outcomes in advanced-stage KRAS- or EGFR-driven NSCLC. Our overall objectives were to evaluate race-associated therapeutic outcomes and to describe molecular features in non-Hispanic Black (NHB) and non-Hispanic White (NHW) patients with NSCLC. RESULTS: A total of 723 NSCLC patients with KRAS and 315 patients with EGFR oncogenic mutations were evaluated. In KRAS-mutant patients, variable outcomes were observed in NHB and NHW patients on the basis of receiving chemotherapy alone or in combination with immune checkpoint inhibitors. NHB patients received treatment at significantly lower rates compared with NHW patients. In the EGFR-mutant cohort, NHB and NHW patients received EGFR-targeted agents at similar rates, and overall survival was not significantly different. Race-associated differences in molecular features included a higher frequency of TP53 comutation in KRAS-mutant NHB patients and higher prevalence of EGFR G719S subtype in NHB patients. CONCLUSION: In a real-world cohort of patients with NSCLC, we identified race-associated differences in therapeutic outcomes and described molecular characteristics in NHB and NHW patients with NSCLC. To proactively identify patients most likely to respond to systemic therapies, a more comprehensive approach is needed to help guide therapy selection in individualized patient populations.

Public Health Sciences

Mallott EK, **Sitarik AR**, Leve LD, Cioffi C, Camargo CA, Jr., Hasegawa K, and Bordenstein SR. Human microbiome variation associated with race and ethnicity emerges as early as 3 months of age. *PLoS Biol* 2023; 21(8):e3002230. PMID: 37590208. Full Text

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Human microbiome variation is linked to the incidence, prevalence, and mortality of many diseases and associates with race and ethnicity in the United States. However, the age at which microbiome variability emerges between these groups remains a central gap in knowledge. Here, we identify that gut microbiome variation associated with race and ethnicity arises after 3 months of age and persists through childhood. One-third of the bacterial taxa that vary across caregiver-identified racial categories in children are taxa reported to also vary between adults. Machine learning modeling of childhood microbiomes from 8 cohort studies (2,756 samples from 729 children) distinguishes racial and ethnic categories with 87% accuracy. Importantly, predictive genera are also among the top 30 most important taxa when childhood microbiomes are used to predict adult self-identified race and ethnicity. Our results highlight a critical developmental window at or shortly after 3 months of age when social and environmental factors drive

race and ethnicity-associated microbiome variation and may contribute to adult health and health disparities.

Public Health Sciences
Martinez-Nunez AE, **Soltanian-Zadeh H**, **Latack K**, Ghazi N, and Mahajan A. Hyposmia and apathy in early, de novo Parkinson's disease: Lessons from structural brain connectivity. *J Neurol Sci* 2023; 452:120767. PMID: 37619327. Full Text

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INTRODUCTION: The neuroanatomical structures implicated in olfactory and emotional processing overlap significantly. Our understanding of the relationship between hyposmia and apathy, common manifestations of early Parkinson's disease (PD), is inadequate. MATERIALS AND METHODS: We analyzed data on 40 patients with early de-novo idiopathic PD enrolled within 2 years of motor symptom onset in the Parkinson's Progression Markers Initiative (PPMI) study. To be included in the analysis, patients must have smell dysfunction but no apathy at the baseline visit and had completed a diffusion MRI (dMRI) at the baseline visit and at the 48-month follow-up visit. We used the FMRIB Software Library's diffusion tool kit to measure fractional anisotropy (FA) in six regions of interest on dMRI: bilateral anterior corona radiata, left cingulum, left superior corona radiata, genu and body of the corpus callosum. We compared the FA in each region from the dMRI done at the beginning of the study with the follow up studies at 4 years. RESULTS: We found a significant decrease of FA at the bilateral anterior corona radiata, and the genu and body of the corpus callosum comparing baseline scans with follow up images at 4-years after starting the study. CONCLUSION: Structural connectivity changes associated with apathy can be seen early in PD patients with smell dysfunction.

Public Health Sciences
Ramkumar SP, Bhardwaj A, Patel A, Seetharaman K, Christman A, Amondikar N, Abouelella DK, Hussaini AS, Barnes JM, **Adjei Boakye E**, Watts TL, and Osazuwa-Peters N. Differences in Receipt of Immunotherapy Treatment Among Patients With Head and Neck Cancer. *JAMA Otolaryngol Head Neck Surg* 2023; Epub ahead of print. PMID: 37651149. Full Text

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IMPORTANCE: The US Food and Drug Administration approved immune checkpoint inhibitors (immunotherapy) for select cases of head and neck squamous cell carcinoma (HNSCC) in 2016. However, it is unclear whether there are clinical or sociodemographic differences among patients receiving immunotherapy as part of their care. Given the known disparities in head and neck cancer care,

we hypothesized that there are differences in receipt of immunotherapy among patients with HNSCC based on clinical and nonclinical characteristics. OBJECTIVE: To characterize clinical and nonclinical factors associated with receipt of immunotherapy among older patients with HNSCC. DESIGN, SETTING, AND PARTICIPANTS: This retrospective cohort study included patients 65 years or older diagnosed with HNSCC (n = 4860) in a community oncology care setting. Electronic health records from Navigating Cancer were assessed from January 1, 2017, to April 30, 2022. MAIN OUTCOMES AND MEASURES: Multivariable logistic regression was used to characterize clinical (tumor stage [localized vs advanced] and anatomical subsite [oropharyngeal vs nonoropharyngeal]) and nonclinical (age, smoking history, race and ethnicity, sex, and marital status) factors associated with receipt of immunotherapy. RESULTS: In the study cohort of 4860 patients, 3593 (73.9%) were men; 4230 (87.0%) were White and 630 (13.0%) were of other races. A total of 552 patients (11.4%) had received immunotherapy. After adjusting for covariates, in the final model, White patients with HNSCC had 80% increased odds of receiving immunotherapy (adjusted odds ratio [AOR], 1.80 [95% CI, 1.30-2.48]) compared with patients of other races. There were no statistically significant differences in the odds of receiving immunotherapy based on age, sex, or smoking history. Patients with nonoropharyngeal disease were significantly more likely to receive immunotherapy than those with oropharyngeal cancer (AOR, 1.29 [95% CI, 1.05-1.59]), as were those with advanced compared with local disease (AOR, 2.39 [95% CI, 1.71-3.34]). CONCLUSIONS AND RELEVANCE: The findings of this cohort study suggest that among older patients with HNSCC, White patients may be more likely to receive immunotherapy as part of their care. Equitable access to immunotherapy and other treatment options will reduce cancer-related health disparities and improve survival of patients with HNSCC.

Public Health Sciences

Redding A, **Santarossa S**, **Murphy D**, **Udumula MP**, **Munkarah A**, **Hijaz M**, and **Rattan R**. A patient perspective on applying intermittent fasting in gynecologic cancer. *BMC Res Notes* 2023; 16(1):190. PMID: 37644560. Full Text

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OBJECTIVE: Researchers sought patient feedback on a proposed randomized controlled trial (RCT) in which gynecological cancer patients would modify their diets with intermittent fasting to gain insight into patients' perspectives, receptivity, and potential obstacles. A convenience sample of 47 patients who met the inclusion criteria of the proposed RCT provided their feedback on the feasibility and protocols of the RCT using a multi-method approach consisting of focus groups (n = 8 patients) and surveys (n = 36 patients). RESULTS: Patients were generally receptive to the concept of intermittent fasting, and many expressed an interest in attempting it themselves. Patients agreed that the study design was feasible in terms of study assessments, clinic visits, and biospecimen collection. Feedback on what could facilitate adherence included convenient appointment scheduling times and the availability of the research team to answer questions. Regarding recruitment, patients offered suggestions for study advertisements, with the majority concurring that a medical professional approaching them would increase their likelihood of participation.

Public Health Sciences

Trendowski MR, Lusk CM, Wenzlaff AS, **Neslund-Dudas C**, **Gadgeel SM**, Soubani AO, and Schwartz AG. Assessing a Polygenic Risk Score for Lung Cancer Susceptibility in Non-Hispanic White and Black Populations. *Cancer Epidemiol Biomarkers Prev* 2023; Epub ahead of print. PMID: 37578347. Request Article

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BACKGROUND: Polygenic risk scores (PRS) have become an increasingly popular approach to evaluate cancer susceptibility, but have not adequately represented Black populations in model development. METHODS: We used a previously published lung cancer PRS based on 80 SNPs associated with lung cancer risk in the OncoArray cohort and validated in UK Biobank. The PRS was evaluated for association with lung cancer risk adjusting for age, sex, total pack-years, family history of lung cancer, history of COPD, and the top five principal components for genetic ancestry. RESULTS: Among the 80 PRS SNPs included in the score, 14 were significantly associated with lung cancer risk ($p<0.05$) in INHALE White participants, while there were no significant SNPs among INHALE Black participants. After adjusting for covariates, the PRS was significantly associated with risk in Whites (continuous score $p=0.007$), but not in Blacks (continuous score $p=0.88$). The PRS remained a statistically significant predictor of lung cancer risk in Whites ineligible for lung cancer screening under current USPSTF guidelines ($p=0.02$). CONCLUSIONS: Using a previously validated PRS, we did find some predictive ability for lung cancer in INHALE White participants beyond traditional risk factors. However, this effect was not observed in Black participants, indicating the need to develop and validate ancestry-specific lung cancer risk models. IMPACT: While a previously published lung cancer PRS was able to stratify White participants into different levels of risk, the model was not predictive in Blacks. Our findings highlight the need to develop and validate ancestry-specific lung cancer risk models.

Public Health Sciences

Yeh HH, **Peltz-Rauchman C**, **Johnson CC**, Pawloski PA, Chesla D, Waring SC, Stevens AB, Epstein M, **Joseph C**, **Miller-Matero LR**, **Gui H**, **Tang A**, Boerwinkle E, Cicek M, Clark CR, Cohn E, Gebo K, Loperena R, Mayo K, Mockrin S, Ohno-Machado L, Schully S, Ramirez AH, Qian J, and **Ahmedani BK**. Examining sociodemographic correlates of opioid use, misuse, and use disorders in the All of Us Research Program. *PLoS One* 2023; 18(8):e0290416. PMID: 37594966. Full Text

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BACKGROUND: The All of Us Research Program enrolls diverse US participants which provide a unique opportunity to better understand the problem of opioid use. This study aims to estimate the prevalence of opioid use and its association with sociodemographic characteristics from survey data and electronic health record (EHR). METHODS: A total of 214,206 participants were included in this study who competed survey modules and shared EHR data. Adjusted logistic regressions were used to explore the associations between sociodemographic characteristics and opioid use. RESULTS: The lifetime prevalence of street opioids was 4%, and the nonmedical use of prescription opioids was 9%. Men had higher odds of lifetime opioid use (aOR: 1.4 to 3.1) but reduced odds of current nonmedical use of prescription opioids (aOR: 0.6). Participants from other racial and ethnic groups were at reduced odds of lifetime use (aOR: 0.2 to 0.9) but increased odds of current use (aOR: 1.9 to 9.9) compared with non-Hispanic White participants. Foreign-born participants were at reduced risks of opioid use and diagnosed with opioid use disorders (OUD) compared with US-born participants (aOR: 0.36 to 0.67). Men, Younger, White, and US-born participants are more likely to have OUD. CONCLUSIONS: All of Us research data can be used as an indicator of national trends for monitoring the prevalence of receiving prescription opioids, diagnosis of OUD, and non-medical use of opioids in the US. The program employs a longitudinal design for routinely collecting health-related data including EHR data, that will contribute to the literature by providing important clinical information related to opioids over time. Additionally, this data will enhance the estimates of the prevalence of OUD among diverse populations, including groups that are underrepresented in the national survey data.

Pulmonary and Critical Care Medicine

Beran A, Mohamed MFH, Shaear M, Nayfeh T, Mhanna M, **Srour O**, Nawras M, Mentrose JA, Assaly R, Kubal CA, Ghabril MS, Hernaez R, and Patidar KR. Plasma exchange for acute and acute-on-chronic liver failure: A systematic review and meta-analysis. *Liver Transpl* 2023; Epub ahead of print. PMID: 37530812. Full Text

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Plasma exchange (PE) is a promising therapeutic option in patients with acute liver failure (ALF) and acute-on-chronic liver failure (ACLF). However, the impact of PE on patient survival in these syndromes is unclear. We aimed to systematically investigate the use of PE in patients with ALF and ACLF compared with standard medical therapy (SMT). We searched PubMed/Embase/Cochrane databases to include all studies comparing PE versus SMT for patients ≥ 18 years of age with ALF and ACLF. Pooled risk ratios (RR) with corresponding 95% CIs were calculated by the Mantel-Haenszel method within a random-effect model. The primary outcome was 30-day survival for ACLF and ALF. Secondary outcomes were overall

and 90-day survival for ALF and ACLF, respectively. Five studies, including 343 ALF patients (n = 174 PE vs. n = 169 SMT), and 20 studies, including 5,705 ACLF patients (n = 2,856 PE vs. n = 2,849 SMT), were analyzed. Compared with SMT, PE was significantly associated with higher 30-day (RR 1.41, 95% CI 1.06-1.87, p = 0.02) and overall (RR 1.35, 95% CI 1.12-1.63, p = 0.002) survival in ALF patients. In ACLF, PE was also significantly associated with higher 30-day (RR 1.36, 95% CI 1.22-1.52, p < 0.001) and 90-day (RR 1.21, 95% CI 1.10-1.34, p < 0.001) survival. On subgroup analysis of randomized controlled trials, results remained unchanged in ALF, but no differences in survival were found between PE and SMT in ACLF. In conclusion, PE is associated with improved survival in ALF and could improve survival in ACLF. PE may be considered in managing ALF and ACLF patients who are not liver transplant (LT) candidates or as a bridge to LT in otherwise eligible patients. Further randomized controlled trials are needed to confirm the survival benefit of PE in ACLF.

Pulmonary and Critical Care Medicine

Brawner CA, and **Lazar MH**. Cardiopulmonary exercise testing criteria for advanced therapies in patients with heart failure. *Heart Fail Rev* 2023; Epub ahead of print. PMID: 37644366. Full Text

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Many cardiology associations endorse the role of the cardiopulmonary exercise test (CPET) to define the severity of impairment of functional capacity in individuals with heart failure with reduced ejection fraction (HFrEF) and when evaluating the need for advanced therapies for these patients. The focus of the CPET within the cardiology community has been on peak volume of oxygen uptake (VO(2)). However, several CPET variables are associated with outcomes in individuals with and without chronic disease and can inform clinical decisions in individuals with HFrEF. In this manuscript, we will review the normal cardiopulmonary response to a graded exercise test and review current guideline recommendations relative to CPET in patients with HFrEF.

Pulmonary and Critical Care Medicine

Gutenschwager DW, **Patel A**, Soyad AT, Patel S, Szandzik EG, **Kelly B**, and **Smith ZR**. Provision of ambrisentan from a health-system specialty pharmacy affiliated with a pulmonary hypertension Center of Comprehensive Care. *Am J Health Syst Pharm* 2023; Epub ahead of print. PMID: 37611180. Full Text

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 PURPOSE: This descriptive report describes the process used to obtain access to providing ambrisentan from a health-system specialty pharmacy (HSSP) affiliated with a pulmonary hypertension Center of Comprehensive Care, develop a pulmonary arterial hypertension (PAH) care team at the HSSP, and characterize medication adherence and access metrics. SUMMARY: PAH is a rare disease treated with several specialty medications requiring intensive monitoring. Historically, specialty medications used to treat PAH have been provided by only select specialty pharmacies due to restricted drug distribution channels. It is recommended that patients with PAH receive their care at centers with expertise in the diagnosis and management of this disorder, but the HSSPs at these expert centers are unable to provide specialty PAH medications. The current care model for PAH leads to patients receiving their medical and pharmaceutical care from separate entities. This descriptive report describes a multidisciplinary team's approach to gaining access to providing ambrisentan and developing a disease state care team within an established HSSP. After implementing this service, specialty pharmacy metrics

were assessed, including proportion of days covered (PDC), time to first fill, patient contact rate, Risk Evaluation and Mitigation Strategy (REMS) program compliance, time to prior authorization (PA) approval, rate of optimal adherence (PDC of >80%), and PA renewal rate, to demonstrate a proof-of-concept HSSP model for PAH. In this model, the HSSP was able to demonstrate high-quality specialty pharmacy metrics with regard to medication adherence, medication access, and REMS program compliance. CONCLUSION: The development of a PAH care team to provide ambrisentan at an existing HSSP was associated with high adherence rates, efficient and reliable medication access, and REMS program compliance.

Radiation Oncology

Al Khatib S, **Bhatnagar A**, **Elshaikh N**, **Ghanem AI**, **Burmeister C**, **Allo G**, **Alkamachi B**, **Paridon A**, and **Elshaikh MA**. The Prognostic Significance of the Depth of Cervical Stromal Invasion in Women With FIGO Stage II Uterine Endometrioid Carcinoma. *Am J Clin Oncol* 2023; Epub ahead of print. PMID: 37525355. Full Text

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OBJECTIVE: The objective of this study was to investigate the prognostic significance of the depth of cervical stromal invasion (CSI) in women with FIGO stage II uterine endometrioid adenocarcinoma (EC). METHODS: Our database of women with EC was quired for patients with stage II EC. Pathologic slides were retrieved and reviewed by gynecologic pathologists to determine cervical stromal thickness and depth of CSI as a percentage of stromal thickness (%CSI). Kaplan-Meier, univariate, and multivariate analyses were used to compare recurrence-free, disease-specific (DSS), and overall survival (OS) between women who had<50% versus ≥50% CSI. Univariate and multivariate analyses were used to assess other prognostic variables associated with survival endpoints. RESULTS: A total of 117 patients were included in our study who had hysterectomy between 1/1990 and 8/2021. Seventy-nine patients (68%) with <50% and 38 (32w%) with ≥50% CSI. After a median follow-up of 131 months, 5-year DSS was significantly worse for women with ≥50% CSI (78% vs. 91%; P=0.04). However, %CSI was not an independent predictor for any of the studied survival endpoints. Independent predictors of worse 5-year recurrence-free survival and DSS included FIGO grade 3 tumors (P=0.02) and the presence of lymphovascular space invasion (P=0.03). Grade 3 tumors were the only independent predictor of worse 5-year OS (P=0.02). CONCLUSIONS: Our results suggest that deep CSI is not an independent prognostic factor for survival endpoints in women with stage II uterine endometroid adenocarcinoma. The lack of independent prognostic significance of the depth CSI needs to be validated in a multi-institutional analysis.

Radiation Oncology

Casey G, Quon H, Meyer T, Sia M, **Thind K**, Das S, Cho D, McGeachy P, Husain S, and Martell K. Estimated absolute percentage of biopsied tissue positive for Gleason pattern 4 (eAPP4) in low dose rate prostate brachytherapy: Evaluation of prognostic utility in a large cohort. *Radiother Oncol* 2023; 188:109859. PMID: 37604278. Full Text

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PURPOSE: To determine whether a system to estimate Absolute Percentage of Biopsied Tissue Positive for Gleason Pattern 4 (eAPP4) is useful as a prognostication tool for patients with intermediate risk prostate cancer (IR-PCa) undergoing low dose rate prostate brachytherapy. METHODS: 497 patients with

IR-PCa and known grade group 2 or 3 disease treated with low dose rate seed brachytherapy (LDR-BT) at a quaternary cancer centre were retrospectively reviewed. Prostate biopsies for each patient included Gleason grading with synoptic reporting that did not include percentage of pattern 4 disease found within the sample. Each core was assigned a grade grouping, however, and that was used with optimized estimates of percentage of pattern four disease to estimate eAPP4. Outcomes including cumulative incidence of recurrence (CIR), treatment of recurrent disease (RRX), and metastasis-free survival (MFS) were then reviewed and the prognostic value of eAPP4 evaluated. RESULTS: 428 (86%) patients had Gleason grade group 2 and 69 (14%) patients had Gleason grade group 3 disease. 230 (46%) patients had National Comprehensive Cancer Network (NCCN) favourable intermediate at baseline, while 267 (54%) of patients had NCCN unfavourable intermediate at baseline. Median follow-up was 7.3 (5.5-9.6) years. eAPP4 was predictive of CIR (p = 0.003), RRX (p = 0.003), or MFS (p = 0.001) events, while Gleason grade grouping alone was not. eAPP4 was strongest as a predictor for MFS when estimates of 30% (grade group 2) and 80% (grade group 3) were used [HR 1.07 (1.03-1.12); p = 0.001]. CONCLUSIONS: eAPP4 was strongly predictive of recurrence and metastasis-free survival in a large cohort of patients receiving LDR-BT treatment for IR-PCa. Treatment of future patients with IR-PCa could include the use of eAPP4 prognostication.

Radiation Oncology

Kadro ZO, Snyder S, Benn R, Fouladbakhsh JM, Greenlee H, Harris RE, Henry NL, Klein KC, Mayhew S, Spratke L, **Walker EM**, Zebrack B, and Zick SM. Impact of the Integrative Oncology Scholars Program on Oncology Providers' Key Knowledge of Dietary Supplements and Antioxidants for Providing Evidence-based Oncology Care. *J Cancer Educ* 2023; Epub ahead of print. PMID: 37526910. Request Article

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Dietary supplements are commonly used among cancer survivors. Oncology providers rarely receive training about dietary supplements. We evaluated whether e-learning modules could improve oncology providers' dietary supplement knowledge. Oncology providers participated in the National Cancer Institute funded Integrative Oncology Scholars (IOS) program. We used posttest readiness assurance tests (RAT) to measure knowledge acquisition from modules. One cohort completed a pre and posttest RAT to assess change in knowledge. Multivariate linear regression models adjusted for gender, race, profession, and years in practice were used to determine if these characteristics were associated with posttest RAT performance and change in pre to posttest RAT scores. Scholars (N = 101) included 86% (N = 87) females; age 44 ± 10 years; 72% (N = 73) Non-Hispanic White; years in practice mean range 11-15 ± 10. There were 37 physicians, 11 physician assistants, 23 nurses, 21 social workers, 2 psychologists, 4 pharmacists, and 2 physical therapists. The posttest dietary supplement and antioxidant RAT scores for all Scholars were 67 ± 18% and 71 ± 14%. In adjusted models there were no significant associations between dietary supplement and antioxidant posttest RAT scores with Scholar characteristics. Change in

RAT scores for dietary supplement and antioxidants were 25% ± 23 and 26% ± 27 ($P < 0.0001$). In adjusted models, there were no significant predictors of change in dietary supplement RATs. For antioxidant RATs, profession was associated with change in scores ($P = 0.021$). Improvement in Scholar's test scores demonstrate the IOS program can significantly increase oncology providers' knowledge of dietary supplements and antioxidants.

Radiation Oncology
Nizar R, **Cazacu S**, **Xiang C**, Krasner M, Barbiro-Michaely E, Gerber D, Schwartz J, Fried I, Yuval S, Brodie A, Kazimirsky G, Amos N, Unger R, **Brown S**, **Rogers L**, **Penning DH**, and **Brodie C**. Propofol Inhibits Glioma Stem Cell Growth and Migration and Their Interaction with Microglia via BDNF-AS and Extracellular Vesicles. *Cells* 2023; 12(15). PMID: 37566001. Full Text

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Glioblastoma (GBM) is the most common and aggressive primary brain tumor. GBM contains a small subpopulation of glioma stem cells (GSCs) that are implicated in treatment resistance, tumor infiltration, and recurrence, and are thereby considered important therapeutic targets. Recent clinical studies have suggested that the choice of general anesthetic (GA), particularly propofol, during tumor resection, affects subsequent tumor response to treatments and patient prognosis. In this study, we investigated the molecular mechanisms underlying propofol's anti-tumor effects on GSCs and their interaction with microglia cells. Propofol exerted a dose-dependent inhibitory effect on the self-renewal, expression of mesenchymal markers, and migration of GSCs and sensitized them to both temozolomide (TMZ) and radiation. At higher concentrations, propofol induced a large degree of cell death, as demonstrated using microfluid chip technology. Propofol increased the expression of the lncRNA BDNF-AS, which acts as a tumor suppressor in GBM, and silencing of this lncRNA partially abrogated propofol's effects. Propofol also inhibited the pro-tumorigenic GSC-microglia crosstalk via extracellular vesicles (EVs) and delivery of BDNF-AS. In conclusion, propofol exerted anti-tumor effects on GSCs, sensitized these cells to radiation and TMZ, and inhibited their pro-tumorigenic interactions with microglia via transfer of BDNF-AS by EVs.

Radiation Oncology
Simone ICB, Serebrenik AA, Gore EM, Mohindra P, **Brown SL**, **Wang D**, Chetty IJ, Vujaskovic Z, Menon S, Thompson J, Fine G, Kaytor MD, and **Movsas B**. Multicenter Phase 1b/2a Clinical Trial of Radioprotectant BIO 300 Oral Suspension for Patients with Non-Small Cell Lung Cancer Receiving Concurrent Chemoradiotherapy. *Int J Radiat Oncol Biol Phys* 2023; Epub ahead of print. PMID: 37652301. Full Text

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PURPOSE: Radiotherapy is part of the standard treatment regimen for non-small cell lung cancer (NSCLC). While radiotherapy is an effective tool to manage NSCLC, it can be associated with significant dose-limiting toxicities. These toxicities can lead to treatment interruption or early termination, worsening clinical outcomes, in addition to reductions in patient quality of life. Based on preclinical efficacy for radioprotection of normal tissues, we evaluated the clinical utility of BIO 300 Oral Suspension (BIO 300; synthetic genistein nanosuspension) in patients with NSCLC. METHODS AND MATERIALS: In this multicenter, open-label, single-arm, ascending dose phase 1b/2a study, patients were enrolled with newly diagnosed stage II-IV NSCLC planned for 60-70/1.8-2.0Gy radiotherapy and concurrent weekly paclitaxel/carboplatin. Oral BIO 300 (cohort 1, 500 mg/day; cohort 2, 1000 mg/day; cohort 3, 1500 mg/day) was self-administered once-daily starting 2-7 days before initiating concurrent chemoradiotherapy and continued until the end of radiotherapy. The primary endpoint was acute dose-limiting toxicities attributable to BIO 300. Secondary outcomes included pharmacokinetics, pharmacodynamics, overall toxicity profile, quality of life, local response rate and survival. RESULTS: Twenty-one participants were enrolled. No dose-limiting toxicities were reported. BIO 300 dosing did not alter chemotherapy pharmacokinetics. Adverse events were not dose-dependent, and those attributable to BIO 300 (N=11) were all mild to moderate in severity (grade 1, N=9; grade 2, N=2) and predominantly gastrointestinal (N=7). A dose-dependent decrease in serum TGFβ1 levels was observed across cohorts. Based on safety analysis, the maximum tolerated dose of BIO 300 was not met. Patient reported quality of life and weight were largely stable throughout the study period. No patient had progression as their best overall response, and a 65% tumor response rate was achieved (20% complete response rate). CONCLUSION: The low toxicity rates, along with the pharmacodynamic results and tumor response rates, support further investigation of BIO 300 as an effective radioprotector.

Research Administration

Cornwell AC, Tisdale AA, Venkat S, Maraszek KE, Alahmari AA, George A, Attwood K, **George M**, **Rempinski D**, Franco-Barraza J, Seshadri M, Parker MD, Cortes Gomez E, Fountzilas C, Cukierman E, Steele NG, and Feigin ME. Lorazepam Stimulates IL6 Production and Is Associated with Poor Survival Outcomes in Pancreatic Cancer. *Clin Cancer Res* 2023; 1-20. Epub ahead of print. PMID: 37587561. Full Text

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PURPOSE: This research investigates the association between benzodiazepines (BZD) and cancer patient survival outcomes, the pancreatic cancer tumor microenvironment, and cancer-associated fibroblast (CAF) signaling. EXPERIMENTAL DESIGN: Multivariate Cox regression modeling was used to retrospectively measure associations between Roswell Park cancer patient survival outcomes and BZD prescription records. IHC, H&E, Masson's trichrome, RNAscope, and RNA sequencing were used to evaluate the impact of lorazepam (LOR) on the murine PDAC tumor microenvironment. ELISA and qPCR were used to determine the impact of BZDs on IL6 expression or secretion by human-immortalized

pancreatic CAFs. PRESTO-Tango assays, reanalysis of PDAC single-cell sequencing/TCGA data sets, and GPR68 CRISPRi knockdown CAFs were used to determine the impact of BZDs on GPR68 signaling. RESULTS: LOR is associated with worse progression-free survival (PFS), whereas alprazolam (ALP) is associated with improved PFS, in pancreatic cancer patients receiving chemotherapy. LOR promotes desmoplasia (fibrosis and extracellular matrix protein deposition), inflammatory signaling, and ischemic necrosis. GPR68 is preferentially expressed on human PDAC CAFs, and n-unsubstituted BZDs, such as LOR, significantly increase IL6 expression and secretion in CAFs in a pH and GPR68-dependent manner. Conversely, ALP and other GPR68 n-substituted BZDs decrease IL6 in human CAFs in a pH and GPR68-independent manner. Across many cancer types, LOR is associated with worse survival outcomes relative to ALP and patients not receiving BZDs. CONCLUSIONS: We demonstrate that LOR stimulates fibrosis and inflammatory signaling, promotes desmoplasia and ischemic necrosis, and is associated with decreased pancreatic cancer patient survival.

Research Administration

Dehghani A, **Soltanian-Zadeh H**, and Hossein-Zadeh GA. Neural modulation enhancement using connectivity-based EEG neurofeedback with simultaneous fMRI for emotion regulation. *Neuroimage* 2023; 279:120320. PMID: 37586444. Full Text

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Emotion regulation plays a key role in human behavior and overall well-being. Neurofeedback is a non-invasive self-brain training technique used for emotion regulation to enhance brain function and treatment of mental disorders through behavioral changes. Previous neurofeedback research often focused on using activity from a single brain region as measured by fMRI or power from one or two EEG electrodes. In a new study, we employed connectivity-based EEG neurofeedback through recalling positive autobiographical memories and simultaneous fMRI to upregulate positive emotion. In our novel approach, the feedback was determined by the coherence of EEG electrodes rather than the power of one or two electrodes. We compared the efficiency of this connectivity-based neurofeedback to traditional activity-based neurofeedback through multiple experiments. The results showed that connectivity-based neurofeedback effectively improved BOLD signal change and connectivity in key emotion regulation regions such as the amygdala, thalamus, and insula, and increased EEG frontal asymmetry, which is a biomarker for emotion regulation and treatment of mental disorders such as PTSD, anxiety, and depression and coherence among EEG channels. The psychometric evaluations conducted both before and after the neurofeedback experiments revealed that participants demonstrated improvements in enhancing positive emotions and reducing negative emotions when utilizing connectivity-based neurofeedback, as compared to traditional activity-based and sham neurofeedback approaches. These findings suggest that connectivity-based neurofeedback may be a superior method for regulating emotions and could be a useful alternative therapy for mental disorders, providing individuals with greater control over their brain and mental functions.

Research Administration

Martinez-Nunez AE, **Soltanian-Zadeh H**, **Latack K**, Ghazi N, and Mahajan A. Hyposmia and apathy in early, de novo Parkinson's disease: Lessons from structural brain connectivity. *J Neurol Sci* 2023; 452:120767. PMID: 37619327. Full Text

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INTRODUCTION: The neuroanatomical structures implicated in olfactory and emotional processing overlap significantly. Our understanding of the relationship between hyposmia and apathy, common manifestations of early Parkinson's disease (PD), is inadequate. MATERIALS AND METHODS: We analyzed data on 40 patients with early de-novo idiopathic PD enrolled within 2 years of motor symptom onset in the Parkinson's Progression Markers Initiative (PPMI) study. To be included in the analysis, patients must have smell dysfunction but no apathy at the baseline visit and had completed a diffusion MRI (dMRI) at the baseline visit and at the 48-month follow-up visit. We used the FMRIB Software Library's diffusion tool kit to measure fractional anisotropy (FA) in six regions of interest on dMRI: bilateral anterior corona radiata, left cingulum, left superior corona radiata, genu and body of the corpus callosum. We compared the FA in each region from the dMRI done at the beginning of the study with the follow up studies at 4 years. RESULTS: We found a significant decrease of FA at the bilateral anterior corona radiata, and the genu and body of the corpus callosum comparing baseline scans with follow up images at 4-years after starting the study. CONCLUSION: Structural connectivity changes associated with apathy can be seen early in PD patients with smell dysfunction.

Rheumatology
Jamil M, **Daneshvar A**, **Nachawati D**, El Sharu H, and **Meysami A**. A Rare Presentation of Zoledronate-Induced Systemic Inflammatory Response. *Cureus* 2023; 15(7):e41524. PMID: 37551226. Full Text

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Zoledronic acid is a bisphosphonate commonly used to treat various conditions involving bone loss. While it is generally well-tolerated, the occurrence of severe inflammatory reactions is rare. We present the case of an 82-year-old female who developed a severe immune reaction, including weakness and tenderness in her upper and lower extremities, following a single dose of zoledronic acid infusion for the treatment of osteoporosis. The onset of symptoms occurred one week after the infusion and persisted, progressively worsening over time, leading to functional impairment and the need for a walker for ambulation. Laboratory studies revealed an elevated erythrocyte sedimentation rate while other autoimmune markers were within normal limits. Differential diagnosis included an adverse reaction to zoledronic acid or underlying polymyalgia rheumatica. The patient showed significant improvement with a prednisone taper, suggesting an immune-mediated response. This case highlights the importance of considering severe immune reactions as a potential side effect of zoledronic acid and emphasizes the need for further research to better understand the underlying mechanisms and optimize patient management.

Sleep Medicine
Cheng P, **Santarossa S**, **Kalmbach D**, **Sagong C**, **Hu K**, and **Drake C**. Patient perspectives on facilitators and barriers to equitable engagement with digital CBT-I. *Sleep Health* 2023; Epub ahead of print. PMID: 37625947. Full Text

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STUDY OBJECTIVES: Digital cognitive behavioral therapy for insomnia has significant advantages for dissemination and scalability vs. in-person cognitive behavioral therapy for insomnia and is, therefore, well-positioned to be the first-line intervention for insomnia. However, only about half of patients remit following digital cognitive behavioral therapy for insomnia. Evidence suggests that treatment engagement is a critical driver of digital cognitive behavioral therapy for insomnia effectiveness, and barriers to engagement disproportionately impact people from under-resourced communities. For digital cognitive

behavioral therapy for insomnia to be effective and scalable, we need to identify facilitators and barriers to digital cognitive behavioral therapy for insomnia engagement. METHODS: Responses from an exit survey about participant experiences with digital cognitive behavioral therapy for insomnia were analyzed using mixed methods. The survey included quantitative measures of treatment engagement and a free-response item, which was coded and analyzed for themes using both inductive and deductive approaches. RESULTS: Analyses revealed five themes that were relevant for engagement: (1) digital person-to-person components, (2) type and extent of information, (3) user's sense of autonomy, (4) app functionality, and (5) importance of tailored content. Facilitators included enjoyment of digital cognitive behavioral therapy for insomnia elements, particularly those that enhanced a sense of connection (eg, a digital therapist avatar); content presented clearly and at an appropriate pace; and smooth app functionality. Barriers included desire for additional human support, perception that digital cognitive behavioral therapy for insomnia did not account for clinical complexities, and factors that interfered with implementation of key treatment recommendations. CONCLUSION: Many barriers and facilitators are influenced by health literacy and technological literacy. Those with access to health and technological literacy are better equipped to engage with digital cognitive behavioral therapy for insomnia. Recommendations for adaptations and enhancements are discussed.

Sleep Medicine

Kalmbach DA, **Cheng P**, **Reffi AN**, Ong JC, Swanson LM, Espie CA, **Seymour GM**, **Hirata M**, Walch O, **Pitts DS**, **Roth T**, and **Drake CL**. Reducing cognitive arousal and sleep effort alleviates insomnia and depression in pregnant women with DSM-5 insomnia disorder treated with a mindfulness sleep program. *Sleep Adv* 2023; 4(1):zpad031. PMID: 37645455. Full Text

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OBJECTIVES: Combining mindfulness with behavioral sleep strategies has been found to alleviate symptoms of insomnia and depression during pregnancy, but mechanisms for this treatment approach remain unclear. The present study examined nocturnal cognitive arousal and sleep effort as potential treatment mechanisms for alleviating insomnia and depression via a mindfulness sleep program for pregnant women. METHODS: Secondary analysis from a proof-of-concept trial of 12 pregnant women with DSM-5 insomnia disorder who were treated with Perinatal Understanding of Mindful Awareness for Sleep (PUMAS), which places behavioral sleep strategies within a mindfulness framework. Data were collected across eight weekly assessments: pretreatment, six sessions, and posttreatment. Measures included the insomnia severity index (ISI), Edinburgh postnatal depression scale (EPDS), pre-sleep arousal scale's cognitive factor (PSASC), and the Glasgow sleep effort scale (GSES). We used linear mixed modeling to test cognitive arousal and sleep effort as concurrent and prospective predictors of insomnia and depression. RESULTS: Most patients reported high cognitive arousal before PUMAS (75.0%), which decreased to 8.3% after treatment. All insomnia remitters reported low cognitive arousal after treatment, whereas half of nonremitters continued reporting high cognitive arousal. Both nocturnal cognitive arousal and sleep effort were associated with same-week changes in insomnia throughout treatment, and sleep effort yielded a prospective effect on insomnia. Lower levels of nocturnal cognitive arousal and sleep effort prospectively predicted reductions in depression. CONCLUSIONS: The present study offers preliminary evidence that reducing sleep effort and nocturnal cognitive arousal may serve as key mechanisms for alleviating insomnia and depression via mindfulness-based insomnia therapy. ClinicalTrials.gov ID: NCT04443959.

Surgery
Behinaein P, Hutchings H, Knapp T, and **Okereke IC**. The growing impact of air quality on lung-related illness: a narrative review. *Journal of Thoracic Disease* 2023; Epub ahead of print. PMID: Not assigned. Full Text

Surgery
Chau LC, **Soheim R**, **Dix M**, **Chung S**, **Obeid N**, **Hodari-Gupta A**, and **Stanton C**. Risk factors and natural history of bedside percutaneous endoscopic versus fluoroscopy-guided gastrostomy tubes in intensive care unit patients. *Surg Endosc* 2023; Epub ahead of print. PMID: 37563346. Full Text

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INTRODUCTION: There is a paucity of literature comparing patients receiving bedside placed percutaneous endoscopic gastrostomy (PEG) versus fluoroscopic-guided percutaneous gastrostomy tubes (G-tube) in an intensive care unit (ICU) setting. This study aims to investigate and compare the natural history and complications associated with PEG versus fluoroscopic G-tube placement in ICU patients. METHODS: All adult patients admitted in the ICU requiring feeding tube placement at our center from 1/1/2017 to 1/1/2022 with at least 12-month follow up were identified through retrospective chart review. Adjusting for patient comorbidities, hospital factors, and indications for enteral access, a 1-to-2 propensity score matched Cox proportional-hazards model was fitted to evaluate the treatment effect of bedside PEG tube placement versus G-tube placement on patient 1-year complication, readmission, and death rates. Major complications were defined as those requiring operative or procedural intervention. RESULTS: This study included 740 patients, with 178 bedside PEG and 562 fluoroscopic G-tube placements. The overall rate of complication was 22.3% (13% PEG, 25.2% G-tube, P = 0.003). The major complication rate was 11.2% (8.5% PEG, 12.1% G-tube, P = 0.09). Most common complications were tube dysfunction (16.7% PEG; 39.4% G-tube; P = 0.04) and dislodgement (58.3% PEG; 40.8% G-tube). After propensity score matching, G-tube recipients had significantly increased risk for all-cause (HR 2.7, 95% CI 1.56-4.87, P < 0.001) and major complications (HR 2.11, 95% CI 1.05-4.23, P = 0.035). There were no significant differences in 1-year rates of readmission (HR 0.90, 95% CI 0.58-1.38, P = 0.62) or death (HR 1.00, 95% CI 0.70-1.44, P = 0.7). CONCLUSIONS: The overall rate of complications for ICU patients requiring feeding tube in our cohort was 22.3%. ICU patients receiving fluoroscopic-guided percutaneous gastrostomy tube placement had significantly elevated risk of 1-year all-cause and major complications compared to those undergoing bedside PEG.

Surgery
Ferber M, **Hecht LM**, **Martens KM**, **Hamann A**, **Carlin AM**, and **Miller-Matero LR**. Examining differences in long-term weight loss outcomes after bariatric surgery: The role of romantic relationship status. *Fam Syst Health* 2023; Epub ahead of print. PMID: 37616105. Request Article

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INTRODUCTION: This study tested for differences based on relationship status at the time of surgery in baseline body mass index (BMI), weight loss outcomes (change in BMI [ΔBMI], percent total weight loss [%TWL], percent excess weight loss [%EWL]), and rates of successful weight loss (defined as ≥ 50%EWL) up to 4-year postbariatric surgery. METHOD: Data came from a secondary analysis of patients (N = 492) who were up to 4-year postsurgery and completed a presurgical psychological evaluation and postsurgical survey. RESULTS: Sixty-nine percent of participants were patients in committed relationships and 31% were single/divorced/widowed patients. Single patients had higher presurgical BMIs than those who were partnered (t = 2.28, p = .02). There were no differences between those who

were partnered and singles regarding ΔBMI and %TWL, although singles had smaller %EWL (t = -2.08, p = .04), which became nonsignificant after controlling for covariates. Most participants had successful weight loss (76.8%); however, this was not related to romantic relationship status. DISCUSSION: The results suggest those who were partnered undergo surgery at better-starting weights than singles and maintain this advantage in the long term. Providers working with patients considering bariatric surgery could inquire about how their romantic and social relationships play a part in their decision-making process. (PsycInfo Database Record (c) 2023 APA, all rights reserved).

Surgery

Kalata S, Reddy RM, Norton EC, Clark MJ, He C, Leyden T, Adams KN, **Popoff AM**, Lall SC, and Lagisetty KH. Quality Improvement Mechanisms to Improve Lymph Node Staging for Lung Cancer: Trends from a Statewide Database. *J Thorac Cardiovasc Surg* 2023; Epub ahead of print. PMID: 37625618. Full Text

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OBJECTIVE: Our statewide thoracic quality collaborative has implemented multiple quality improvement initiatives to improve lung cancer nodal staging. We subsequently implemented a value-based reimbursement initiative to further incentivize quality improvement. We compare the impact of these programs to steer future quality improvement initiatives. METHODS: Since 2016, our collaborative focused on improving lymph node staging for lung cancer by leveraging unblinded, hospital-level metrics and collaborative feedback. In 2021, a value-based reimbursement initiative was implemented with statewide yearly benchmark rates for:1) preoperative mediastinal staging for ≥T2N0 lung cancer, and 2) sampling ≥5 lymph node stations. Participating surgeons would receive additional reimbursement if either benchmark was met. We reviewed patients from January 2015-March 2023 at the 21 participating hospitals to determine the differential effects on quality improvement. RESULTS: We analyzed 6,228 patients. In 2015, 212(39%) patients had ≥5 nodal stations sampled, and 99(51%) patients had appropriate preoperative mediastinal staging. During 2016-2020, this increased to 2,253(62%) patients and 739(56%) patients, respectively. After 2020, 1,602(77%) patients had ≥5 nodal stations sampled, and 403(73%) patients had appropriate preoperative mediastinal staging. Interrupted time-series analysis demonstrated significant increases in adequate nodal sampling and mediastinal staging prior to value-based reimbursement. Afterward, pre-operative mediastinal staging rates briefly dropped but significantly increased while nodal sampling did not change. CONCLUSIONS: Collaborative quality improvement made significant progress prior to value-based reimbursement, which reinforces the effectiveness of leveraging unblinded data to a collaborative group of thoracic surgeons. Value-based reimbursement may still play a role within a quality collaborative to maintain infrastructure and incentivize participation.

Surgery

Khan SA, Ahmed FA, **Hafeez MS**, Feng LR, Seth A, Kwon YK, and Aziz H. Outcomes in elderly patients undergoing hepatic resection compared to liver transplant for hepatocellular carcinoma. *J Surg Oncol* 2023; Epub ahead of print. PMID: 37638401. Full Text

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BACKGROUND: Hepatic resection (HR) is an excellent option for patients with hepatocellular carcinoma (HCC). For patients meeting the Milan criteria, a liver transplant (LT) is also a viable option for patients with HCC, especially those with end-stage liver disease. With increasing rates of LTs amongst the elderly, we sought to determine long-term outcomes in patients who underwent HR compared to LTs in this patient population. METHODS: We queried the national cancer database for elderly patients (≥70 years) diagnosed with HCC between 2004 and 2020. The primary outcome was overall survival (OS) computed using the Kaplan-Meier method and Cox proportional hazard regression. One-to-one propensity score matching was conducted on the basis of clinicodemographic features to account for baseline differences between patients undergoing each procedure. RESULTS: Of the 5090 patients included, 4674 (91.8%) and 416 (8.2%) patients underwent HR and LT, respectively. Compared with HR patients, patients receiving LT had better OS ($p < 0.001$) and greater median survival time (65.6 months HR vs. 97.9 months LT, $p < 0.001$). On multivariable analysis, a LT was independently associated with improved survival (adjusted hazard ratio: 0.61, 95% confidence interval: 0.50-0.76, $p < 0.001$). CONCLUSIONS: LT is associated with improved survival for well-selected elderly patients with HCC. Age alone should not be used as the sole parameter for the candidacy of LT in elderly patients.

Surgery

Segal A, **Pearl E**, **Fatabhoy M**, **Zohr SJ**, **Bryce K**, **Gonzalez HC**, and **Miller-Matero LR**. Factors associated with a positive phosphatidylethanol test during liver transplantation evaluation. *Clin Transplant* 2023; e15100. Epub ahead of print. PMID: 37577900. Full Text

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BACKGROUND: Early identification of alcohol use is crucial for informing recommendations of appropriate follow-up treatment pre-liver transplant and optimizing post-liver transplant outcomes. The purpose of the study was to investigate whether there are psychosocial factors associated with a positive PEth test. METHODS: All patients who underwent a routine pre-surgical psychological evaluation for liver transplant listing (all etiologies, including acute liver failure, dual organ, and re-transplantation) at a single health care system in 2020 were included in a retrospective chart review. Data extraction included results from PEth testing and information from the psychological evaluation (i.e., demographic, psychiatric symptoms, and cognitive functioning). RESULTS: There were 158 patients (73.8%) who had a PEth test, of whom 21.5% had a positive result ($n = 34$). Younger age was associated with a positive PEth ($p < .001$). ALD status and type of ALD (hepatitis vs. cirrhosis) were also associated with a positive PEth test. Other demographic characteristics and psychiatric symptoms were not associated with a positive PEth result ($p > .05$). CONCLUSION: Younger age was the only significant demographic variable associated with a positive PEth test. Given the difficulty of predicting who may be using alcohol, it may be useful to use PEth testing for all patients during the pre-liver transplant evaluation and while patients are listed for liver transplant. Early identification of alcohol use through routine PEth testing will help identify patients who are using alcohol and need further treatment for alcohol use to optimize health and post-transplant outcomes.

Urology

Agarwal A, Farkouh A, Saleh R, Hamoda TAA, Salvio G, **Rambhatla A**, et al. Technical Aspects and Clinical Limitations of Sperm DNA Fragmentation Testing in Male Infertility: A Global Survey, Current Guidelines, and Expert Recommendations. *World J Mens Health* 2023; Epub ahead of print. PMID: 37635341. Full Text

PURPOSE: Sperm DNA fragmentation (SDF) is a functional sperm abnormality that can impact reproductive potential, for which four assays have been described in the recently published sixth edition of the WHO laboratory manual for the examination and processing of human semen. The purpose of this study was to examine the global practices related to the use of SDF assays and investigate the barriers and limitations that clinicians face in incorporating these tests into their practice. MATERIALS AND

METHODS: Clinicians managing male infertility were invited to complete an online survey on practices related to SDF diagnostic and treatment approaches. Their responses related to the technical aspects of SDF testing, current professional society guidelines, and the literature were used to generate expert recommendations via the Delphi method. Finally, challenges related to SDF that the clinicians encounter in their daily practice were captured. RESULTS: The survey was completed by 436 reproductive clinicians. Overall, terminal deoxynucleotidyl transferase deoxyuridine triphosphate Nick-End Labeling (TUNEL) is the most commonly used assay chosen by 28.6%, followed by the sperm chromatin structure assay (24.1%), and the sperm chromatin dispersion (19.1%). The choice of the assay was largely influenced by availability (70% of respondents). A threshold of 30% was the most selected cut-off value for elevated SDF by 33.7% of clinicians. Of respondents, 53.6% recommend SDF testing after 3 to 5 days of abstinence. Although 75.3% believe SDF testing can provide an explanation for many unknown causes of infertility, the main limiting factors selected by respondents are a lack of professional society guideline recommendations (62.7%) and an absence of globally accepted references for SDF interpretation (50.3%). CONCLUSIONS: This study represents the largest global survey on the technical aspects of SDF testing as well as the barriers encountered by clinicians. Unified global recommendations regarding clinician implementation and standard laboratory interpretation of SDF testing are crucial.

Urology

Davis M, **Stephens A**, **Butaney M**, **Morrison C**, **Corsi N**, Sood A, **Levin AM**, Cole A, Trinh QD, **Rogers C**, and **Abdollah F**. Trends in prostate cancer screening in the pre- and peri-COVID-19 Pandemic period. *Urol Pract* 2023; Epub ahead of print. PMID: 37647197. Full Text

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PURPOSE: This study sought to examine prostate-specific antigen testing rates before, early in, and later in the COVID-19 Pandemic. MATERIALS AND METHODS: Our cohort included test results from men >45 years who received prostate-specific antigen testing at least once at our institution from November 2018-September 2021 and were alive at the end of that period. Monthly trends were evaluated for three periods: Pre-COVID (November 2018-February 2020), early-COVID (March-May 2020), and late-COVID (June 2020-September 2021). Univariable and multivariable analysis tested the impact of these periods on prostate-specific antigen testing rate, after accounting for available confounders. All analyses were stratified by prostate cancer diagnosis status. RESULTS: A total of 141,777 prostate-specific antigen tests met inclusion criteria. The monthly number of tests in men without prostate cancer declined from 3,669 pre-COVID to 1,760 early-COVID (52% decrease; P=0.0086) before increasing to 4,171 (14% increase from pre-COVID; P<0.0001) late-COVID. The monthly average of first-time tests declined from 805 pre-COVID to 315 early-COVID (61% decrease; P=0.008) before rebounding to 795 (1% decrease from pre-COVID; P=0.7) late-COVID. The monthly number of tests in prostate cancer patients declined from 343 pre-COVID to 195 early-COVID (43% decrease; P=0.008) before partially rebounding to 313 (9% decrease; P=0.03) late-COVID. These differences remained within multivariable models. CONCLUSIONS: A number of men have forgone first-time prostate-specific antigen testing opportunities following the COVID-19 outbreak; thus, early cancer diagnoses in some individuals might have been missed. Likewise, many prostate cancer patients have forgone follow-up in the late-COVID period, which might compromise their oncologic outcomes.

Urology

Griffiths L, Aro T, Samson P, Derisavifard S, Alaiev D, Mullen G, Gaines J, Rai A, Williams TR, Patel V, **Leavitt DA**, Guanay G, Hartman C, Smith A, Hoenig DM, and Okeke Z. Prospective Randomized Trial of Antibiotic Prophylaxis Duration for Percutaneous Nephrolithotomy in Low-Risk Patients. *J Endourol* 2023; Epub ahead of print. PMID: 37578113. Full Text

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Introduction Post operative infection and sepsis account for the most common complication following Percutaneous nephrolithotomy, with numbers as high as 14% in low-risk patients. Although the American Urologic Association (AUA) recommends 24 hours or less of perioperative antibiotics for percutaneous nephrolithotomy (PCNL), practice patterns vary regarding duration of antibiotic therapy. We aimed to compare the efficacy of 24-hour antibiotic coverage versus short-course protocol of antibiotic prophylaxis for PCNL. Methods Low-risk patients with a sterile pre-operative urine culture undergoing PCNL were prospectively randomized to antibiotics for 24 hours (24Hr) or until external urinary catheters were removed (CR). Patients were given a 1st generation cephalosporin, or ciprofloxacin in patients with penicillin allergy. Exclusion criteria included age <18 years, receiving antibiotics immediately prior to the procedure, history of urosepsis, presence of indwelling catheter >1 week, multi-stage procedure, immunosuppression, pregnancy, multiple antibiotic allergies, and patients who are breastfeeding. Results Ninety-eight patients were randomized to either 24Hr (n=49) or CR (n=49) and analyzed. Mean duration of antibiotic administration was 20.6 hours and 34.0 hours in the 24Hr and CR groups (p=0.04), respectively. Age, comorbidities, stone size, operative time, number of punctures, dilations, and proportion of "tubeless" procedures were similar between groups. There were no differences in febrile episodes, rates of systemic inflammatory response syndrome, bacteremia, or culture-proven post-operative urinary tract infection between the 24Hr and CR groups. Overall complication rates were similar between groups. In a subgroup analysis which excluded "tubeless" patients (24 and 29 patients in 24Hr and CR groups, respectively), no differences were seen in postoperative outcomes. Conclusions In a randomized, prospective study, we found that a 24-hour protocol for antibiotic prophylaxis is not associated with increased risk of infection-related events compared to giving antibiotics until external catheters are removed in patients with low infectious risk undergoing PCNL.

Urology

Javid M, Reddiboina M, and **Bhandari M**. Emergence of artificial generative intelligence and its potential impact on urology. *Can J Urol* 2023; 30(4):11588-11598. PMID: 37633285. Full Text

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INTRODUCTION: Artificial generative intelligence (AGI) and large language models (LLMs) have gained significant attention in healthcare and hold enormous promise for transforming every aspect of our life and urology is no exception. MATERIALS AND METHODS: We conducted a comprehensive literature search of electronic databases and included articles discussing AGI and LLMs in healthcare. Additionally, we have incorporated our experiences interacting with the ChatGPT and GPT-4 in different situations with real case reports and case constructs. RESULTS: Our review highlights the potential applications and likely impact of these technologies in urology, for differential diagnosis, prioritizing treatment options, and facilitating research, surgeon, and patient education. At their current developmental stage, we have recognized the need for concurrent validation and continuous human interaction necessary to induce inverse reinforced learning with human feedback to mature them to authenticity. We need to consciously adjust to the hallucinations and guard patients' confidentiality before their extensive implementations in clinical practice. We propose possible remedies for these shortcomings and emphasize the critical role of human interaction in their evolution. CONCLUSION: The integration of these tools has the potential to revolutionize urology, but it also presents several challenges needing attention. To harness the full potential of these models, urologists must consistently engage in training these tools with their clinical sense and experience. We urge the urology community to actively participate in AGI and LLM development to address potential challenges. These models could help us in unleashing our full potential and help us achieve a better work-life balance.

Urology
Madhavan K, Jena R, Bhargava P, Pradhan A, and **Bhandari M**. Comparison of outcomes after open versus robotic kidney transplantation: A systematic review and meta-analysis. *Indian J Urol* 2023; 39(3):186-194. PMID: 37575161. Full Text

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INTRODUCTION: This meta-analysis compares the clinical outcomes of robot-assisted kidney transplant (RAKT) to open kidney transplant (OKT). METHODS: A systematic search of Scopus and MEDLINE databases was carried out using a combination of keywords to identify studies comparing RAKT to OKT. Baseline characteristics and preoperative and postoperative data were collected along with data on the short- and long-term outcomes. The study was registered in PROSPERO and Assessing the Methodological Quality of Systematic Reviews and Preferred Reporting Items for Systematic Review and Meta-Analysis (PRISMA) guidelines were followed. RESULTS: A total of 16 studies were included with a total of 2555 patients, of which 677 underwent RAKT and 1878 underwent OKT. This meta-analysis shows a significant benefit of RAKT over OKT in terms of less intra-operative blood loss, smaller incision length, less postoperative pain scores at 24 and 48 hours, and a lower incidence of surgical site infections (SSIs), especially in obese patients. In addition, the incidence of postoperative lymphoceles was lower in the RAKT group compared to the OKT group, although not statistically significant. There was no difference between the two groups in terms of short-term graft functional outcomes and overall survival. The number of deceased donor recipients undergoing RAKT was very small. At the time of reporting this meta-analysis, no randomized controlled trials (RCTs) had been published. CONCLUSION: This meta-analysis showed that RAKT is a safe and feasible alternative to OKT, especially in obese individuals. Further trials are needed to confirm the safety, efficacy, and cost-effectiveness of RAKT.

Urology

Rakic I, Rakic N, **Stephens A**, **Corsi N**, **Davis M**, **Tinsley S**, **Butaney M**, **Arora S**, Sood A, Autorino R, **Rogers C**, and **Abdollah F**. Assessing the impact of lymphovascular invasion on overall survival in surgically treated renal cell carcinoma patients: A nationwide cohort analysis. *Urol Oncol* 2023; Epub ahead of print. PMID: 37625905. Full Text

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INTRODUCTION: Lymph-vascular invasion (LVI) is recognized as an adverse pathological feature in patients with renal cell carcinoma (RCC). However, its impact on overall survival (OS) is not clear and scarcely addressed in the literature. We aimed to assess the prognostic ability of LVI as a predictor of OS in RCC patients using a large, North American cohort. METHODS: We included 95,783 cM0 RCC patients, diagnosed between 2010 and 2015, who underwent partial or radical nephrectomy within the National Cancer Database. Kaplan-Meier curves and log-rank tests were used to depict and compare survival curves. Cox regression analysis tested the impact of LVI on OS, after adjusting for all available confounders. RESULTS: Mean age (SD) was 59 (12), and most patients had pT1 stage (72.2%). Nodal status was pN0, pN1, and pNx, in 14.5%, 2.3%, and 83.3%, respectively. Overall, 9.0% of patients had LVI. The mean (SD) follow-up of the cohort was 39 months (24). At 5 years, OS was 65% in patients with LVI vs. 86% in patients without LVI (p<.0001). When patients were stratified based on nodal stage, these rates were 64% vs. 78% in pN0 patients, 31% vs. 41% in pN1 patients, and 69% vs. 87% in pNx patients (all P < 0.001). On multivariable analysis, and in comparison to patients without LVI, those with LVI had 1.37- (P < 0.001), 1.18- (P = 0.068), and 1.53-fold (P < 0.001) greater risk of death, when also harboring pN0, pN1, and pNx disease, respectively. CONCLUSIONS: Our findings are the first, to our best knowledge, to illustrate the clear detrimental impact of LVI on OS in surgically treated RCC patients. These findings might be useful in postoperative patient counseling and need to be accounted for when designing future clinical trials.

Urology

Soputro NA, Ferguson EL, Ramos-Carpinteyro R, Sauer Calvo R, Nguyen J, Moschovas MC, **Wilder S**, Chavali JS, Okhawere KE, De La Rosa RS, Saini I, **Peabody J**, Badani KK, **Rogers C**, Joseph J, Patel V, Stifelman M, Ahmed M, Crivellaro S, Kim M, Nix J, and Kaouk J. Low Risk of Postoperative Hernia Following Single-port Robot-assisted Radical Prostatectomy: A Report From the Single-port Advanced Research Consortium (SPARC). *Urology* 2023; Epub ahead of print. PMID: 37454768. Full Text

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OBJECTIVE: To evaluate the risk of postoperative hernia following different approaches of single-port robot-assisted radical prostatectomy (SP-RARP). METHODS: A retrospective review was performed on patients who underwent SP-RARP between February 2019 and December 2022. Demographic and clinical information was collected from the multi-institutional, prospectively-maintained Single-Port Advanced Research Consortium (SPARC) database. Data were analyzed using IBM Statistical Packaging for Social Sciences (SPSS) version 29.0 with descriptive statistics as presented. RESULTS: A total of 1103 patients were identified, consisting of 244 (22.1%), 712 (64.6%), and 147 (13.3%) cases performed via transperitoneal, extraperitoneal (EP), and transvesical (TV) approaches, respectively. During a median follow-up time of 11 months (interquartile range 5.7-17.1 months), only two cases of incisional hernia were reported. Both cases occurred following transperitoneal SP-RARP with one patient requiring surgical repair. There remains no evidence of postoperative hernia following EP and TV SP-RARP at the completion of our review. CONCLUSION: SP-RARP was associated with low risk for postoperative hernia. The risk was lower following TV and EP SP-RARP where the peritoneum is preserved.