Sladen Library
Great Research • Great Care • Start Here

HENRY FORD HEALTH

Henry Ford Health Publication List – December 2022

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 90 unique citations listed this month, including 78 articles and 12 conference abstracts.

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

Click the "Full Text" link to view the articles to which Sladen Library provides access. If the full-text of the article is not available, you may request it through ILLiad by clicking on "Request Article," or calling us at (313) 916-2550. If you would like to be added to the monthly email distribution list to automatically receive a PDF of this bibliography, or you have any questions or comments, please contact smoore31@hfhs.org. If your published work has been missed, please use this form to notify us for inclusion on next month's list. All articles and abstracts listed here are deposited into Scholarly Commons, the Henry Ford Health institutional repository.

Articles

Administration
Anesthesiology
Behavioral Health Services/Psychiatry/Neuropsychology
Cardiology/Cardiovascular Research
Center for Health Policy and Health Services Research
Center for Individualized and Genomic Medicine Research
Clinical Quality and Safety
Dermatology
Diagnostic Radiology
Emergency Medicine
Endocrinology and Metabolism
Family Medicine
Gastroenterology
Graduate Medical Education
Hematology-Oncology
Hypertension and Vascular Research
Internal Medicine
Neurology
Neurosurgery
Obstetrics, Gynecology and Women's Health Services
Ophthalmology and Eye Care Services
Orthopedics/Bone and Joint Center
Otolaryngology – Head and Neck Surgery
Pathology and Laboratory Medicine
Pharmacy
Public Health Sciences
Pulmonary and Critical Care Medicine
Radiation Oncology
Sleep Medicine
Surgery
Urology

Conference Abstracts

Otolaryngology – Head and Neck Surgery
Radiation Oncology
Sleep Medicine

Articles

Administration
Aronow HD. Presidential Address: Mission-driven. *Vasc Med* 2022; 27(6):615-618. PMID: 36475563. Full Text

Department of Medicine, Michigan State University, East Lansing, MI.
Heart & Vascular Services, Henry Ford Health, Detroit, MI, USA.

Administration
Brooks-Williams D. An Effective Response to Healthcare Disparities Begins With a Strategic Plan. *Front Health Serv Manage* 2022; 39(2):27-31. PMID: 36413473. Full Text

Denise Brooks-Williams, FACHE, is senior vice president and CEO of market operations at Henry Ford Health System, Detroit, Michigan.

For too long, healthcare disparities have negatively affected underrepresented groups in urban areas throughout the United States. Disparities in care and outcomes related to social determinants were known, and efforts were made to address them. Effective change for all moved up to top priority in the wake of COVID-19's arrival, police brutality, social unrest, and the murders of Black Americans, including George Floyd. Henry Ford Health (HFH), working with leading local community organizations, immediately pledged to address social and racial injustices. Unfortunately, many neighborhoods still suffer disproportionately from maternal and infant mortality, food insecurity, and other social vulnerabilities. HFH's commitment to equity includes creatively meeting the needs of the underserved. HFH has developed innovative ways to address the social, economic, and educational challenges to the health of Metro Detroit. Through thoughtful consideration and passionate leadership, HFH is strategically creating authentic and scalable social change to address racism and discrimination in healthcare.

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 Multi-Ancestry Genome-Wide Association Study in the Diabetes Prevention Program (DPP). *Diabetes* 2022; Epub ahead of print. PMID: 36525397. Full Text

Center for Genomic Medicine, Massachusetts General Hospital, Boston, Massachusetts.
Diabetes Unit, Department of Medicine, Massachusetts General Hospital, Boston, Massachusetts.
Programs in Metabolism and Medical & Population Genetics, Broad Institute of Harvard and MIT, Cambridge, Massachusetts.
Department of Medicine, Harvard Medical School, Boston, Massachusetts.
Department of Medicine, University of Maryland School of Medicine, Baltimore, Maryland.
Department of Epidemiology and Biostatistics, George Washington University Biostatistics Center, Washington, District of Columbia.
Division of Pediatric Endocrinology and Diabetes, Department of Pediatrics, University of California at San Francisco, San Francisco, California.
Division of Population Health and Genomics, Ninewells Hospital and School of Medicine, University of Dundee, Dundee, Scotland, U.K.
Department of Bioengineering and Therapeutic Sciences, University of California at San Francisco, San Francisco, California.
Division of Quantitative Sciences, Department of Obstetrics and Gynecology, Vanderbilt University Medical Center, Nashville, Tennessee.
Division of Nephrology and Hypertension, Department of Medicine, Vanderbilt University Medical Center, Nashville, Tennessee.
Center for Individualized and Genomic Medicine Research (CIGMA), Department of Internal Medicine, Henry Ford Health System, Detroit, Michigan.

Genetic and Molecular Epidemiology Unit, Lund University Diabetes Centre, Lund University, Malmo, Sweden.
Diabetes Epidemiology and Clinical Research Section, National Institute of Diabetes and Digestive and Kidney Diseases, Phoenix, Arizona.
Division of Metabolism, Endocrinology and Nutrition, Department of Medicine, VA Puget Sound Health Care System and University of Washington, Seattle, Washington.

Genome-wide significant loci for metformin response in type 2 diabetes reported elsewhere have not replicated in the Diabetes Prevention Program (DPP). To assess pharmacogenetic interactions in pre-diabetes, we conducted a genome-wide association study (GWAS) in the DPP. Cox proportional hazards models tested associations with diabetes incidence in metformin (MET, n=876) and placebo (PBO, n=887) arms. Multiple linear regression assessed association with one-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 ($p<9\times10\text{-}9$). In MET, rs144322333 near ENOSF1 (minor allele frequency [MAF]AFR=0.07, MAFEUR=0.002) was associated with an increase in % glycated hemoglobin (per minor allele $\beta=0.39$ [95% CI 0.28, 0.50], $p=2.8\times10\text{-}12$). Rs145591055 near OMSR (MAF=0.10 in American Indians), was associated with weight loss (kg) (per G allele $\beta=-7.55$ [95% CI -9.88, -5.22], $p=3.2\times10\text{-}10$) in MET. Neither variant was significant in PBO; gene-by-treatment interaction was significant for both variants ($p(G\times T)<1.0\times10\text{-}4$). Replication in individuals with diabetes did not yield significant findings. A GWAS for metformin response in pre-diabetes revealed novel ethnic-specific associations that require further investigation but may have implications for tailored therapy.

Administration
Lucas SR, **Pollak E**, and **Makowski C**. A failure in the medication delivery system-how disclosure and systems investigation improve patient safety. *J Healthc Risk Manag* 2022; Epub ahead of print. PMID: 36463558. Full Text

Biomedical Engineering Forensic Services, Jensen Hughes, Baltimore, Maryland, USA.
Quality and Performance Excellence, Anesthesiology and Perioperative Medicine, Henry Ford Health, Detroit, Michigan, USA.
Department of Pharmacy Services, Henry Ford Health, Detroit, Michigan, USA.

A recent medication error at Vanderbilt University Medical Center contributed to the death of a patient. The ensuing criminal indictment of the administering nurse has shaken the medical community. This has led to clinical staff questioning whether they can disclose patient safety incidents without fear of criminal prosecution. However, because of the publicity of this case, hospitals can benefit from the lessons learned and mitigate the risk of this and similar events at their facilities. To uncover the most impactful and relevant safety recommendations, the Vanderbilt case is examined from a systems investigation perspective using the available public information gathered from media reports, the Tennessee Bureau of Investigation report, and Vanderbilt's corrective action plan submitted to CMS. We present an example of how hospitals can benefit from disclosure: Henry Ford Health used the Vanderbilt case study as part of its medication safety continuous improvement initiatives, which are underpinned by available medication safety recommendations from the Institute for Safe Medication Practices. Using this experience and the lessons learned from the Vanderbilt case, a proactive action plan is presented for hospitals nationwide to prevent the recurrence of this medication error. Without disclosure, these analyses and safety recommendations would not have been possible.

Anesthesiology
Sayed D, Grider J, Strand N, Hagedorn JM, Falowski S, Lam CM, Tieppo Francio V, Beall DP, Tomycz ND, Davanzo JR, **Aiyer R**, Lee DW, Kalia H, Sheen S, Malinowski MN, Verdolin M, Vodapally S, Carayannopoulos A, Jain S, Azeem N, Tolba R, Chang Chien GC, Ghosh P, Mazzola AJ, Amirdelfan K, Chakravarthy K, Petersen E, Schatman ME, and Deer T. The American Society of Pain and Neuroscience (ASPN) Evidence-Based Clinical Guideline of Interventional Treatments for Low Back Pain. *J Pain Res* 2022; 15:3729-3832. PMID: 36510616. Full Text

Department of Anesthesiology and Pain Medicine, The University of Kansas Medical Center, Kansas City, KS, USA.
University of Kentucky, Lexington, KY, USA.
Interventional Pain Management, Mayo Clinic, Scottsdale, AZ, USA.
iSpine Pain Physicians, Maple Grove, MN, USA.
Functional Neurosurgery, Neurosurgical Associates of Lancaster, Lancaster, PA, USA.
Department of Rehabilitation Medicine, University of Kansas Medical Center, Kansas City, KS, USA.
Comprehensive Specialty Care, Edmond, OK, USA.
AHN Neurosurgery, Allegheny General Hospital, Pittsburgh, PA, USA.
AHN Neurosurgery, Forbes Hospital, Monroeville, PA, USA.
Interventional Pain Management and Pain Psychiatry, Henry Ford Health System, Detroit, MI, USA.
Physical Medicine & Rehabilitation and Pain Medicine, Fullerton Orthopedic Surgery Medical Group, Fullerton, CA, USA.
Rochester Regional Health System, Rochester, NY, USA.
Department of Physical Medicine & Rehabilitation, University of Rochester, Rochester, NY, USA.
Adena Spine Center, Adena Health System, Chillicothe, OH, USA.
Ohio University Heritage College of Osteopathic Medicine, Athens, OH, USA.
Anesthesiology and Pain Medicine, Pain Consultants of San Diego, San Diego, CA, USA.
Physical Medicine and Rehabilitation, Michigan State University, East Lansing, MI, USA.
Department of Physical Medicine and Rehabilitation, Rhode Island Hospital, Newport Hospital, Lifespan Physician Group, Providence, RI, USA.
Comprehensive Spine Center at Rhode Island Hospital, Newport Hospital, Providence, RI, USA.
Neurosurgery, Brown University, Providence, RI, USA.
Interventional Pain Management, Pain Treatment Centers of America, Little Rock, AR, USA.
Department of Neurology, University of South Florida, Tampa, FL, USA.
Florida Spine & Pain Specialists, Riverview, FL, USA.
Pain Management, Cleveland Clinic, Abu Dhabi, United Arab Emirates.
Anesthesiology, Cleveland Clinic Lerner College of Medicine, Cleveland, OH, USA.
Pain Management, Ventura County Medical Center, Ventura, CA, USA.
Center for Regenerative Medicine, University Southern California, Los Angeles, CA, USA.
Remedy Medical Group, San Francisco, CA, USA.
Mount Sinai Health System, New York City, NY, USA.
IPM Medical Group, Inc., Walnut Creek, CA, USA.
Division of Pain Medicine, Department of Anesthesiology, University of California San Diego, San Diego, CA, USA.
Va San Diego Healthcare, San Diego, CA, USA.
Department of Neurosurgery, University of Arkansas for Medical Science, Little Rock, AR, USA.
Department of Anesthesiology, Perioperative Care, and Pain Medicine, NYU Grossman School of Medicine, New York, New York, USA.
Department of Population Health - Division of Medical Ethics, NYU Grossman School of Medicine, New York, New York, USA.
The Spine and Nerve Center of the Virginias, Charleston, WV, USA.

INTRODUCTION: Painful lumbar spinal disorders represent a leading cause of disability in the US and worldwide. Interventional treatments for lumbar disorders are an effective treatment for the pain and disability from low back pain. Although many established and emerging interventional procedures are currently available, there exists a need for a defined guideline for their appropriateness, effectiveness, and safety. OBJECTIVE: The ASPN Back Guideline was developed to provide clinicians the most comprehensive review of interventional treatments for lower back disorders. Clinicians should utilize the ASPN Back Guideline to evaluate the quality of the literature, safety, and efficacy of interventional treatments for lower back disorders. METHODS: The American Society of Pain and Neuroscience (ASPN) identified an educational need for a comprehensive clinical guideline to provide evidence-based recommendations. Experts from the fields of Anesthesiology, Physiatry, Neurology, Neurosurgery, Radiology, and Pain Psychology developed the ASPN Back Guideline. The world literature in English was searched using Medline, EMBASE, Cochrane CENTRAL, BioMed Central, Web of Science, Google

Scholar, PubMed, Current Contents Connect, Scopus, and meeting abstracts to identify and compile the evidence (per section) for back-related pain. Search words were selected based upon the section represented. Identified peer-reviewed literature was critiqued using United States Preventive Services Task Force (USPSTF) criteria and consensus points are presented. RESULTS: After a comprehensive review and analysis of the available evidence, the ASPN Back Guideline group was able to rate the literature and provide therapy grades to each of the most commonly available interventional treatments for low back pain. CONCLUSION: The ASPN Back Guideline represents the first comprehensive analysis and grading of the existing and emerging interventional treatments available for low back pain. This will be a living document which will be periodically updated to the current standard of care based on the available evidence within peer-reviewed literature.

Behavioral Health Services/Psychiatry/Neuropsychology
Hecht LM, Schruff MA, Young J, **Carlin AM**, and **Miller-Matero LR**. Psychometric Evaluation of a Measure of Health Numeracy Among Individuals Seeking Bariatric Surgery. *Obes Surg* 2022; Epub ahead of print. PMID: 36562961. Full Text

Center for Health Policy and Health Services Research, Henry Ford Health, Detroit, MI, 48202, USA. lhecht1@hawk.iit.edu.
Department of Psychology, University of Mississippi, University, Oxford, MS, 38677, USA.
Department of Surgery, Henry Ford Health, Detroit, MI, 48202, USA.
Center for Health Policy and Health Services Research, Henry Ford Health, Detroit, MI, 48202, USA.
Behavioral Health, Henry Ford Health, Detroit, MI, 48202, USA.

Behavioral Health Services/Psychiatry/Neuropsychology
Li L, Merchant M, **Gordon S**, Lang B, Ramsey S, Huber AM, Gillespie J, Lovas D, and Stringer E. High rates of symptoms of major depressive disorder and panic disorder in a Canadian sample of adolescents with JIA. *J Rheumatol* 2022; Epub ahead of print. PMID: 36521911. Full Text

Grants or industrial support: Ms. Li was supported by the Dalhousie Medical Research Foundation (DMRF) Bergmann-Porter Studentship. Li, L. MSc, MD Candidate 2022, Dalhousie Medical School, Halifax, Nova Scotia, Canada. Merchant, M, MD FRCPC, Clinical Lecturer, Division of Rheumatology, Department of Medicine, University of Calgary, Calgary, Alberta, Canada. Gordon, S, LMSW, MSW, Clinical Care Coordinator, Henry Ford Health System, Detroit, Michigan, USA. Lang, B, MD FRCPC, Professor of Pediatrics, IWK Health, Dalhousie University, Halifax, Nova Scotia, Canada. Ramsey, S, MD FRCPC Associate Professor of Pediatrics, IWK Health, Dalhousie University, Halifax, Nova Scotia, Canada. Huber, AM, MD MSc FRCPC, Professor of Pediatrics, IWK Health, Dalhousie University, Halifax, Nova Scotia, Canada. Gillespie, J. M. PhD, RPsych Pediatric Health Psychology Service, IWK Health, and Department of Psychology and Neuroscience, Dalhousie University Lovas, D, MD FRCPC. Assistant Professor of Psychiatry, IWK Health, Dalhousie University, Halifax, Nova Scotia, Canada. Stringer, E. MD MSc FRCPC, Associate Professor of Pediatrics, IWK Health, Dalhousie University, Halifax, Nova Scotia, Canada. Conflict of interest: The authors have no conflicts of interest to declare. Address correspondence to Elizabeth Stringer, Division of Pediatric Rheumatology, IWK Health, 5850 University Ave, Halifax, NS, B3K 6R8. Elizabeth.stringer@iwk.nshealth.ca.

OBJECTIVE: We aimed to evaluate the rate of depressive and/or anxiety symptoms in adolescents with JIA and explore the association with demographic and disease activity measures. METHODS: Depressive and anxiety symptoms were assessed in adolescents with JIA aged 12-18 at a Canadian tertiary-care hospital, using the Revised Child Anxiety and Depression Scale (RCADS). The RCADS includes 6 subscales: Separation Anxiety, Social Phobia, Generalized Anxiety, Panic Disorder, Obsessive Compulsive, and Major Depressive Disorder. Scores above "clinical threshold" on the RCADS subscales indicate that an individual's responses reflect symptoms similar to those diagnosed with the corresponding mental health disorder. Fisher's exact test and Mann-Whitney U test were used to compare demographic and disease-related between participants who scored above and below clinical threshold on each of the subscales. RESULTS: 32/80 (40%) of participants scored above clinical threshold on at least one subscale. Scores above clinical threshold were most frequent for Major Depressive Disorder (23.8%) and Panic Disorder (22.5%) subscales. Social Phobia and Separation

Anxiety followed with 16.3% and 13.8% respectively. Females were more likely to have scores above clinical threshold on the Panic Disorder subscale. Participants with higher self-reported disease activity were more likely to have scores above clinical threshold for all anxiety subscales except Separation Anxiety. CONCLUSION: We report high rates of symptoms of depression and anxiety (panic in particular) in adolescents with JIA. This highlights the ongoing need for mental health screening protocols and services. The relationships between concomitant mental health disorders, disease activity and patient-reported outcomes requires further research.

Behavioral Health Services/Psychiatry/Neuropsychology
Taber DJ, Gordon EJ, **Jesse MT**, Myaskovsky L, Peipert JD, Jaure A, George R, and Fitzsimmons W. A viewpoint describing the American Society of Transplantation rationale to conduct a comprehensive patient survey assessing unmet immunosuppressive therapy needs. *Clin Transplant* 2022. Epub ahead of print. PMID: 36465024. Full Text

Department of Surgery, Medical University of South Carolina, Charleston, South Carolina, USA.
Department of Surgery, Vanderbilt University Medical Center, Nashville, Tennessee, USA.
Henry Ford Transplant Institute, Internal Medicine, Henry Ford Health, Detroit, Michigan, USA.
Center for Healthcare Equity in Kidney Disease and Department of Internal Medicine, University of New Mexico, Health Sciences Center, Albuquerque, New Mexico, USA.
Department of Medical Social, Sciences & Northwestern University Transplant Outcomes Research Collaboration, Northwestern University Feinberg School of Medicine, Chicago, Illinois, USA.
Sydney School of Public Health, The University of Sydney, Camperdown, Sydney, Australia.
Emory University and Children's Healthcare of Atlanta, Atlanta, Georgia.
Colleges of Pharmacy and Medicine, University of Illinois at Chicago, Chicago, Illinois, USA.

This viewpoint aims to "set the stage" and provide the rationale for the proposed development of a large-scale, comprehensive survey assessing transplant patients' perceived unmet immunosuppressive therapy needs. Research in organ transplantation has historically focused on reducing the incidence and impact of rejection on allograft survival and minimizing or eliminating the need for chronic immunosuppressive therapies. There has been less emphasis and investment in therapies to improve patient-reported outcomes including health-related quality of life and side-effects. Patient-focused drug development (PFDD) is a new and important emphasis of the Food and Drug Administration (FDA) that provides a guiding philosophy for incorporating the patient experience into drug development and evaluation. The American Society of Transplantation (AST) Board of Directors commissioned this working group to prepare for the conduct of a comprehensive patient survey assessing unmet immunosuppressive therapy needs. This paper aims to describe the basis for why it is important to conduct this survey and briefly outline the plan for broad stakeholder engagement to ensure the information gained is diverse, inclusive, and relevant for advancing PFDD in organ transplant recipients.

Cardiology/Cardiovascular Research
Aronow HD. Presidential Address: Mission-driven. *Vasc Med* 2022; 27(6):615-618. PMID: 36475563. Full Text

Department of Medicine, Michigan State University, East Lansing, MI.
Heart & Vascular Services, Henry Ford Health, Detroit, MI, USA.

Cardiology/Cardiovascular Research
Eleid MF, **Wang DD**, Pursnani A, Kodali SK, George I, Palacios I, Russell H, Makkar RR, Kar S, Satler LF, Rajagopal V, Dangas G, Tang GHL, McCabe JM, Whisenant BK, Fang K, Kaptzan T, Lewis B, Douglas P, Hahn R, Thaden J, Oh JK, Leon M, **O'Neill W**, Rihal CS, and Guerrero ME. 2-Year Outcomes of Transcatheter Mitral Valve Replacement in Patients With Annular Calcification, Rings, and Bioprostheses. *J Am Coll Cardiol* 2022; 80(23):2171-2183. PMID: 36456047. Full Text

Department of Cardiovascular Medicine, Mayo Clinic, Rochester, Minnesota, USA.
Center for Structural Heart Disease, Henry Ford Hospital, Detroit, Michigan, USA.
Division of Cardiology, NorthShore University HealthSystem, Evanston, Illinois, USA.

Division of Cardiology, Columbia University Medical Center, New York, New York, USA.
Department of Surgery, Columbia University Medical Center, New York, New York, USA.
Division of Cardiology, Massachusetts General Hospital, Boston, Massachusetts, USA.
Division of Cardiovascular Surgery, NorthShore University HealthSystem, Evanston, Illinois, USA.
Department of Cardiology, Cedars-Sinai Heart Institute, Los Angeles, California, USA.
Division of Cardiology, Los Robles Regional Medical Center, Thousand Oaks, California, USA.
Division of Cardiology, Medstar Washington Hospital Center, Washington, DC, USA.
Division of Cardiology, Piedmont Hospital, Atlanta, Georgia, USA.
Division of Cardiology, Mount Sinai Health System, New York, New York, USA.
Department of Cardiovascular Surgery, Mount Sinai Health System, New York, New York, USA.
Division of Cardiology, University of Washington Medical Center, Seattle, Washington, USA.
Division of Cardiology, Intermountain Heart Institute, Salt Lake City, Utah, USA.
Division of Cardiology, Banner University Medical Center, Phoenix, Arizona, USA.
Cardiovascular Research Unit, Mayo Clinic, Rochester, Minnesota, USA.
Division of Biostatistics and Informatics, Mayo Clinic, Rochester, Minnesota, USA.
Duke Clinical Research Institute, Duke University, Durham, North Carolina, USA.
Department of Cardiovascular Medicine, Mayo Clinic, Rochester, Minnesota, USA. Electronic address: Guerrero.mayra@mayo.edu.

BACKGROUND: The MITRAL (Mitral Implantation of Transcatheter Valves) trial is the first prospective study for valve-in-mitral annular calcification (ViMAC), mitral valve-in-ring (MViR), and mitral valve-in-valve (MViV) using balloon-expandable aortic transcatheter heart valves. Procedural outcomes beyond 1 year are not well described. OBJECTIVES: This study evaluated 2-year outcomes in ViMAC, MViR, and MViV in the MITRAL trial. METHODS: This multicenter prospective study enrolled patients with severe MAC, prior failed mitral annuloplasty ring repair, or prior failed bioprosthetic MV replacement who were at high surgical risk at 13 U.S. sites. RESULTS: Between February 1, 2015, and December 31, 2017, 91 patients were enrolled (31 with ViMAC, 30 with MViR, and 30 with MViV). In the ViMAC group, 2-year all-cause mortality was 39.3%, 66.7% were New York Heart Association (NYHA) functional class I-II, and mean MV gradient was 5.6 ± 2.0 mm Hg. In the MViR group, 2-year all-cause mortality was 50%, 65% were NYHA functional class I-II, and mean MV gradient was 6.5 ± 2.7 mm Hg. In the MViV group, 2-year all-cause mortality was 6.7%, 85% were NYHA functional class I-II, and mean MV gradient was 6.9 ± 2.4 mm Hg. At 2 years, all patients had ≤mild mitral regurgitation and survivors in all 3 arms showed sustained improvement in Kansas City Cardiomyopathy Questionnaire scores compared to baseline. CONCLUSIONS: Use of balloon-expandable aortic transcatheter heart valves in selected patients with severe MAC, failed annuloplasty ring, and bioprosthetic MV dysfunction is associated with improvements in symptoms, quality of life, and stable prosthesis function at 2-year follow-up. Between 1 and 2 years, the MViR group experienced higher mortality rates than the MViV and ViMAC groups.

Cardiology/Cardiovascular Research

Hanzel GS, Abbas AE, Schreiber TL, and **O'Neill WW**. Account of the First Transcatheter Aortic Valve Replacement in North America. *JACC Cardiovasc Interv* 2022; 15(23):2440-2444. PMID: 36480987. Full Text

Division of Cardiovascular Medicine, Emory University School of Medicine, Atlanta, Georgia, USA. Electronic address: ghanzel@emory.edu.
Department of Cardiovascular Medicine, Beaumont Hospital, Royal Oak, Beaumont Health and Spectrum Health, Royal Oak, Michigan, USA.
Division of Cardiovascular Medicine, St John Hospital, Detroit, Michigan, USA.
Department of Cardiovascular Medicine, Henry Ford Hospital, Detroit, Michigan, USA.

Cardiology/Cardiovascular Research

Karacsonyi J, Deffenbacher K, Benzuly KH, Flaherty JD, **Alaswad K**, **Basir M**, **Megaly MS**, Jaffer F, Doshi D, Poommipanit P, Khatri J, Patel M, Riley R, Sheikh A, Wollmuth JR, Korngold E, Uretsky BF, Yeh RW, Chandwaney RH, Elguindy AM, Tammam K, AbiRafeh N, Schmidt CW, Okeson B, Kostantinis S, Simsek B, Rangan BV, Brilakis ES, and Schimmel DR. Use of Mechanical Circulatory Support in Chronic Total Occlusion Percutaneous Coronary Intervention. *Am J Cardiol* 2022; 189:76-85. PMID: 36512989. Full Text

Center for Coronary Artery Disease, Minneapolis Heart Institute and Minneapolis Heart Institute Foundation, Abbott Northwestern Hospital, Minneapolis, Minnesota.
Interventional Cardiology, Feinberg School of Medicine, Northwestern University, Chicago, Illinois.
Interventional Cardiology, Henry Ford Hospital, Detroit, Michigan.
Cardiovascular Research Center, Cardiology Division, Massachusetts General Hospital, Boston, Massachusetts.
Cardiac Catheterization Laboratory, University Hospitals, Case Western Reserve University, Cleveland, Ohio.
Cardiovascular Medicine, Cleveland Clinic, Cleveland, Ohio.
Interventional Cardiology, VA San Diego Healthcare System and University of California San Diego, San Diego, California.
Cardiology, Overlake Medical Center, Bellevue, Washington.
Cardiovascular Medicine, Wellstar Health System, Marietta, Georgia.
Interventional Cardiology, Providence Heart Institute, Portland, Oregon.
Interventional Cardiology, Central Arkansas Veterans Healthcare System, and University of Arkansas for Medical Sciences, Little Rock, Arkansas.
Medicine Department, Beth Israe, Deaconess Medical Center, Boston, Massachusetts.
Interventional Cardiology, Oklahoma Heart Institute, Tulsa, Oklahoma.
Department of Cardiology, Aswan Heart Centre, Magdi Yacoub Foundation, Aswan, Egypt.
Interventional Cardiology, International Medical Center, Jeddah, Saudi Arabia.
Cardiology, North Oaks Health System, Hammond, Louisiana.
Interventional Cardiology, Feinberg School of Medicine, Northwestern University, Chicago, Illinois.
Electronic address: dschimme@nm.org.

The use of mechanical circulatory support (MCS) in chronic total occlusion (CTO) percutaneous coronary intervention (PCI) has received limited study. We analyzed the clinical and angiographic characteristics, and procedural outcomes of 7,171 CTO PCIs performed between 2012 and 2021 at 35 international centers. Mean age was 64.5 ± 10 years, mean left ventricular ejection fraction was 50 ± 13%. MCS was used in 4.5%, prophylactically in 78.7%, and urgently in 21.3%. The most common type of MCS overall was Impella CP (Abiomed) (55.5%), followed by intra-aortic balloon pump (14.8%) and TandemHeart (LivaNova Inc.) (10.0%). Prophylactic MCS patients were more likely to have diabetes mellitus (55% vs 42%, p <0.001) and had more complex lesions compared with cases without prophylactic MCS (Japan-CTO score: 2.80 ± 1.22 vs 2.39 ± 1.27, p <0.001). Cases with prophylactic MCS had similar technical (86% vs 87%, p = 0.643) but lower procedural (80% vs 86%, p = 0.028) success rates and higher rates of periprocedural major cardiac adverse events compared with no prophylactic MCS use (6.55% vs 1.68%, p <0.001). Urgent MCS use was associated with lower technical (68% vs 87%, p <0.001) and procedural (39% vs 86%, p <0.001) success rates and higher major cardiac adverse events compared with no-MCS use (32.26% vs 1.68%, p <0.001). The differences persisted in multivariable analyses. In summary, in this contemporary multicenter registry, MCS was used in 4.5% of CTO PCIs, mostly prophylactically (78.7%). Elective MCS cases had similar technical success but a higher risk of complications. Urgent MCS cases had lower technical and procedural success and higher periprocedural major complication rates.

Cardiology/Cardiovascular Research

Maxwell DL, **Bryson TD**, **Taube D**, **Xu J**, **Peterson E**, and **Harding P**. Deleterious effects of cardiomyocyte-specific prostaglandin E2 EP3 receptor overexpression on cardiac function after myocardial infarction. *Life Sci* 2022; 313:121277. PMID: 36521546. Full Text

Department of Physiology, Wayne State University School of Medicine, USA; Hypertension and Vascular Research Division, Department of Internal Medicine, Henry Ford Health, Detroit, MI, USA.
Hypertension and Vascular Research Division, Department of Internal Medicine, Henry Ford Health, Detroit, MI, USA.
Department of Public Health Sciences, Henry Ford Health, Detroit, MI, USA.
Department of Physiology, Wayne State University School of Medicine, USA; Hypertension and Vascular Research Division, Department of Internal Medicine, Henry Ford Health, Detroit, MI, USA. Electronic address: phardin1@hfhs.org.

AIMS: Prostaglandin E2 (PGE2) is a lipid hormone that signals through 4 different G-protein coupled receptor subtypes which act to regulate key physiological processes. Our laboratory has previously reported that PGE2 through its EP3 receptor reduces cardiac contractility at the level of isolated cardiomyocytes and in the isolated working heart preparation. We therefore hypothesized that cardiomyocyte specific overexpression of the PGE2 EP3 receptor further decreases cardiac function in a mouse model of heart failure produced by myocardial infarction. MAIN METHODS: Our study tested this hypothesis using EP3 transgenic mice (EP3 TG), which overexpress the porcine analogue of human EP3 in the cardiomyocytes, and their wildtype (WT) littermates. Mice were analyzed 2 wks after myocardial infarction (MI) or sham operation by echocardiography, RT-PCR, immunohistochemistry, and histology. KEY FINDINGS: We found that the EP3 TG sham controls had a reduced ejection fraction, reduced fractional shortening, and an increased left ventricular dimension at systole and diastole compared to the WT sham controls. Moreover, there was a further reduction in the EP3 TG mice after myocardial infarction. Additionally, single-cell analysis of cardiomyocytes isolated from EP3 TG mice showed reduced contractility under basal conditions. Overexpression of EP3 significantly increased cardiac hypertrophy, interstitial collagen fraction, macrophage, and T-cell infiltration in the sham operated group. Interestingly, after MI, there were no changes in hypertrophy but there were changes in collagen fraction, and inflammatory cell infiltration. SIGNIFICANCE: Overexpression of EP3 reduces cardiac function under basal conditions and this is exacerbated after myocardial infarction.

Cardiology/Cardiovascular Research

Mehra MR, Nayak A, Morris AA, **Lanfear DE**, **Nemeh H**, Desai S, Bansal A, Guerrero-Miranda C, Hall S, Cleveland JC, Jr., Goldstein DJ, Uriel N, Chen L, Bailey S, Anyanwu A, Heatley G, Chuang J, and Estep JD. Prediction of Survival After Implantation of a Fully Magnetically Levitated Left Ventricular Assist Device. *JACC Heart Fail* 2022; 10(12):948-959. PMID: 36456068. Full Text

Brigham and Women's Hospital, Boston, Massachusetts, USA. Electronic address: mmehra@bwh.harvard.edu.
Emory University, Atlanta, Georgia, USA.
Henry Ford Hospital, Detroit, Michigan, USA.
Ochsner Medical Center, New Orleans, Louisiana, USA.
Baylor University Medical Center, Dallas, Texas, USA.
University of Colorado School of Medicine, Aurora, Colorado, USA.
Montefiore Einstein Center for Heart and Vascular Care, New York, New York, USA.
NewYork-Presbyterian Hospital, Columbia University College of Physicians and Surgeons, New York, New York, USA.
University of Rochester Medical Center, Rochester, New York, USA.
Allegheny Health Network, Pittsburgh, Pennsylvania.
Icahn School of Medicine at Mount Sinai, New York, New York, USA.
Abbott, Abbott Park, Illinois, USA.
Cleveland Clinic Florida, Weston, Florida, USA.

BACKGROUND: Clinical trials inform on average efficacy, but individualized risk assessments for outcome prediction are important in guiding treatment implementation. OBJECTIVES: The authors developed and validated a patient-specific risk score to predict survival at 1 and 2 years after HeartMate 3 (HM3) left ventricular assist device (LVAD) implantation. METHODS: The MOMENTUM 3 (Multicenter Study of MagLev Technology in Patients Undergoing Mechanical Circulatory Support Therapy with HeartMate 3) trial includes 2,200 HM3 LVAD patients in the pivotal trial and Continued Access Protocol

study (2014-2018). The authors randomly assigned all patients to a derivation cohort (n = 1,540) or validation cohort (n = 660). Univariate mortality predictors were screened for potential model inclusion, stepwise selection was used to build the multivariable Cox proportional hazards regression model, and performance (discrimination and calibration) was evaluated. RESULTS: Age, prior cardiac surgery (coronary artery bypass grafting [CABG] or valve procedure), lower serum sodium, higher blood urea nitrogen (BUN), small left ventricular size, and right atrial pressure-to-pulmonary capillary wedge pressure (RAP/PCWP) ratio >0.6 were significant risk factors for mortality. Receiver-operating characteristic (ROC) analysis in the validation cohort demonstrated an area under the curve (AUC) of 0.76 (95% CI: 0.70-0.81) at 1 year and 0.71 (95% CI: 0.66-0.77) at 2 years. Calibration between predicted and observed survival of the risk quintiles was high, with Pearson correlation coefficients of 0.986 and 0.994 at 1 and 2 years, respectively. Patients were successfully stratified into tertiles with higher-than-average, average, and lower-than-average survival, and observed mortality risk increased by 2-fold from one tertile to the next. CONCLUSIONS: A practical, easy-to-use HM3 Survival Risk Score with 6 components was developed to accurately predict 1- and 2-year survival after HM3 LVAD implantation. The survival risk score can be used to provide individual survival estimates to facilitate shared decision making when considering HM3 LVAD therapy. (MOMENTUM 3 Trial Portfolio; NCT02224755, NCT02892955).

Cardiology/Cardiovascular Research

Torpoco Rivera DM, **Williams CT**, and Karpawich PP. TTR Val142Ile: Bystander Genetic Finding or Diagnosis? Response to Editor. *Pediatr Cardiol* 2022; Epub ahead of print. PMID: 36583756. Full Text

Division of Cardiology, The Children's Hospital of Michigan, 3901 Beaubien Boulevard, Detroit, MI, 48201, USA.
Department of Pediatrics, Central Michigan University College of Medicine, Mount Pleasant, MI, USA.
Division of Cardiology, Henry Ford Health, Detroit, MI, USA. cwillia6@hfhs.org.

Cardiology/Cardiovascular Research

Zile MR, Mehra MR, Ducharme A, Sears SF, Desai AS, Maisel A, Paul S, Smart F, **Grafton G**, Kumar S, Nossuli TO, Johnson N, Henderson J, Adamson PB, Costanzo MR, and Lindenfeld J. Hemodynamically-Guided Management of Heart Failure Across the Ejection Fraction Spectrum: The GUIDE-HF Trial. *JACC Heart Fail* 2022; 10(12):931-944. PMID: 36456066. Full Text

Medical University of South Carolina, RJH Department of Veterans Affairs Medical Center, Charleston, South Carolina, USA. Electronic address: zilem@musc.edu.
Cardiology Division, Brigham and Women's Hospital, and Harvard Medical School, Boston, Massachusetts, USA.
Montreal Heart Institute, Université de Montréal, Montreal, Quebec, Canada.
East Carolina University, Greenville, North Carolina, USA.
University of California-San Diego, La Jolla, California, USA.
Catawba Valley Health System, Conover, North Carolina, USA.
Louisiana State University School of Medicine, New Orleans, Louisiana, USA.
Henry Ford Hospital, Detroit, Michigan, USA.
Memorial Hermann Hospital, Houston, Texas, USA.
The Heart Group of Lancaster General Health, Lancaster, Pennsylvania, USA.
Abbott, Abbott Park, Illinois, USA.
Midwest Cardiovascular Institute, Naperville, Illinois, USA.
Vanderbilt Heart and Vascular Institute, Nashville, Tennessee, USA.

BACKGROUND: Hemodynamically-guided management using an implanted pulmonary artery pressure sensor is indicated to reduce heart failure (HF) hospitalizations in patients with New York Heart Association (NYHA) functional class II-III with a prior HF hospitalization or those with elevated natriuretic peptides. OBJECTIVES: The authors sought to evaluate the effect of left ventricular ejection fraction (EF) on treatment outcomes in the GUIDE-HF (Hemodynamic-GUIDEd management of Heart Failure) randomized trial. METHODS: The GUIDE-HF randomized arm included 1,000 NYHA functional class II-IV patients (with HF hospitalization within the prior 12 months or elevated natriuretic peptides adjusted for EF and body mass index) implanted with a pulmonary artery pressure sensor, randomized 1:1 to a

hemodynamically-guided management group (treatment) or a control group (control). The primary endpoint was the composite of HF hospitalizations, urgent HF visits, and all-cause mortality at 12 months. The authors assessed outcomes by EF in guideline-defined subgroups ≤40%, 41%-49%, and ≥50%, within the trial specified pre-COVID-19 period cohort. RESULTS: There were 177 primary events (0.553/patient-year) in the treatment group and 224 events (0.682/patient-year) in the control group (HR: 0.81 [95% CI: 0.66-1.00]; P = 0.049); HF hospitalization was lower in the treatment vs control group (HR: 0.72 [95% CI: 0.57-0.92]; P = 0.0072). Within each EF subgroup, primary endpoint and HF hospitalization rates were lower in the treatment group (HR <1.0 across the EF spectrum). Event rate reduction by EF in the treatment groups was correlated with reduction in pulmonary artery pressures and medication changes. CONCLUSIONS: Hemodynamically-guided HF management decreases HF-related endpoints across the EF spectrum in an expanded patient population of patients with HF. (Hemodynamic-GUIDEd Management of Heart Failure [GUIDE-HF]; NCT03387813).

Center for Health Policy and Health Services Research

Danysh HE, Johannes CB, Beachler DC, Layton JB, Ziemiecki R, Arana A, Dinh J, Li L, Calingaert B, **Pladevall-Vila M**, Hunt PR, Chen H, Karlsson C, Johnsson K, and Gilsenan A. Post-Authorization Safety Studies of Acute Liver Injury and Severe Complications of Urinary Tract Infection in Patients with Type 2 Diabetes Exposed to Dapagliflozin in a Real-World Setting. *Drug Saf* 2022; Epub ahead of print. PMID: 36583828. Full Text

Department of Pharmacoepidemiology and Risk Management, RTI Health Solutions, 307 Waverley Oaks Road, Suite 101, Waltham, MA, 02452-8413, USA. hdanysh@rti.org.
Department of Pharmacoepidemiology and Risk Management, RTI Health Solutions, 307 Waverley Oaks Road, Suite 101, Waltham, MA, 02452-8413, USA.
Department of Safety and Epidemiology, HealthCore, Inc., Wilmington, DE, USA.
Department of Pharmacoepidemiology and Risk Management, RTI Health Solutions, Research Triangle Park, NC, USA.
Department of Biostatistics, RTI Health Solutions, Research Triangle Park, NC, USA.
Department of Pharmacoepidemiology and Risk Management, RTI Health Solutions, Barcelona, Spain.
Department of Research Operations, HealthCore, Inc., Wilmington, DE, USA.
The Center for Health Policy and Health Services Research, Henry Ford Health System, Detroit, MI, USA.
BioPharmaceuticals Business Unit, AstraZeneca, Gaithersburg, MD, USA.
BioPharmaceuticals R&D, AstraZeneca, Gothenburg, Sweden.

INTRODUCTION: At the time of dapagliflozin's approval in Europe (2012) to treat patients with type 2 diabetes mellitus, concerns regarding acute liver injury and severe complications of urinary tract infection (sUTI) led to two post-authorization safety (PAS) studies of these outcomes to monitor the safety of dapagliflozin in real-world use. OBJECTIVE: To investigate the incidence of hospitalization for acute liver injury (hALI) or sUTI (pyelonephritis or urosepsis) among patients initiating dapagliflozin compared with other glucose-lowering drugs (GLDs). METHODS: These two noninterventional cohort studies identified initiators of dapagliflozin and comparator GLDs in November 2012-February 2019 using data from three longitudinal, population-based data sources: Clinical Practice Research Datalink (UK), the HealthCore Integrated Research Database (USA), and the Medicare database (USA). Outcomes (hALI and sUTI) were identified with electronic algorithms. Incidence rates were estimated by exposure group. Incidence rate ratios (IRRs) were calculated comparing dapagliflozin to comparator GLDs, using propensity score trimming and stratification to address confounding. The sUTI analyses were conducted separately by sex. RESULTS: In all data sources, hALI and sUTI incidence rates were generally lower in dapagliflozin initiators than comparator GLD initiators. The adjusted IRR (95% confidence interval) pooled across data sources for hALI was 0.85 (0.59-1.24) and for sUTI was 0.76 (0.60-0.96) in females and 0.74 (0.56-1.00) in males. Findings from sensitivity analyses were largely consistent with the primary analyses. CONCLUSIONS: These real-world studies do not suggest increased risks of hALI or sUTI, and they suggest a potential decreased risk of sUTI with dapagliflozin exposure compared with other GLDs.

Center for Health Policy and Health Services Research

Drake CL, **Kalmbach DA**, **Cheng P**, **Ahmedani BK**, **Peterson EL**, **Joseph CLM**, **Roth T**, Kidwell KM, and **Sagong C**. Sleep to Reduce Incident Depression Effectively (STRIDE): study protocol for a randomized controlled trial comparing stepped-care cognitive-behavioral therapy for insomnia versus sleep education control to prevent major depression. *Trials* 2022; 23(1):967. PMID: 36457045. Full Text

Thomas Roth Sleep Disorders & Research Center, Henry Ford Health, Detroit, MI, 48202, USA. cdrake1@hfhs.org.
Thomas Roth Sleep Disorders & Research Center, Henry Ford Health, Detroit, MI, 48202, USA.
Center for Health Policy & Health Services Research, Henry Ford Health, Detroit, MI, 48202, USA.
Department of Public Health Services, Henry Ford Health, Detroit, MI, 48202, USA.
Department of Biostatistics, University of Michigan, Ann Arbor, MI, 48109, USA.

BACKGROUND: Prevention of major depressive disorder (MDD) is a public health priority. Strategies targeting individuals at elevated risk for MDD may guide effective preventive care. Insomnia is a reliable precursor to depression, preceding half of all incident and relapse cases. Thus, insomnia may serve as a useful entry point for preventing MDD. Cognitive-behavioral therapy for insomnia (CBT-I) is recommended as the first-line treatment for insomnia, but widespread implementation is limited by a shortage of trained specialists. Innovative stepped-care approaches rooted in primary care can increase access to CBT-I and reduce rates of MDD. METHODS/DESIGN: We propose a large-scale stepped-care clinical trial in the primary care setting that utilizes a sequential, multiple assignment, randomized trial (SMART) design to determine the effectiveness of dCBT-I alone and in combination with clinician-led CBT-I for insomnia and the prevention of MDD incidence and relapse. Specifically, our care model uses digital CBT-I (dCBT-I) as a first-line intervention to increase care access and reduce the need for specialist resources. Our proposal also adds clinician-led CBT-I for patients who do not remit with first-line intervention and need a more personalized approach from specialty care. We will evaluate negative repetitive thinking as a potential treatment mechanism by which dCBT-I and CBT-I benefit insomnia and depression outcomes. DISCUSSION: This project will test a highly scalable model of sleep care in a large primary care system to determine the potential for wide dissemination and implementation to address the high volume of population need for safe and effective insomnia treatment and associated prevention of depression. TRIAL REGISTRATION: ClinicalTrials.gov NCT03322774. Registered on October 26, 2017.

Center for Health Policy and Health Services Research

Hecht LM, Schruff MA, Young J, **Carlin AM**, and **Miller-Matero LR**. Psychometric Evaluation of a Measure of Health Numeracy Among Individuals Seeking Bariatric Surgery. *Obes Surg* 2022; Epub ahead of print. PMID: 36562961. Full Text

Center for Health Policy and Health Services Research, Henry Ford Health, Detroit, MI, 48202, USA. lhecht1@hawk.iit.edu.
Department of Psychology, University of Mississippi, University, Oxford, MS, 38677, USA.
Department of Surgery, Henry Ford Health, Detroit, MI, 48202, USA.
Center for Health Policy and Health Services Research, Henry Ford Health, Detroit, MI, 48202, USA.
Behavioral Health, Henry Ford Health, Detroit, MI, 48202, USA.

Center for Health Policy and Health Services Research

Johannes CB, Beachler DC, Layton JB, Danysh HE, Ziemiecki R, Arana A, Dinh J, Li L, Calingaert B, **Pladevall-Vila M**, Hunt PR, Chen H, Karlsson C, Johnsson K, and Gilsenan A. Post-Authorization Safety Study of Hospitalization for Acute Kidney Injury in Patients with Type 2 Diabetes Exposed to Dapagliflozin in a Real-World Setting. *Drug Saf* 2022; Epub ahead of print. PMID: 36528670. Full Text

Department of Pharmacoepidemiology and Risk Management, RTI Health Solutions, 307 Waverley Oaks Road, Suite 101, Waltham, MA, 02452, USA. cjohannes@rti.org.
Department of Safety and Epidemiology, HealthCore, Inc., Wilmington, DE, USA.
Department of Pharmacoepidemiology and Risk Management, RTI Health Solutions, Research Triangle Park, NC, USA.

Department of Pharmacoepidemiology and Risk Management, RTI Health Solutions, 307 Waverley Oaks Road, Suite 101, Waltham, MA, 02452, USA.
Department of Biostatistics, RTI Health Solutions, Research Triangle Park, NC, USA.
Department of Pharmacoepidemiology and Risk Management, RTI Health Solutions, Barcelona, Spain.
Department of Research Operations, HealthCore, Inc., Wilmington, DE, USA.
The Center for Health Policy and Health Services Research, Henry Ford Health System, Detroit, MI, USA.
BioPharmaceuticals Business Unit, AstraZeneca, Gaithersburg, MD, USA.
BioPharmaceuticals R&D, AstraZeneca, Gothenburg, Sweden.

INTRODUCTION: Dapagliflozin is a sodium-glucose cotransporter 2 inhibitor approved to treat type 2 diabetes mellitus (T2DM), among other conditions. When dapagliflozin was approved in Europe for treating T2DM (2012), potential safety concerns regarding its effect on kidney function resulted in this post-authorization safety study to assess hospitalization for acute kidney injury (hAKI) among dapagliflozin initiators in a real-world setting. OBJECTIVE: The aim of this study was to evaluate the incidence of hAKI in adults with T2DM initiating dapagliflozin compared with other glucose-lowering drugs (GLDs). METHODS: This noninterventional cohort study identified new users of dapagliflozin and comparator GLDs from November 2012 to February 2019 from three longitudinal, population-based data sources: Clinical Practice Research Datalink (CPRD; United Kingdom), the HealthCore Integrated Research Database (HIRD; United States [US]), and Medicare (US). Electronic algorithms identified occurrences of hAKI, from which a sample underwent validation. Incidence rates for hAKI were calculated, and incidence rate ratios (IRRs) compared hAKI in dapagliflozin with comparator GLDs. Propensity score trimming and stratification were conducted for confounding adjustment. RESULTS: In all data sources, dapagliflozin initiators had a lower hAKI incidence rate than comparator GLD initiators (adjusted IRRs: CPRD, 0.44 [95% confidence interval (CI), 0.22-0.86]; HIRD, 0.76 [95% CI, 0.62-0.93]; Medicare, 0.69 [95% CI, 0.59-0.79]). The adjusted IRR pooled across the data sources was 0.70 (95% CI, 0.62-0.78). Results from sensitivity and stratified analyses were consistent with the primary analysis. CONCLUSIONS: This study, with > 34,000 person-years of real-world dapagliflozin exposure, suggests a decreased risk of hAKI in patients with T2DM exposed to dapagliflozin, aligning with results from dapagliflozin clinical trials. STUDY REGISTRATION: European Union Post-Authorisation Studies Register, EUPAS 11684; ClinicalTrials.gov, NCT02695082.

Center for Health Policy and Health Services Research
Liberman JN, Pesa J, Rui P, Teeple A, Lakey S, Wiggins E, and **Ahmedani B**. Predicting Poor Outcomes Among Individuals Seeking Care for Major Depressive Disorder. *Psychiatr Res Clin Pract* 2022; 4(4):102-112. PMID: 36545504. Full Text

Health Analytics, LLC Clarksville Maryland USA.
Janssen Scientific Affairs Titusville New Jersey.
Henry Ford Health System Detroit Michigan.

OBJECTIVE: To develop and validate algorithms to identify individuals with major depressive disorder (MDD) at elevated risk for suicidality or for an acute care event. METHODS: We conducted a retrospective cohort analysis among adults with MDD diagnosed between January 1, 2018 and February 28, 2019. Generalized estimating equation models were developed to predict emergency department (ED) visit, inpatient hospitalization, acute care visit (ED or inpatient), partial-day hospitalization, and suicidality in the year following diagnosis. Outcomes (per 1000 patients per month, PkPPM) were categorized as all-cause, psychiatric, or MDD-specific and combined into composite measures. Predictors included demographics, medical and pharmacy utilization, social determinants of health, and comorbid diagnoses as well as features indicative of clinically relevant changes in psychiatric health. Models were trained on data from 1.7M individuals, with sensitivity, positive predictive value, and area-under-the-curve (AUC) derived from a validation dataset of 0.7M. RESULTS: Event rates were 124.0 PkPPM (any outcome), 21.2 PkPPM (psychiatric utilization), and 7.6 PkPPM (suicidality). Among the composite models, the model predicting suicidality had the highest AUC (0.916) followed by any psychiatric acute care visit (0.891) and all-cause ED visit (0.790). Event-specific models all achieved an AUC >0.87, with the highest AUC noted for partial-day hospitalization (AUC = 0.938). Select predictors of all three outcomes included younger age, Medicaid insurance, past psychiatric ED visits, past suicidal ideation,

and alcohol use disorder diagnoses, among others. CONCLUSIONS: Analytical models derived from clinically-relevant features identify individuals with MDD at risk for poor outcomes and can be a practical tool for health care organizations to divert high-risk populations into comprehensive care models.

Center for Health Policy and Health Services Research
Squires M, **Schultz L**, **Schwalb J**, Park P, **Chang V**, **Nerenz D**, Perez-Cruet M, **Abdulhak M**, Khalil J, and Aleem I. Correlation of mJOA, PROMIS Physical Function, and Patient Satisfaction in Patients with Cervical Myelopathy: An Analysis of the Michigan Spine Surgery Improvement Collaborative (MSSIC) Database. *Spine J* 2022; Epub ahead of print. PMID: 36567055. Full Text

Department of Orthopedic Surgery, University of Michigan, 1500 E Medical Center Dr, Ann Arbor, MI 48109, USA. Electronic address: mdsquire@med.umich.edu.
Henry Ford Health System, 1 Ford Place, Detroit, MI 48202, USA. Electronic address: LSCHULT1@hfhs.org.
Henry Ford Health System, 1 Ford Place, Detroit, MI 48202, USA. Electronic address: JSCHWAL1@hfhs.org.
Department of Neurosurgery, University of Michigan, 1500 E Medical Center Dr, Ann Arbor, MI 48109, USA. Electronic address: ppark@med.umich.edu.
Henry Ford Health System, 1 Ford Place, Detroit, MI 48202, USA. Electronic address: VCHANG1@hfhs.org.
Henry Ford Health System, 1 Ford Place, Detroit, MI 48202, USA. Electronic address: DNERENZ1@hfhs.org.
Beaumont Health System, 3601 W. 13 Mile Rd., Royal Oak, MI 48073, USA. Electronic address: Miguelangelo.Perez-Cruet@beaumont.edu.
Henry Ford Health System, 1 Ford Place, Detroit, MI 48202, USA. Electronic address: MABDULH1@hfhs.org.
Beaumont Health System, 3601 W. 13 Mile Rd., Royal Oak, MI 48073, USA. Electronic address: Jad.Khalil@beaumont.org.
Department of Orthopedic Surgery, University of Michigan, 1500 E Medical Center Dr, Ann Arbor, MI 48109, USA. Electronic address: ialeem@med.umich.edu.

BACKGROUND CONTEXT: Patient-reported outcomes (PROs) are increasingly utilized to evaluate the efficacy and value of spinal procedures. Among patients with cervical myelopathy, the modified Japanese Orthopaedic Association (mJOA) remains the standard instrument, with Patient-Reported Outcomes Measurement Information System (PROMIS) physical function (PF) and patient satisfaction also frequently assessed. These outcomes have not all been directly compared using a large spine registry at 2 years follow-up for cervical myelopathic patients undergoing surgery. PURPOSE: To determine the correlation and association of PROMIS PF, mJOA, and patient satisfaction outcomes in patients undergoing surgery for cervical myelopathy. STUDY DESIGN/SETTING: Retrospective review of a multi-center spine registry database. PATIENT SAMPLE: Adult patients with cervical myelopathy who underwent cervical spine surgery between 2/26/2018 and 4/17/2021. OUTCOME MEASURES: PROMIS PF, mJOA, and North American Spine Society (NASS) patient satisfaction index. METHODS: The MSSIC database was accessed to gather pre- and postoperative outcome data on patients with cervical myelopathy. Spearman's correlation coefficients relating mJOA and PROMIS PF were quantified up to 2 years postoperatively. The effect sizes of the relationship between patient satisfaction with mJOA and PROMIS were determined. Kappa statistics were used to evaluate for agreement between those reaching the minimum clinically important difference (MCID) for mJOA and PROMIS PF. Odds ratios were calculated to determine the association between patient satisfaction and those reaching MCID for mJOA and PROMIS PF. Support for MSSIC is provided by BCBSM and Blue Care Network as part of the BCBSM Value Partnerships program. RESULTS: Data from 2023 patients were included. Moderate to strong correlations were found between mJOA and PROMIS PF at all time points ($p<0.001$). These outcomes had fair agreement at all postoperative time points when comparing those who reached MCID. Satisfaction was strongly related to changes from baseline for both mJOA and PROMIS PF at all time points ($p<0.001$). Odds ratios associating satisfaction with PROMIS PF MCID were higher at all time points compared to mJOA, although the differences were not significant. CONCLUSIONS: PROMIS PF has a strong positive correlation with mJOA up to 2 years postoperatively in patients undergoing surgery

for cervical myelopathy, with similar odds of achieving MCID with both instruments. Patient satisfaction is predicted similarly by these outcome measures by 2 years postoperatively. These results affirm the validity of PROMIS PF in the cervical myelopathic population. Given its generalizability and ease of use, PROMIS PF may be a more practical outcome measure for clinical use compared to mJOA.

Center for Health Policy and Health Services Research
Vázquez-Otero C, and **Lockhart E**. The adoption of the HPV vaccine school-entry requirement in Puerto Rico: How practical lessons can inform future vaccine policies. *Prev Med Rep* 2022; 30:102025. PMID: 36325250. Full Text

Department of Public Health, College for Health, Community and Policy, The University of Texas at San Antonio, TX, USA.
Henry Ford Health System, Detroit, MI, USA.

Vaccine requirements are policy-level strategies used to improve population health outcomes; however, discourse politicization of vaccines may hinder adoption and implementation. An example of the complexities related to adoption of vaccine policies in the United States (US) is the human papillomavirus (HPV) vaccine school-entry requirement. In 2018, Puerto Rico's (PR) Department of Health adopted this policy. This study assessed stakeholders' recommendations for adoption of the HPV vaccine school-entry requirement that could inform future vaccine policies. Stakeholders (e.g., researchers, members of medical and non-profit organizations) were interviewed from May to August 2018. Participants (n = 20) discussed recommendations for public health professionals interested in adopting such policy. Data were analyzed using applied thematic techniques. Participants emphasized the importance of raising HPV vaccine awareness and providing education prior to the requirement. They recommended using real stories and making the problem relevant by using local data. Participants recommended considering the local culture and government bureaucracies, and promoting multisectoral collaborations to combine limited resources. The combination of education efforts, local data, and multisectoral collaborations facilitated the adoption of the HPV vaccine school-entry requirement in PR. Findings highlight the need to understand the contextual distinctions of the communities where vaccination requirements may be adopted and implemented to anticipate barriers and leverage existing resources. Consideration of the politico-cultural context may be important as political beliefs have become entrenched with vaccine policy. These practical lessons can inform public health professionals and policymakers who are seeking to adopt and implement vaccine policies in other settings to ensure equitable vaccine access.

Center for Health Policy and Health Services Research
Wartko PD, Qiu H, Idu AE, Yu O, McCormack J, Matthews AG, Bobb JF, Saxon AJ, Campbell CI, Liu D, **Braciszewski JM**, Murphy SM, Burganowski RP, Murphy MT, Horigian VE, Hamilton LK, Lee AK, Boudreau DM, and Bradley KA. Baseline representativeness of patients in clinics enrolled in the PRimary care Opioid Use Disorders treatment (PROUD) trial: comparison of trial and non-trial clinics in the same health systems. *BMC Health Serv Res* 2022; 22(1):1593. PMID: 36581845. Full Text

Kaiser Permanente Washington Health Research Institute, 1730 Minor Ave, Ste 1600, Seattle, WA, 98101, United States. paige.d.wartko@kp.org.
Kaiser Permanente Washington Health Research Institute, 1730 Minor Ave, Ste 1600, Seattle, WA, 98101, United States.
Department of Biostatistics, University of Washington, 1705 NE Pacific Street, Seattle, WA, 98195, United States.
Department of Statistics and Data Science, University of Pennsylvania, 3451 Walnut St Philadelphia, Philadelphia, PA, 19104, United States.
The Emmes Company, 401 N Washington St #700, Rockville, MD, 20850, United States.
Center of Excellence in Substance Addiction Treatment and Education, VA Puget Sound Health Care System, 1660 S Columbian Way, Seattle, WA, 98108, United States.
Kaiser Permanente Northern California Division of Research, 2000 Broadway, Oakland, CA, 94612, United States.
National Institute on Drug Abuse Center for Clinical Trials Network, Three White Flint North, 11601 Landsdown Street, North Bethesda, MD, 20852, United States.

Henry Ford Health, One Ford Place, Suite 3A, Detroit, MI, 48202, United States.
Department of Population Health Sciences, Weill Cornell Medical College, 1300 York Ave, New York, NY, 10065, United States.
MultiCare Health System, 315 Martin Luther King Jr. Way, Tacoma, WA, 98415, United States.
Department of Public Health Sciences, Miller School of Medicine, University of Miami, 1120 NW 14th St, CRB 919, Miami, FL, 33136, United States.
Genentech, 1 DNA Way, South San Francisco, CA, 94080, United States.

BACKGROUND: Pragmatic primary care trials aim to test interventions in "real world" health care settings, but clinics willing and able to participate in trials may not be representative of typical clinics. This analysis compared patients in participating and non-participating clinics from the same health systems at baseline in the PRimary care Opioid Use Disorders treatment (PROUD) trial. METHODS: This observational analysis relied on secondary electronic health record and administrative claims data in 5 of 6 health systems in the PROUD trial. The sample included patients 16-90 years at an eligible primary care visit in the 3 years before randomization. Each system contributed 2 randomized PROUD trial clinics and 4 similarly sized non-trial clinics. We summarized patient characteristics in trial and non-trial clinics in the 2 years before randomization ("baseline"). Using mixed-effect regression models, we compared trial and non-trial clinics on a baseline measure of the primary trial outcome (clinic-level patient-years of opioid use disorder (OUD) treatment, scaled per 10,000 primary care patients seen) and a baseline measure of the secondary trial outcome (patient-level days of acute care utilization among patients with OUD). RESULTS: Patients were generally similar between the 10 trial clinics (n = 248,436) and 20 non-trial clinics (n = 341,130), although trial clinics' patients were slightly younger, more likely to be Hispanic/Latinx, less likely to be white, more likely to have Medicaid/subsidized insurance, and lived in less wealthy neighborhoods. Baseline outcomes did not differ between trial and non-trial clinics: trial clinics had 1.0 more patient-year of OUD treatment per 10,000 patients (95% CI: - 2.9, 5.0) and a 4% higher rate of days of acute care utilization than non-trial clinics (rate ratio: 1.04; 95% CI: 0.76, 1.42). CONCLUSIONS: trial clinics and non-trial clinics were similar regarding most measured patient characteristics, and no differences were observed in baseline measures of trial primary and secondary outcomes. These findings suggest trial clinics were representative of comparably sized clinics within the same health systems. Although results do not reflect generalizability more broadly, this study illustrates an approach to assess representativeness of clinics in future pragmatic primary care trials.

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 Multi-Ancestry Genome-Wide Association Study in the Diabetes Prevention Program (DPP). *Diabetes* 2022; Epub ahead of print. PMID: 36525397. Full Text

Center for Genomic Medicine, Massachusetts General Hospital, Boston, Massachusetts.
Diabetes Unit, Department of Medicine, Massachusetts General Hospital, Boston, Massachusetts.
Programs in Metabolism and Medical & Population Genetics, Broad Institute of Harvard and MIT, Cambridge, Massachusetts.
Department of Medicine, Harvard Medical School, Boston, Massachusetts.
Department of Medicine, University of Maryland School of Medicine, Baltimore, Maryland.
Department of Epidemiology and Biostatistics, George Washington University Biostatistics Center, Washington, District of Columbia.
Division of Pediatric Endocrinology and Diabetes, Department of Pediatrics, University of California at San Francisco, San Francisco, California.
Division of Population Health and Genomics, Ninewells Hospital and School of Medicine, University of Dundee, Dundee, Scotland, U.K.
Department of Bioengineering and Therapeutic Sciences, University of California at San Francisco, San Francisco, California.
Division of Quantitative Sciences, Department of Obstetrics and Gynecology, Vanderbilt University Medical Center, Nashville, Tennessee.

Division of Nephrology and Hypertension, Department of Medicine, Vanderbilt University Medical Center, Nashville, Tennessee.
Center for Individualized and Genomic Medicine Research (CIGMA), Department of Internal Medicine, Henry Ford Health System, Detroit, Michigan.
Genetic and Molecular Epidemiology Unit, Lund University Diabetes Centre, Lund University, Malmo, Sweden.
Diabetes Epidemiology and Clinical Research Section, National Institute of Diabetes and Digestive and Kidney Diseases, Phoenix, Arizona.
Division of Metabolism, Endocrinology and Nutrition, Department of Medicine, VA Puget Sound Health Care System and University of Washington, Seattle, Washington.

Genome-wide significant loci for metformin response in type 2 diabetes reported elsewhere have not replicated in the Diabetes Prevention Program (DPP). To assess pharmacogenetic interactions in pre-diabetes, we conducted a genome-wide association study (GWAS) in the DPP. Cox proportional hazards models tested associations with diabetes incidence in metformin (MET, n=876) and placebo (PBO, n=887) arms. Multiple linear regression assessed association with one-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 ($p<9\times10^{-9}$). In MET, rs144322333 near ENOSF1 (minor allele frequency [MAF]AFR=0.07, MAFEUR=0.002) was associated with an increase in % glycated hemoglobin (per minor allele β=0.39 [95% CI 0.28, 0.50], $p=2.8\times10^{-12}$). Rs145591055 near OMSR (MAF=0.10 in American Indians), was associated with weight loss (kg) (per G allele β=-7.55 [95% CI -9.88, -5.22], $p=3.2\times10^{-10}$) in MET. Neither variant was significant in PBO; gene-by-treatment interaction was significant for both variants ($p(G\times T)<1.0\times10^{-4}$). Replication in individuals with diabetes did not yield significant findings. A GWAS for metformin response in pre-diabetes revealed novel ethnic-specific associations that require further investigation but may have implications for tailored therapy.

Clinical Quality and Safety

Condon M, **Smith N**, **Ayyash M**, and **Goyert G**. The impact of COVID-19 vaccinations on stillbirth rates among pregnant women in the Metro-Detroit area. *J Natl Med Assoc* 2022; Epub ahead of print. PMID: 36581519. Full Text

Department of Clinical Quality and Safety, Henry Ford Health System, Detroit, MI, United States.
Department of Women's Health, Henry Ford Hospital, Detroit, MI, United States. Electronic address: NSmith22@hfhs.org.
Department of Women's Health, Henry Ford Hospital, Detroit, MI, United States.
Department of Maternal Fetal Medicine, Henry Ford Hospital, Detroit, MI, United States.

Infection by COVID-19 increases maternal morbidity and mortality prompting both the American College of Obstetrics and Gynecology and the Society of Maternal Fetal Medicine to strongly recommend vaccination during pregnancy. Limited data exist assessing the risk of intrauterine fetal death (IUFD) associated with COVID vaccination during pregnancy. This was a retrospective chart review at a large multisite hospital system in Metro Detroit which reviewed data from 13,368 pregnancies. We compared IUFD rates between vaccinated and unvaccinated patients. The rate of stillbirths among unvaccinated women (0.75%) was not statistically different from those who were vaccinated (0.60%). Individuals with government insurance were less likely to be vaccinated and more likely to have IUFD in comparison to patients with private insurance. The rate of stillbirths among Black women was significantly higher than among White women at a rate of 1.1% compared to 0.53% (p=0.008) with no difference in stillbirth rates among vaccinated vs unvaccinated racial distribution. Lastly, it is worth noting that the overall vaccination rate at our healthcare system in pregnancy was very poor (0.26%). In conclusion, this is a large population of highly diverse patients which indicates that COVID-19 vaccination does not lead to IUFD. We plan to use this data to help drive an educational vaccination campaign to try to increase our COVID-19 vaccination rate in our pregnant patients. Systemic racism and social determinants of health have played a large factor in COVID-19 outcomes, and our data highlights that this is the case for IUFD in Black women. Improvements must be made to identify barriers for these women to allow for better

pregnancy outcomes. We acknowledge that individuals with government insurance may also have other barriers to healthcare or face healthcare inequity which leaves room for improvement on getting these individuals vaccinated and getting the resources they need to have better pregnancy outcomes.

Dermatology
Dozier L, **Ceresnie M**, Habashy J, and Kerdel F. Improvement of refractory pyoderma gangrenosum with adjunctive maggot debridement therapy. *Int J Dermatol* 2022; Epub ahead of print. PMID: 36468819. Full Text

Department of Dermatology, Larkin Community Hospital/Lake Erie College of Osteopathic Medicine Graduate Medical Education, South Miami, FL, USA.
Department of Dermatology, Henry Ford Hospital, Detroit, MI, USA.
Department of Dermatology, Florida International University, Miami, FL, USA.
Florida Academic Dermatology Center, Coral Gables, FL, USA.

Dermatology
Haque MZ, Rehman R, **Guan L**, and **Kerr H**. Recommendations to Optimize Patient Education for Allergic Contact Dermatitis: Our Approach. *Contact Dermatitis* 2022; Epub ahead of print. PMID: 36533894. Full Text

Michigan State University College of Human Medicine, East Lansing, MI, USA.
Department of Dermatology, Wayne State University School of Medicine, Detroit, MI, USA.
Department of Dermatology, Henry Ford Hospital, Detroit, MI, USA.

Dermatology
Midgette B, Strunk A, Akilov O, Alavi A, Ardon C, Bechara FG, Cohen AD, Cohen S, Daveluy S, Del Marmol V, Delage M, Esmann S, Fisher S, Giamarellos-Bourboulis EJ, Glowaczewska A, Goldfarb N, Brant EG, Grimstad Ø, Guilbault S, **Hamzavi I**, Hughes R, Ingram JR, Jemec GBE, Ju Q, Kappe N, Kirby B, Kirby JS, Lowes MA, Matusiak L, Micha S, Micheletti R, **Miller AP**, Moseng D, Naik H, Nassif A, Nikolakis G, Paek SY, Pascual JC, Prens E, Resnik B, Riad H, Sayed C, Smith SD, Soliman Y, Szepietowski JC, Tan J, Thorlacius L, Tzellos T, van der Zee HH, Villumsen B, Wang L, Zouboulis C, and Garg A. Factors associated with treatment satisfaction in patients with hidradenitis suppurativa: results from the Global VOICE project. *Br J Dermatol* 2022; 187(6):927-935. PMID: 36056741. Full Text

Department of Dermatology, Donald & Barbara Zucker School of Medicine at Hofstra Northwell, Hempstead, NY, USA.
Department of Dermatology, University of Pittsburgh, Pittsburgh, PA, USA.
Department of Dermatology, Mayo Clinic Alix School of Medicine, Rochester, MN, USA.
Department of Dermatology, Erasmus University Medical Center, Rotterdam, Netherlands.
Department of Dermatology, Venereology and Allergology, St Josef Hospital, Ruhr-University, Bochum, Germany.
Department of Quality Measures and Research, Clalit Health Services, Tel Aviv, Israel.
Division of Dermatology, Albert Einstein College of Medicine, Bronx, NY, USA.
Department of Dermatology, Wayne State University School of Medicine, Detroit, MI, USA.
Department of Dermatology, Erasme Hospital, Université Libre de Bruxelles, Brussels, Belgium.
Centre Médical, Institut Pasteur, Université de Paris, Paris, France.
Department of Dermatology, Zealand University Hospital, Roskilde, Denmark.
Dermatology Department, Emek Medical Center, Afula, Israel.
4th Department of Internal Medicine, National and Kapodistrian University of Athens, Medical School, Athens, Greece.
Department of Dermatology, Venereology and Allergology, Wroclaw Medical University, Wroclaw, Poland.
Departments of Dermatology, University of Minnesota, Minneapolis, MN, USA.
Department of Dermatology, Faculty of Health Sciences, University Hospital of North Norway, Institute of Clinical Medicine, UiT - The Arctic University of Norway, Tromsø, Norway.
Hope For HS, Detroit, MI, USA.
Department of Dermatology, Henry Ford Hospital, Detroit, MI, USA.

Department of Dermatology, St Vincent's University Hospital, and Charles Institute, University College Dublin, Dublin, Ireland.
Division of Infection and Immunity, Cardiff University, University Hospital of Wales, Heath Park, Cardiff, UK.
Department of Dermatology, Renji Hospital School of Medicine, Shanghai Jiaotong University, Shanghai, China.
Department of Dermatology, Penn State Milton S Hershey Medical Center, Hershey, PA, USA.
The Rockefeller University, New York City, NY, USA.
Department of Dermatology, Perelman School of Medicine, University of Pennsylvania, Philadelphia, PA, USA.
Department of Dermatology, University of California, San Francisco, CA, USA.
Departments of Dermatology, Venereology, Allergology and Immunology, Dessau Medical Center, Brandenburg Medical School Theodor Fontane and Faculty of Health Sciences Brandenburg, Dessau, Germany.
Department of Dermatology, Baylor University Medical Center, Texas A&M College of Medicine, Dallas, TX, USA.
Department of Dermatology, Alicante University General Hospital, Alicante Institute for Health and Biomedical Research (ISABIAL-FISABIO Foundation), Alicante, Spain.
Department of Dermatology and Cutaneous Surgery, Miller School of Medicine, Miami, FL, USA.
Dermatology Department, Al Wakra Hospital, Hamad Medical Corporation, Doha, Qatar.
Department of Dermatology, University of North Carolina School of Medicine, Chapel Hill, NC, USA.
Department of Dermatology, Northern Clinical School, Sydney Medical School, The University of Sydney, Sydney, NSW, Australia.
Department of Medicine, Western University, Windsor campus, Windsor, ON, Canada.
Danish HS Patients' Association, Copenhagen, Denmark.

BACKGROUND: Nearly half of patients with hidradenitis suppurativa (HS) report dissatisfaction with their treatment. However, factors related to treatment satisfaction have not been explored. OBJECTIVES: To measure associations between treatment satisfaction and clinical and treatment-related characteristics among patients with HS. METHODS: Treatment satisfaction was evaluated utilizing data from a cross-sectional global survey of patients with HS recruited from 27 institutions, mainly HS referral centres, in 14 different countries from October 2017 to July 2018. The primary outcome was patients' self-reported overall satisfaction with their current treatments for HS, rated on a five-point scale from 'very dissatisfied' to 'very satisfied'. RESULTS: The final analysis cohort comprised 1418 patients with HS, most of whom were European (55%, 780 of 1418) or North American (38%, 542 of 1418), and female (85%, 1210 of 1418). Overall, 45% (640 of 1418) of participants were either dissatisfied or very dissatisfied with their current medical treatment. In adjusted analysis, patients primarily treated by a dermatologist for HS had 1·99 [95% confidence interval (CI) 1·62-2·44, P < 0·001] times the odds of being satisfied with current treatment than participants not primarily treated by a dermatologist. Treatment with biologics was associated with higher satisfaction [odds ratio (OR) 2·36, 95% CI 1·74-3·19, P < 0·001] relative to treatment with nonbiologic systemic medications. Factors associated with lower treatment satisfaction included smoking (OR 0·78, 95% CI 0·62-0·99; active vs. never), depression (OR 0·69, 95% CI 0·54-0·87), increasing number of comorbidities (OR 0·88 per comorbidity, 95% CI 0·81-0·96) and increasing flare frequency. CONCLUSIONS: There are several factors that appear to positively influence satisfaction with treatment among patients with HS, including treatment by a dermatologist and treatment with a biologic medication. Factors that appear to lower treatment satisfaction include active smoking, depression, accumulation of comorbid conditions and increasing flare frequency. Awareness of these factors may support partnered decision making with the goal of improving treatment outcomes. What is already known about this topic? Nearly half of patients with hidradenitis suppurativa report dissatisfaction with their treatments. What does this study add? Satisfaction with treatment is increased by receiving care from a dermatologist and treatment with biologics. Satisfaction with treatment is decreased by tobacco smoking, accumulation of comorbid conditions including depression, and higher flare frequency. What are the clinical implications of this work? Awareness of the identified factors associated with poor treatment satisfaction may support partnered decision making and improve treatment outcomes.

Dermatology

Wang Q, Dong Z, Lou F, Yin Y, Zhang J, Wen H, Lu T, and Wang Y. Phenylboronic ester-modified polymeric nanoparticles for promoting TRP2 peptide antigen delivery in cancer immunotherapy. *Drug Deliv* 2022; 29(1):2029-2043. PMID: 35766157. Full Text

Key Laboratory of Biomedical Functional Materials, School of Sciences, China Pharmaceutical University, Nanjing, Jiangsu, China.
Center for Cutaneous Biology and Immunology Research, Department of Dermatology, Henry Ford Health System, Detroit, Michigan, USA.
Immunology Research program, Henry Ford Cancer Institute, Henry Ford Health System, Detroit, Michigan, USA.

The tremendous development of peptide-based cancer vaccine has attracted incremental interest as a powerful approach in cancer management, prevention and treatment. As successful as tumor vaccine has been, major challenges associated with achieving efficient immune response against cancer are (1) drainage to and retention in lymph nodes; (2) uptake by dendritic cells (DCs); (3) activation of DCs. In order to overcome these barriers, here we construct PBE-modified TRP2 nanovaccine, which comprises TRP2 peptide tumor antigen and diblock copolymer PEG-b-PAsp grafted with phenylboronic ester (PBE). We confirmed that this TRP2 nanovaccine can be effectively trapped into lymph node, uptake by dendritic cells and induce DC maturation, relying on increased negative charge, ROS response and pH response. Consistently, this vehicle loaded with TRP2 peptide could boost the strongest T cell immune response against melanoma in vivo and potentiate antitumor efficacy both in tumor prevention and tumor treatment without any exogenous adjuvant. Furthermore, the TRP2 nanovaccine can suppress the tumor growth and prolong animal survival time, which may result from its synergistic effect of inhibiting tumor immunosuppression and increasing cytotoxic lymphocyte (CTL) response. Hence this type of PBE-modified nanovaccine would be widely used as a simple, safe and robust platform to deliver other antigen in cancer immunotherapy.

Diagnostic Radiology

Morrison CK, **Macdonald EB**, and **Bevins NB**. Variations in signal-to-noise characteristics of tissue-equivalent attenuators for mammographic automatic exposure control system performance evaluation. *J Appl Clin Med Phys* 2022; Epub ahead of print. PMID: 36519622. Full Text

Department of Radiology, Henry Ford Health, Detroit, Michigan, USA.
Department of Radiology, Duke University Medical Center, Durham, North Carolina, USA.

PURPOSE: This work investigates the impact of tissue-equivalent attenuator choice on measured signal-to-noise ratio (SNR) for automatic exposure control (AEC) performance evaluation in digital mammography. It also investigates how the SNR changes for each material when used to evaluate AEC performance across different mammography systems. METHODS: AEC performance was evaluated for four mammography systems using seven attenuator sets at two thicknesses (4 and 8 cm). All systems were evaluated in 2D imaging mode, and one system was evaluated in digital breast tomosynthesis (DBT) mode. The methodology followed the 2018 ACR digital mammography quality control (DMQC) manual. Each system-attenuator-thickness combination was evaluated using For Processing images in ImageJ with standard ROI size and location. The closest annual physicist testing results were used to explore the impact of varying measured AEC performance on image quality. RESULTS: The measured SNR varied by 44%-54% within each system across all attenuators at 4 cm thickness in 2D mode. The variation appeared to be largely due to changes in measured noise, with variations of 46%-67% within each system across all attenuators at 4 cm thickness in 2D mode. Two systems had failing SNR levels for two of the materials using the minimum SNR criterion specified in the ACR DMQC manual. Similar trends were seen in DBT mode and at 8 cm thickness. Within each material, there was 115%-131% variation at 4 cm and 82%-114% variation at 8 cm in the measured SNR across the four imaging systems. Variation in SNR did not correlate with system operating level based on visual image quality and average glandular dose (AGD). CONCLUSION: Choice of tissue-equivalent attenuator for AEC performance evaluation affects measured SNR values. Depending on the material, the difference may be enough to result in failure following the longitudinal and absolute thresholds specified in the ACR DMQC manual.

Emergency Medicine

Bunch CM, Zackariya N, Thomas AV, Langford JH, Aboukhaled M, Thomas SJ, Ansari A, Patel SS, Buckner H, **Miller JB**, Annis CL, Quate-Operacz MA, Schmitz LA, Pulvirenti JJ, Konopinski JC, Kelley KM, Hassna S, Nelligan LG, and Walsh MM. COVID-associated non-vasculitic thrombotic retiform purpura of the face and extremities: A case report. *Clin Case Rep* 2022; 10(12):e6790. PMID: 36590660. Full Text

Departments of Emergency Medicine and Internal Medicine Henry Ford Hospital Detroit Michigan USA.
Indiana University School of Medicine-South Bend South Bend Indiana USA.
Departments of Emergency Medicine and Internal Medicine Saint Joseph Regional Medical Center Mishawaka Indiana USA.
Kidney Care of Michiana Mishawaka Indiana USA.
Department of Infectious Disease Saint Joseph Regional Medical Center Mishawaka Indiana USA.
Department of Pathology South Bend Medical Foundation South Bend Indiana USA.
Department of Dermatology Beacon Medical Group Granger Indiana USA.
Department of Internal Medicine Saint Joseph Regional Medical Center Mishawaka Indiana USA.
Department of Family Medicine Marian University College of Osteopathic Medicine Indianapolis Indiana USA.

SARS-CoV-2 infection can manifest many rashes. However, thrombotic retiform purpura rarely occurs during COVID-19 illness. Aggressive anti-COVID-19 therapy with a high-dose steroid regimen led to rapid recovery. This immunothrombotic phenomenon likely represents a poor type 1 interferon response and complement activation on the endothelial surface in response to acute infection.

Emergency Medicine

Carvajal D, Bevilacqua KG, **Caldwell MT**, and Zambrana RE. Provider Perspectives on Patient-Centered Contraceptive Counseling for Latinas in Baltimore, MD. *Contraception* 2022; Epub ahead of print. PMID: 36535412. Full Text

Department of Family & Community Medicine, University of Maryland School of Medicine, 29 S Paca St, Baltimore, MD 21201. Electronic address: dcarvajal@som.umaryland.edu.
Department of Population, Family and Reproductive Health, Johns Hopkins Bloomberg School of Public Health, 615 N Wolfe St, Baltimore, MD 21205.
Department of Emergency Medicine, Henry Ford Health System, 2799 W Grand Blvd, Detroit, MI 48202.
Harriet Tubman Department of Women, Gender and Sexuality Studies, University of Maryland, 4302 Chapel Lane, College Park, MD 20742.

OBJECTIVES: This study explores: 1) provider narratives of their contraceptive counseling practices with Latina patients within the context of patient-centered care (PCC); and 2) provider perceptions about the barriers to the provision of patient-centered contraceptive counseling in general and more specifically, with Latina patients in Baltimore, MD. STUDY DESIGN: We conducted 25 semi-structured qualitative interviews with physicians (MD/DO) and nurse practitioners from four specialties (family medicine, internal medicine, pediatrics, obstetrics/gynecology) who provide contraceptive care to Latinas in Baltimore, MD. We analyzed data using a directed content analysis approach. We discuss findings with attention to major constructs of PCC, applying a reproductive justice framework. RESULTS: Providers described a contraceptive counseling approach focused on pregnancy prevention as the primary goal during contraceptive encounters with Latina patients. Most respondents described using a tiered-effectiveness approach when counseling even while noting the importance of PCC and its main tenets. Providers noted both health system and patient-attributed barriers to PCC. Health system barriers to PCC included time constraints and insurance status. Patient-attributed barriers reported by providers included low patient education/health literacy, culturally-attributed misconceptions about contraception, and the language barrier. CONCLUSION: Providers described knowledge of and intention to practice PCC during contraceptive care but had limited integration of it in their own counseling practices with Latinas. Provider responses suggest tension between an expressed desire to provide PCC and paternalistic counseling paradigms that prioritize the prevention of unintended pregnancy over patient preferences. Moreover,

inequitable health system barriers also interfere with true implementation of contraceptive PCC. IMPLICATIONS: Translating contraceptive PCC into practice, especially for marginalized communities, is paramount. Training should teach clinicians to recognize systems of structural inequity and discrimination that have informed approaches to counseling but are not reflective of PCC. Institutional policies must address health system barriers (e.g., time constraints; insurance) that also hamper PCC.

Emergency Medicine

Mangus CW, Parker SJ, DeLaroche AM, Zhang X, Gunnink S, **Hayes J**, **Heath G**, Michiels E, and Mahajan P. Impact of COVID-19 on the associated complications of high-risk conditions in a statewide pediatric emergency network. *J Am Coll Emerg Physicians Open* 2022; 3(6):e12865. PMID: 36540333. Full Text

Department of Emergency Medicine University of Michigan Ann Arbor Michigan USA.
Department of Pediatrics University of Michigan Ann Arbor Michigan USA.
Division of Pediatric Emergency Medicine, Department of Pediatrics Children's Hospital of Michigan Detroit Michigan USA.
Thomas E. Starzl Transplantation Institute University of Pittsburgh Medical Center Pittsburgh Pennsylvania USA.
Department of Nursing University of Michigan Ann Arbor Michigan USA.
Department of Emergency Medicine, Helen DeVos Children's Hospital Michigan State University College of Human Medicine Grand Rapids Michigan USA.
Department of Emergency Medicine Henry Ford Hospital Detroit Michigan USA.

BACKGROUND: The COVID-19 pandemic affected the volume and epidemiology of pediatric emergency department (ED) visits. We aimed to determine the rate of associated complications for 16 high-risk conditions in a Michigan statewide network of academic and community EDs during the pandemic. METHODS: We conducted a cross-sectional study of pediatric ED visits among a network of 5 Michigan health systems during the pre-pandemic (March 1, 2019-March 10, 2020) and pandemic (March 11, 2020-March 31, 2021) periods. Data were collected from the medical record and included patient demographics, ED visit characteristics, procedure codes, and final International Classification of Diseases, 10th Revision, Clinical Modification diagnosis codes. Selection of codes for 16 high-risk conditions and diagnostic complications were identified using previously described methods. Characteristics of ED visits were compared before versus during the pandemic using $\chi(2)$ and Fisher's exact tests. We used multilevel logistic regression to analyze covariates and potential confounders for being diagnosed with a high-risk condition or a complication of a high-risk condition. RESULTS: A total of 417,038 pediatric ED visits were analyzed. The proportion of patients presenting with 10 of 16 high-risk conditions (including appendicitis, sepsis, and stroke) was higher in the pandemic period compared with pre-pandemic ($P < 0.01$). Despite this, there was no significant increase in the frequency of complications for any of the 16 high-risk conditions during the pandemic. The adjusted odds of being diagnosed with appendicitis (pre-pandemic 0.23% vs pandemic 0.52%; odds ratio [OR], 1.19 [95% confidence interval, CI, 1.00-1.41]), diabetic ketoacidosis (pre-pandemic 0.16% vs pandemic 0.52%; OR, 2.40 [95% CI, 2.07-2.78]), intussusception (pre-pandemic 0.05% vs pandemic 0.07%; OR, 1.64 [95% CI, 1.22-2.21)], and testicular torsion (pre-pandemic 0.10% vs pandemic 0.14%; OR, 1.64 [95% CI, 1.18-2.28]) was higher during the pandemic. CONCLUSIONS: Despite a higher proportion of ED visits attributed to high-risk conditions, there was no increase in complications, suggesting minimal impact of the pandemic on outcomes of pediatric ED visits.

Emergency Medicine

Nesbit CE, Mastenbrook JD, **Ball MT**, Rinnert KJ, and Edgar L. Emergency medical services Milestones 2.0: What has changed? *AEM Educ Train* 2022; 6(6):e10821. PMID: 36518230. Full Text

Allegheny Health Network Pittsburgh Pennsylvania USA.
Homer Stryker M.D. School of Medicine Western Michigan University Kalamazoo Michigan USA.
Henry Ford Health Detroit Michigan USA.
University of Texas Southwestern Medical Center Dallas Texas USA.
Accreditation Council for Graduate Medical Education Chicago Illinois USA.

BACKGROUND: Since 2015, development of competencies by emergency medical services (EMS) fellows have been evaluated using the EMS Milestones 1.0 developed by a working group consisting of relevant stakeholders convened by the Accreditation Council for Graduate Medical Education (ACGME). Feedback from users and data collected from the milestones assessments in the interim indicated a need for revision of the original milestones. In May 2021, the Milestones 2.0 working group was convened for the purpose of revising this specialty-specific assessment tool. METHODS: A working group consisting of representatives from American Board of Emergency Medicine, the Review Committee for Emergency Medicine, and volunteers selected by the ACGME Milestones Committee, chaired by the ACGME vice president for milestones development, was convened using a virtual platform to revise the milestones and develop a supplemental guide for use along with the Milestones 2.0. There were no in-person meetings of this working group due to the COVID-19 pandemic. RESULTS: Data from milestones reporting, discussion within the working group, stakeholder input, and public commentary were used to revise the original milestones. A new supplemental guide to enhance milestone usability and provide recommended resource materials was also developed for use alongside the milestones. DISCUSSION: The EMS Milestones 2.0 and accompanying supplemental guide provide an updated framework for fellowship programs to use as a guide for developing the competencies necessary for independent practice as EMS physicians and in the formal, competency-based evaluation of trainees as required by the ACGME.

Emergency Medicine

Short NA, van Rooij SJH, Murty VP, Stevens JS, An X, Ji Y, McLean SA, House SL, Beaudoin FL, Zeng D, Neylan TC, Clifford GD, Linnstaedt SD, Germine LT, Bollen KA, Rauch SL, Haran JP, **Lewandowski C**, Musey PI, Jr., Hendry PL, Sheikh S, Jones CW, Punches BE, Swor RA, McGrath ME, Hudak LA, Pascual JL, Seamon MJ, Datner EM, Pearson C, Peak DA, Merchant RC, Domeier RM, Rathlev NK, O'Neil BJ, Sergot P, Sanchez LD, Bruce SE, Pietrzak RH, Joormann J, Barch DM, Pizzagalli DA, Sheridan JF, Smoller JW, Harte SE, Elliott JM, Kessler RC, Koenen KC, and Jovanovic T. Anxiety sensitivity as a transdiagnostic risk factor for trajectories of adverse posttraumatic neuropsychiatric sequelae in the AURORA study. *J Psychiatr Res* 2022; 156:45-54. PMID: 36242943. Full Text

Anxiety sensitivity, or fear of anxious arousal, is cross-sectionally associated with a wide array of adverse posttraumatic neuropsychiatric sequelae, including symptoms of posttraumatic stress disorder, depression, anxiety, sleep disturbance, pain, and somatization. The current study utilizes a large-scale, multi-site, prospective study of trauma survivors presenting to emergency departments. Hypotheses tested whether elevated anxiety sensitivity in the immediate posttrauma period is associated with more severe and persistent trajectories of common adverse posttraumatic neuropsychiatric sequelae in the eight weeks posttrauma. Participants from the AURORA study (n = 2,269 recruited from 23 emergency departments) completed self-report assessments over eight weeks posttrauma. Associations between heightened anxiety sensitivity and more severe and/or persistent trajectories of trauma-related symptoms identified by growth mixture modeling were analyzed. Anxiety sensitivity assessed two weeks posttrauma was associated with severe and/or persistent posttraumatic stress, depression, anxiety, sleep disturbance, pain, and somatic symptoms in the eight weeks posttrauma. Effect sizes were in the small to medium range in multivariate models accounting for various demographic, trauma-related, pre-trauma mental health-related, and personality-related factors. Anxiety sensitivity may be a useful transdiagnostic risk factor in the immediate posttraumatic period identifying individuals at risk for the development of adverse posttraumatic neuropsychiatric sequelae. Further, considering anxiety sensitivity is malleable via brief intervention, it could be a useful secondary prevention target. Future research should continue to evaluate associations between anxiety sensitivity and trauma-related pathology.

Endocrinology and Metabolism

Galindo RJ, Aleppo G, Parkin CG, Baidal DA, Carlson AL, Cengiz E, Forlenza GP, **Kruger DF**, Levy C, McGill JB, and Umpierrez GE. Increase Access, Reduce Disparities: Recommendations for Modifying Medicaid CGM Coverage Eligibility Criteria. *J Diabetes Sci Technol* 2022; Epub ahead of print. PMID: 36524477. Full Text

Emory University School of Medicine, Atlanta, GA, USA.
Center for Diabetes Metabolism Research, Emory University Hospital Midtown, Atlanta, GA, USA.

Hospital Diabetes Taskforce, Emory Healthcare System, Atlanta, GA, USA.
Division of Endocrinology, Metabolism and Molecular Medicine, Feinberg School of Medicine, Northwestern University, Chicago, IL, USA.
CGParkin Communications, Inc., Henderson, NV, USA.
Diabetes Research Institute, University of Miami Miller School of Medicine, Miami, FL, USA.
International Diabetes Center, Minneapolis, MN, USA.
Regions Hospital & HealthPartners Clinics, St. Paul, MN, USA.
Diabetes Education Programs, HealthPartners and Stillwater Medical Group, Stillwater, MN, USA.
University of Minnesota Medical School, Minneapolis, MN, USA.
Pediatric Diabetes Program, Division of Pediatric Endocrinology, Department of Pediatrics, University of California, San Francisco, San Francisco, CA, USA.
Barbara Davis Center, Division of Pediatric Endocrinology, Department of Pediatrics, University of Colorado Denver, Denver, CO, USA.
Division of Endocrinology, Diabetes, Bone & Mineral, Henry Ford Health System, Detroit, MI, USA.
Division of Endocrinology, Diabetes, and Metabolism, Icahn School of Medicine at Mount Sinai, New York, NY, USA.
Mount Sinai Diabetes Center and T1D Clinical Research, Icahn School of Medicine at Mount Sinai, New York, NY, USA.
Division of Endocrinology, Metabolism & Lipid Research, School of Medicine, Washington University in St. Louis, St. Louis, MO, USA.
Division of Endocrinology, Metabolism, Emory University School of Medicine, Atlanta, GA, USA.
Diabetes and Endocrinology, Grady Memorial Hospital, Atlanta, GA, USA.

Numerous studies have demonstrated the clinical value of continuous glucose monitoring (CGM) in type 1 diabetes (T1D) and type 2 diabetes (T2D) populations. However, the eligibility criteria for CGM coverage required by the Centers for Medicare & Medicaid Services (CMS) ignore the conclusive evidence that supports CGM use in various diabetes populations that are currently deemed ineligible. In an earlier article, we discussed the limitations and inconsistencies of the agency's CGM eligibility criteria relative to current scientific evidence and proposed practice solutions to address this issue and improve the safety and care of Medicare beneficiaries with diabetes. Although Medicaid is administered through CMS, there is no consistent Medicaid policy for CGM coverage in the United States. This article presents a rationale for modifying and standardizing Medicaid CGM coverage eligibility across the United States.

Endocrinology and Metabolism

Qiu S, **Divine G**, and **Rao SD**. Effect of vitamin D metabolites on bone histomorphometry in healthy black and white women: An attempt to unravel the so-called vitamin D paradox in blacks. *Bone Rep* 2023; 18:101650. PMID: 36588780. Full Text

Bone and Mineral Research Laboratory, Henry Ford Hospital, Detroit, MI, USA.
Department of Public Health Sciences, Henry Ford Hospital, Detroit, MI, USA.
Division of Endocrinology, Diabetes, and Bone & Mineral Disorders, Henry Ford Hospital, Detroit, MI, USA.

An apparent vitamin D paradox, characterized by lower serum 25-hydroxyvitamin D (25(OH)D) levels and higher bone mineral density, is present in black population. In contrast, blacks have higher serum 1,25-dihydroxyvitamin D (1,25(OH)(2)D) levels. The effect of 1,25(OH)(2)D on the skeleton is not fully understood. We examined serum 25(OH)D, 1,25(OH)(2)D and bone histomorphometry in 50 black and white women (25 each) matched for age, menstrual status, and BMI. Histomorphometric indices related to bone structure, remodeling and mineralization were measured in cancellous bone in iliac bone biopsies. Data analyses led to the following results: 1) serum 25(OH)D was significantly lower and 1,25(OH)(2)D was significantly higher in black than in white women, but neither blacks nor whites revealed significant correlation between these two vitamin D metabolites. 2) there was no significant difference in PTH levels between blacks and whites. 3) except for greater trabecular thickness (Tb.Th) in blacks, there were no significant differences in other histomorphometric variables between the two ethnic groups. 4) osteoid surface (OS/BS), unlabeled osteoid surface (ulOS/BS), and osteoblast surface (ObS/BS) significantly correlated with serum 1,25(OH)(2)D levels. We conclude that lower serum 25(OH)D levels in blacks do

not impair bone structure and remodeling, nor decrease bone mineralization. Higher serum 1,25(OH)(2)D levels in blacks may help preserve bone mass by stimulating bone formation via increasing osteoblast number and function, but moderately inhibit terminal bone mineralization as shown by higher ulOS/BS.

Family Medicine

Graboyes EM, Maurer S, Balliet W, Li H, **Williams AM**, Osazuwa-Peters N, Yan F, Padgett L, Rush A, Ruggiero KJ, and Sterba KR. Efficacy of a Brief Tele-Cognitive Behavioral Treatment vs Attention Control for Head and Neck Cancer Survivors With Body Image Distress: A Pilot Randomized Clinical Trial. *JAMA Otolaryngol Head Neck Surg* 2022; Epub ahead of print. PMID: 36454561. Full Text

Department of Otolaryngology-Head and Neck Surgery, College of Medicine, Medical University of South Carolina, Charleston.
Department of Public Health Sciences, College of Medicine, Medical University of South Carolina, Charleston.
Department of Psychiatry and Behavioral Sciences, College of Medicine, Medical University of South Carolina, Charleston.
Department of Family Medicine, Henry Ford Health, Detroit, Michigan.
Department of Head and Neck Surgery & Communication Sciences, Duke University School of Medicine, Durham, North Carolina.
Department of Otolaryngology-Head and Neck Surgery, Lewis Katz School of Medicine, Temple University, Philadelphia, Pennsylvania.
Office of Research and Development, US Department of Veteran Affairs, Washington, DC.
Head and Neck Cancer Alliance, Charleston, South Carolina.
College of Nursing, Medical University of South Carolina, Charleston.

IMPORTANCE: Although 1 in 4 head and neck cancer (HNC) survivors experience clinically significant body image distress (BID), a psychosocial morbidity that adversely affects quality of life, effective interventions for these patients are lacking. OBJECTIVE: To evaluate the acceptability and preliminary efficacy of BRIGHT (Building a Renewed ImaGe after Head and neck cancer Treatment), a brief tele-cognitive behavioral therapy, at reducing BID among HNC survivors. DESIGN, SETTING, AND PARTICIPANTS: This parallel-group pilot randomized clinical trial recruited adult HNC survivors with BID between August 13, 2020, and December 9, 2021, from the Medical University of South Carolina HNC clinic during a routine survivorship encounter. Data were analyzed from May 3 to June 16, 2022. INTERVENTIONS: BRIGHT consisted of 5 weekly psychologist-led video tele-cognitive behavioral therapy sessions. Attention control (AC) consisted of dose- and delivery-matched survivorship education. MAIN OUTCOMES AND MEASURES: Change in HNC-related BID was assessed using IMAGE-HN (Inventory to Measure and Assess imaGe disturbancE-Head and Neck), a validated patient-reported outcome (score range, 0-84, with higher scores indicating greater HNC-related BID). Clinical response rate was measured as the proportion of patients with a clinically meaningful change in IMAGE-HN scores. RESULTS: Of the 44 HNC survivors with BID allocated to BRIGHT (n = 20) or AC (n = 24), the median (range) age was 63 (41-80) years, and 27 patients (61%) were female. Patients rated BRIGHT's acceptability highly (all metrics had a mean rating of ≥4.5/5), and 19 of 20 patients (95%) receiving BRIGHT were likely or highly likely to recommend it to other HNC survivors with BID. BRIGHT decreased HNC-related BID from baseline to 1 month postintervention relative to AC (mean model-based difference in change in IMAGE-HN score, -7.9 points; 90% CI, -15.9 to 0.0 points) and from baseline to 3 months postintervention relative to AC (mean model-based difference in change in IMAGE-HN score, -17.1 points; 90% CI, -25.6 to -8.6 points). At 3 months postintervention, the clinical response rate of BRIGHT was 6.6-fold higher than AC (model-based odds ratio, 6.6; 90% CI, 2.0-21.8). The improvement in HNC-related BID for BRIGHT vs AC at 3 months was clinically significant, and the effect size was large (Cohen d, -0.9; 90% CI, -1.4 to -0.4). CONCLUSIONS AND RELEVANCE: In this pilot randomized clinical trial, BRIGHT was acceptable, may result in a clinically meaningful improvement in HNC-related BID, and showed a high clinical response rate. These promising preliminary data support conducting a large efficacy trial to establish BRIGHT as the first evidence-based treatment for HNC survivors with BID. TRIAL REGISTRATION: ClinicalTrials.gov Identifier: NCT03831100.

Gastroenterology

Howell R, Tang A, Allen J, Altaye M, Amin M, Bayan S, Belafsky P, Cervenka B, deSilva B, Dion G, Ekbom D, Friedman A, Fritz M, Giliberto JP, Guardiani E, Harmon J, Kasperbauer JL, Khosla S, Kim B, Kuhn M, Kwak P, Ma Y, Madden L, Matrka L, **Mayerhoff R**, **Piraka C**, Rosen C, Tabangin ME, Wahab SA, Wilson K, Wright SC, Young V, Yuen S, and Postma GN. Killian Jamieson Diverticulum, the Great Mimicker: A Case Series and Contemporary Review. *Laryngoscope* 2022; Epub ahead of print. PMID: 36453465. Full Text

Department of Otolaryngology-Head and Neck Surgery, University of Cincinnati, Cincinnati, Ohio, USA.
Department of Surgery, University of Auckland, Auckland, New Zealand.
Division of Biostatistics and Epidemiology, Cincinnati Children's Hospital Medical Center, Cincinnati, Ohio, USA.
Department of Otolaryngology-Head and Neck Surgery, New York University, New York, New York, USA.
Department of Otolaryngology-Head and Neck Surgery, Mayo Clinic, Rochester, Minnesota, USA.
Department of Otolaryngology-Head and Neck Surgery, University of California, Davis, Davis, California, USA.
Department of Otolaryngology-Head and Neck Surgery, Ohio State University, Columbus, Ohio, USA.
Department of Otolaryngology-Head and Neck Surgery, University of Kentucky, Lexington, Kentucky, USA.
Department of Otolaryngology-Head and Neck Surgery, University of Washington, Seattle, Washington, USA.
Department of Otolaryngology-Head and Neck Surgery, Wake Forest University, Winston-Salem, North Carolina, USA.
Department of Otolaryngology-Head and Neck Surgery, University of California - San Francisco, San Francisco, California, USA.
Department of Otolaryngology-Head and Neck Surgery, Henry Ford Health System, Detroit, Michigan, USA.
Department of Gastroenterology/Hepatology, Henry Ford Health System, Detroit, Michigan, USA.
Department of Radiology, University of Cincinnati, Cincinnati, Ohio, USA.
Department of Otolaryngology-Head and Neck Surgery, University of Maryland, Baltimore, Maryland, USA.
Department of Otolaryngology-Head and Neck Surgery, Medical College of Georgia at Augusta University Health, Augusta, Georgia, USA.

OBJECTIVE: To assess barium esophagram (BAS) as a diagnostic marker for patients with Killian Jamieson diverticula (KJD). METHODS: Prospective, multicenter cohort study of individuals enrolled in the Prospective OUtcomes of Cricopharyngeus Hypertonicity (POUCH) Collaborative. Patient demographics, comorbidities, radiographic imaging reports, laryngoscopy findings, patient-reported outcome measures (PROM), and operative reporting were abstracted from a REDCap database and summarized using means, medians, percentages, frequencies. Paired t-tests and Wilcoxon Signed Rank test were used to test pre- to post-operative differences in RSI, EAT-10, and VHI-10 scores. Diagnostic test evaluation including sensitivity, specificity, positive, and negative predictive value with 95% confidence intervals were calculated comparing BAS findings to operative report. RESULTS: A total of 287 persons were enrolled; 13 (4%) patients were identified with confirmed KJD on operative reports. 100% underwent open transcervical excision. BAS has a 46.2% (95% confidence interval [CI]: 23.2, 70.9) sensitivity and 97.8% (95% CI: 95.3, 99.0) specificity in detecting a KJD and 50% (95% CI: 25.4, 74.6) positive predictive value but 97.4% (95%CI: 94.8, 98.7) negative predictive value. Preoperatively, patients reported mean (SD) RSI and EAT-10 of 19.4 (9) and 8.3 (7.5) accordingly. Postoperatively, patients reported mean (SD) RSI and EAT-10 as 5.4 (6.2) and 2.3 (3.3). Both changes in RSI and EAT-10 were statistically significant ($p = 0.008$, $p = 0.03$). CONCLUSION: KJD are rare and represent <5% of hypopharyngeal diverticula undergoing surgical intervention. Open transcervical surgery significantly improves symptoms of dysphagia. BAS has high specificity but low sensitivity in detecting KJD. LEVEL OF EVIDENCE: Level 4 Laryngoscope, 2022.

Gastroenterology

Shimada S, **Shamaa T**, **Ivanics T**, **Kitajima T**, **Adhnan M**, **Collins K**, **Rizzari M**, **Yoshida A**, **Abouljoud M**, **Salgia R**, and **Nagai S**. ASO Visual Abstract: Multiple Pretransplant Treatments for Patients Without Pathological Complete Response may Worsen Posttransplant Outcomes in Patients With Hepatocellular Carcinoma. *Ann Surg Oncol* 2022; Epub ahead of print. PMID: 36496492. Full Text

Division of Transplant and Hepatobiliary Surgery, Henry Ford Health System, Detroit, MI, USA.
Division of Gastroenterology and Hepatology, Henry Ford Health System, Detroit, MI, USA.
Division of Transplant and Hepatobiliary Surgery, Henry Ford Health System, Detroit, MI, USA.
snagai1@hfhs.org.

Graduate Medical Education

Kokas MS, **Passalacqua KD**, **Mortimore A**, and **Hoffert MM**. Advice for women considering a career in medicine: A qualitative study of women physicians' perspectives. *Work* 2022; Epub ahead of print. PMID: 36591668. Full Text

Department of Graduate Medical Education, Henry Ford Hospital, Detroit, MI, USA.

BACKGROUND: Research has explored the problems that women encounter during a medical career; however, the advice that experienced women physicians would give to women who have not yet entered the field is needed to reveal how the medical work landscape is evolving and to provide real-world narratives to help career seekers make informed choices. OBJECTIVE: By eliciting women's perspectives on their medical careers by asking them what advice they would give to aspiring women physicians. We aimed to reveal areas for improving career satisfaction of women physicians and to inform those who advise women considering a medical career. METHODS: In this qualitative study, we used a phenomenological approach to conduct semi-structured one-on-one interviews with 24 women physicians to query the advice they would give to women contemplating a career in medicine. RESULTS: Thematic analysis of interview transcriptions revealed 10 themes that women physicians communicated as being important to consider before deciding to become a physician. Although some advice had a cautionary tone, encouraging and practical advice was also conveyed. The most abundant themes concerned the centrality of patient care, a passion for practicing medicine, and the importance of planning. Other key topics included family and friends, self-reflection, life balance, finances, ethics, maintaining presence, and two overt cautionary statements. CONCLUSION: Interviews revealed that meaning and purpose derived from a medical career and maintaining work-life balance are valued by some women physicians. Participants were encouraging in recommending medicine as a career choice for women, while highlighting some challenges.

Hematology-Oncology

Drilon A, Horan JC, Tangpeerachaikul A, Besse B, Ou SI, **Gadgeel SM**, Camidge DR, van der Wekken AJ, Nguyen-Phuong L, Acker A, Keddy C, Nicholson KS, Yoda S, Mente S, Sun Y, Soglia JR, Kohl NE, Porter JR, Shair MD, Zhu V, Davare MA, Hata AN, Pelish HE, and Lin JJ. NVL-520 is a selective, TRK-sparing, and brain-penetrant inhibitor of ROS1 fusions and secondary resistance mutations. *Cancer Discov* 2022; Epub ahead of print. PMID: 36511802. Full Text

Memorial Sloan Kettering Cancer Center, New York, NY, United States.
Nuvalent, Inc., Cambridge, MA, United States.
Nuvalent, Inc., Cambridge, United States.
Institut Gustave Roussy, Villejuif, France.
University of California, Irvine, Orange, California, United States.
Henry Ford Cancer Institute/Henry Ford Health System, Detroit, MI, United States.
University of Colorado Cancer Center, Aurora, Colorado, United States.
University of Groningen, University Medical Center Groningen, Groningen, Netherlands.
Massachusetts General Hospital, Boston, Massachusetts, United States.
Massachusetts General Hospital, Boston, United States.
Oregon Health & Science University, Portland, OR, United States.
OHSU, Portland, OR, United States.

Massachusetts General Hospital, Charlestown, MA, United States.
Nuvalent, Inc., United States.
Nuvalent, Cambridge, MA, United States.
Nuvalent, United States.
Kohl Consulting, Wellesley, MA, United States.

ROS1 tyrosine kinase inhibitors (TKIs) have been approved (crizotinib and entrectinib) or explored (lorlatinib, taletrectinib, and repotrectinib) for the treatment of ROS1 fusion-positive cancers, although none simultaneously address the need for broad resistance coverage, avoidance of clinically dose-limiting TRK inhibition, and brain penetration. NVL-520 is a rationally designed macrocycle with >50-fold ROS1 selectivity over 98% of the kinome tested. It is active in vitro against diverse ROS1 fusions and resistance mutations and exhibits 10-to-1,000-fold improved potency for the ROS1 G2032R solvent-front mutation over crizotinib, entrectinib, lorlatinib, taletrectinib, and repotrectinib. In vivo, it induces tumor regression in G2032R-inclusive intracranial and patient-derived xenograft models. Importantly, NVL-520 has a ~100-fold increased potency for ROS1 and ROS1 G2032R over TRK. As clinical proof-of-concept, NVL-520 elicited objective tumor responses in three patients with TKI-refractory ROS1 fusion-positive lung cancers, including two with ROS1 G2032R and one with intracranial metastases, with no observed neurological toxicities.

Hematology-Oncology

Safa H, **Abu Rous F**, Belani N, Borghaei H, **Gadgeel S**, and Halmos B. Emerging Biomarkers in Immune Oncology to Guide Lung Cancer Management. *Target Oncol* 2022; Epub ahead of print. PMID: 36577876. Full Text

Department of Internal Medicine, Montefiore Medical Center, Albert Einstein College of Medicine, Bronx, NY, USA.
Division of Hematology and Oncology, Department of Internal Medicine, Henry Ford Cancer Institute/Henry Ford Health, Detroit, MI, USA.
Department of Hematology-Oncology, Fox Chase Cancer Center, Temple University Health System, Philadelphia, PA, USA.
Department of Oncology, Montefiore Medical Center, Albert Einstein College of Medicine, 1695 Eastchester Road, Room 258, Bronx, NY, 10461, USA. bahalmos@montefiore.org.

Over the last decade, the use of targeted therapies and immune therapies led to drastic changes in the management lung cancer and translated to improved survival outcomes. This growing arsenal of therapies available for the management of non-small cell lung cancer added more complexity to treatment decisions. The genomic profiling of tumors and the molecular characterization of the tumor microenvironment gradually became essential steps in exploring and identifying markers that can enhance patient selection to facilitate treatment personalization and narrow down therapy options. The advent of innovative diagnostic platforms, such as next-generation sequencing and plasma genotyping (also known as liquid biopsies), has aided in this quest. Currently, programmed cell death ligand 1 expression remains the most recognized and fully validated predictive biomarker of response to immune checkpoint inhibitors. Other markers such as tumor mutational burden, tumor infiltrating lymphocytes, driver mutations, and other molecular elements of the tumor microenvironment bear the potential to be predictive tools; however, the majority are still investigational. In this review, we describe the advances noted thus far on currently validated as well as novel emerging biomarkers that have the potential to guide the use of immunotherapy agents in the management of non-small cell lung cancer.

Hematology-Oncology

Tempero MA, Pelzer U, O'Reilly EM, Winter J, Oh DY, Li CP, Tortora G, Chang HM, Lopez CD, Bekaii-Saab T, Ko AH, Santoro A, Park JO, Noel MS, Frassineti GL, Shan YS, Dean A, Riess H, Van Cutsem E, Berlin J, **Philip P**, Moore M, Goldstein D, Tabernero J, Li M, Ferrara S, Le Bruchec Y, Zhang G, Lu B, Biankin AV, and Reni M. Adjuvant nab-Paclitaxel + Gemcitabine in Resected Pancreatic Ductal Adenocarcinoma: Results From a Randomized, Open-Label, Phase III Trial. *J Clin Oncol* 2022; Epub ahead of print. PMID: 36521097. Full Text

University of California, San Francisco, Helen Diller Family Comprehensive Cancer Center, San Francisco, CA.
Charité-Universitätsmedizin Berlin, Freie Universität Berlin, Humboldt-Universität zu Berlin, Berlin Institute of Health, Berlin, Germany.
Memorial Sloan Kettering Cancer Center, New York, NY.
Thomas Jefferson University Hospital, Philadelphia, PA.
Seoul National University Hospital, Cancer Research Institute, Seoul National University College of Medicine, Seoul, South Korea.
Integrated Major in Innovative Medical Science, Seoul National University Graduate School, Seoul, South Korea.
Division of Clinical Skills Training, Department of Medical Education, Taipei Veterans General Hospital, Taipei, Taiwan.
Division of Gastroenterology and Hepatology, Department of Medicine, Taipei Veterans General Hospital, Taipei, Taiwan.
School of Medicine, College of Medicine, National Yang Ming Chiao Tung University, Taipei, Taiwan.
Azienda Ospedaliera Universitaria, Verona, Italy.
Fondazione Policlinico Universitario Gemelli IRCCS, Rome, Italy.
Asan Medical Center, University of Ulsan College of Medicine, Seoul, South Korea.
Oregon Health & Science University, Knight Cancer Institute, Portland, OR.
Mayo Clinic Cancer Center, Mayo Clinic, Phoenix, AZ.
Department of Biomedical Sciences, Humanitas University, Pieve Emanuele, Milan, Italy.
IRCCS Humanitas Research Hospital, Humanitas Cancer Center, Rozzano, Milan, Italy.
Division of Hematology/Oncology, Samsung Medical Center, Sungkyunkwan University School of Medicine, Seoul, South Korea.
Division of Hematology/Oncology, Georgetown Lombardi Cancer Center, Washington, DC.
Department of Medical Oncology, Istituto Scientifico Romagnolo per lo Studio e la Cura dei Tumori (IRST) IRCCS, Meldola, Italy.
Department of Surgery, Institute of Clinical Medicine, College of Medicine, National Cheng Kung University Hospital, Tainan, Taiwan.
Department of Medical Oncology, St John of God Subiaco Hospital, Subiaco, Western Australia, Australia.
University Hospitals Gasthuisberg/Leuven and KU Leuven, Leuven, Belgium.
Vanderbilt-Ingram Cancer Center, Nashville, TN.
Karmanos Cancer Institute, Detroit, MI.
Henry Ford Cancer Institute, Detroit, MI.
Princess Margaret Hospital, Toronto, Ontario, Canada.
Nelune Cancer Center, Prince of Wales Hospital, University of New South Wales, Randwick, New South Wales, Australia.
Vall d'Hebron Hospital Campus and Institute of Oncology (VHIO), IOB-Quiron, UVic-UCC, Barcelona, Spain.
Bristol Myers Squibb, Princeton, NJ.
Celgene Research SLU, a Bristol Myers Squibb Company, Boudry, Switzerland.
Wolfson Wohl Cancer Research Center, Institute of Cancer Sciences, University of Glasgow, Glasgow, United Kingdom.
West of Scotland Pancreatic Unit, Glasgow Royal Infirmary, Glasgow, United Kingdom.
South Western Sydney Clinical School, Faculty of Medicine, University of New South Wales, Liverpool, New South Wales, Australia.
IRCCS Ospedale San Raffaele Vita e Salute University, Milan, Italy.

PURPOSE: This randomized, open-label trial compared the efficacy and safety of adjuvant nab-paclitaxel + gemcitabine with those of gemcitabine for resected pancreatic ductal adenocarcinoma (ClinicalTrials.gov identifier: NCT01964430). METHODS: We assigned 866 treatment-naive patients with pancreatic ductal adenocarcinoma to nab-paclitaxel (125 mg/m(2)) + gemcitabine (1,000 mg/m(2)) or gemcitabine alone to one 30-40 infusion on days 1, 8, and 15 of six 28-day cycles. The primary end point was independently assessed disease-free survival (DFS). Additional end points included investigator-assessed DFS, overall survival (OS), and safety. RESULTS: Two hundred eighty-seven of 432 patients

and 310 of 434 patients completed nab-paclitaxel + gemcitabine and gemcitabine treatment, respectively. At primary data cutoff (December 31, 2018; median follow-up, 38.5 [interquartile range [IQR], 33.8-43 months), the median independently assessed DFS was 19.4 (nab-paclitaxel + gemcitabine) versus 18.8 months (gemcitabine; hazard ratio [HR], 0.88; 95% CI, 0.729 to 1.063; P = .18). The median investigator-assessed DFS was 16.6 (IQR, 8.4-47.0) and 13.7 (IQR, 8.3-44.1) months, respectively (HR, 0.82; 95% CI, 0.694 to 0.965; P = .02). The median OS (427 events; 68% mature) was 40.5 (IQR, 20.7 to not reached) and 36.2 (IQR, 17.7-53.3) months, respectively (HR, 0.82; 95% CI, 0.680 to 0.996; P = .045). At a 16-month follow-up (cutoff, April 3, 2020; median follow-up, 51.4 months [IQR, 47.0-57.0]), the median OS (511 events; 81% mature) was 41.8 (nab-paclitaxel + gemcitabine) versus 37.7 months (gemcitabine; HR, 0.82; 95% CI, 0.687 to 0.973; P = .0232). At the 5-year follow-up (cutoff, April 9, 2021; median follow-up, 63.2 months [IQR, 60.1-68.7]), the median OS (555 events; 88% mature) was 41.8 versus 37.7 months, respectively (HR, 0.80; 95% CI, 0.678 to 0.947; P = .0091). Eighty-six percent (nab-paclitaxel + gemcitabine) and 68% (gemcitabine) of patients experienced grade ≥ 3 treatment-emergent adverse events. Two patients per study arm died of treatment-emergent adverse events. CONCLUSION: The primary end point (independently assessed DFS) was not met despite favorable OS seen with nab-paclitaxel + gemcitabine.

Hypertension and Vascular Research

Maxwell DL, **Bryson TD**, **Taube D**, **Xu J**, **Peterson E**, and **Harding P**. Deleterious effects of cardiomyocyte-specific prostaglandin E2 EP3 receptor overexpression on cardiac function after myocardial infarction. *Life Sci* 2022; 313:121277. PMID: 36521546. Full Text

Department of Physiology, Wayne State University School of Medicine, USA; Hypertension and Vascular Research Division, Department of Internal Medicine, Henry Ford Health, Detroit, MI, USA.
Hypertension and Vascular Research Division, Department of Internal Medicine, Henry Ford Health, Detroit, MI, USA.
Department of Public Health Sciences, Henry Ford Health, Detroit, MI, USA.
Department of Physiology, Wayne State University School of Medicine, USA; Hypertension and Vascular Research Division, Department of Internal Medicine, Henry Ford Health, Detroit, MI, USA. Electronic address: phardin1@hfhs.org.

AIMS: Prostaglandin E2 (PGE2) is a lipid hormone that signals through 4 different G-protein coupled receptor subtypes which act to regulate key physiological processes. Our laboratory has previously reported that PGE2 through its EP3 receptor reduces cardiac contractility at the level of isolated cardiomyocytes and in the isolated working heart preparation. We therefore hypothesized that cardiomyocyte specific overexpression of the PGE2 EP3 receptor further decreases cardiac function in a mouse model of heart failure produced by myocardial infarction. MAIN METHODS: Our study tested this hypothesis using EP3 transgenic mice (EP3 TG), which overexpress the porcine analogue of human EP3 in the cardiomyocytes, and their wildtype (WT) littermates. Mice were analyzed 2 wks after myocardial infarction (MI) or sham operation by echocardiography, RT-PCR, immunohistochemistry, and histology. KEY FINDINGS: We found that the EP3 TG sham controls had a reduced ejection fraction, reduced fractional shortening, and an increased left ventricular dimension at systole and diastole compared to the WT sham controls. Moreover, there was a further reduction in the EP3 TG mice after myocardial infarction. Additionally, single-cell analysis of cardiomyocytes isolated from EP3 TG mice showed reduced contractility under basal conditions. Overexpression of EP3 significantly increased cardiac hypertrophy, interstitial collagen fraction, macrophage, and T-cell infiltration in the sham operated group. Interestingly, after MI, there were no changes in hypertrophy but there were changes in collagen fraction, and inflammatory cell infiltration. SIGNIFICANCE: Overexpression of EP3 reduces cardiac function under basal conditions and this is exacerbated after myocardial infarction.

Internal Medicine

Ellauzi H, Arora H, Elefteriades JA, Zaffar MA, **Ellauzi R**, and Popescu WM. Cerebrospinal Fluid Drainage for Prevention of Spinal Cord Ischemia in Thoracic Endovascular Aortic Surgery-Pros and Cons. *Aorta (Stamford)* 2022; 10(6):290-297. PMID: 36539146. Full Text

Aortic Institute at Yale New-Haven, Department of Cardiac Surgery, Yale University School of Medicine, New Haven, Connecticut.
Department of Surgery, Istishari Hospital, Amman, Jordan.
Department of Anesthesiology, University of North Carolina School of Medicine, Chapel Hill, North Carolina.
Department of Internal Medicine, Henry Ford Hospital, Detroit, Michigan.
Department of Anesthesiology, Yale University School of Medicine, New Haven, Connecticut.

Thoracic endovascular aortic repair (TEVAR) carries a risk of spinal cord ischemia (SCI) which exerts a devastating impact on patient's quality of life and life expectancy. Although routine prophylactic cerebrospinal fluid (CSF) drainage is not unequivocally supported by current data, several studies have demonstrated favorable outcomes. Patients at high risk for SCI following TEVAR likely will benefit from prophylactic CSF drains. However, the intervention is not risk free, and thorough risk/benefit analysis should be individualized to each patient.

Neurology
Beg AZ, **Rashid F**, Talat A, Haseen MA, Raza N, Akhtar K, Dueholm MKD, and Khan AU. Functional Amyloids in Pseudomonas aeruginosa Are Essential for the Proteome Modulation That Leads to Pathoadaptation in Pulmonary Niches. *Microbiol Spectr* 2022; Epub ahead of print. PMID: 36475836. Full Text

Medical Microbiology Lab, Interdisciplinary Biotechnology Unit, Aligarh Muslim University, Aligarh, Uttar Pradesh, India.
Henry Ford Health System Detroit, Michigan, USA.
Department of Cardiothoracic Surgery, Jawaharlal Nehru Medical College, Aligarh Muslim University, Aligarh, Uttar Pradesh, India.
Department of Anaesthesiology, Jawaharlal Nehru Medical College, Aligarh Muslim University, Aligarh, Uttar Pradesh, India.
Pathology Department, Jawaharlal Nehru Medical College, Aligarh Muslim University, Aligarh, Uttar Pradesh, India.
Center for Microbial Communities, Department of Chemistry and Bioscience, Aalborg University, Aalborg, Denmark.

Persistence and survival of Pseudomonas aeruginosa in chronic lung infections is closely linked to the biofilm lifestyle. One biofilm component, functional amyloid of P. aeruginosa (Fap), imparts structural adaptations for biofilms; however, the role of Fap in pathogenesis is still unclear. Conservation of the fap operon encoding Fap and P. aeruginosa being an opportunistic pathogen of lung infections prompted us to explore its role in lung infection. We found that Fap is essential for establishment of lung infection in rats, as its genetic exclusion led to mild focal infection with quick resolution. Moreover, without an underlying cystic fibrosis (CF) genetic disorder, overexpression of Fap reproduced the CF pathotype. The molecular basis of Fap-mediated pulmonary adaptation was explored through surface-associated proteomics in vitro. Differential proteomics positively associated Fap expression with activation of known proteins related to pulmonary pathoadaptation, attachment, and biofilm fitness. The aggregative bacterial phenotype in the pulmonary niche correlated with Fap-influenced activation of biofilm sustainability regulators and stress response regulators that favored persistence-mediated establishment of pulmonary infection. Fap overexpression upregulated proteins that are abundant in the proteome of P. aeruginosa in colonizing CF lungs. Planktonic lifestyle, defects in anaerobic pathway, and neutrophilic evasion were key factors in the absence of Fap that impaired establishment of infection. We concluded that Fap is essential for cellular equilibration to establish pulmonary infection. Amyloid-induced bacterial aggregation subverted the immune response, leading to chronic infection by collaterally damaging tissue and reinforcing bacterial persistence. IMPORTANCE Pseudomonas aeruginosa is inextricably linked with chronic lung infections. In this study, the well-conserved Fap operon was found to be essential for pathoadaptation in pulmonary infection in a rat lung model. Moreover, the presence of Fap increased pathogenesis and biofilm sustainability by modulating bacterial physiology. Hence, a pathoadaptive role of Fap in pulmonary infections can be exploited for clinical application by targeting amyloids. Furthermore,

genetic conservation and extracellular exposure of Fap make it a commendable target for such interventions.

Neurology
Calderazzo S, Covert M, Alba D, Bowley BE, Pessina MA, Rosene DL, **Buller B**, Medalla M, and Moore TL. Neural recovery after cortical injury: Effects of MSC derived extracellular vesicles on motor circuit remodeling in rhesus monkeys. *IBRO Neurosci Rep* 2022; 13:243-254. PMID: 36590089. Full Text

Anatomy and Neurobiology Dept, BUSM, USA.
Center for Systems Neuroscience, BU, USA.
Henry Ford Health Care System, USA.

Reorganization of motor circuits in the cortex and corticospinal tract are thought to underlie functional recovery after cortical injury, but the mechanisms of neural plasticity that could be therapeutic targets remain unclear. Recent work from our group have shown that systemic treatment with mesenchymal stem cell derived (MSCd) extracellular vesicles (EVs) administered after cortical damage to the primary motor cortex (M1) of rhesus monkeys resulted in a robust recovery of fine motor function and reduced chronic inflammation. Here, we used immunohistochemistry for cfos, an activity-dependent intermediate early gene, to label task-related neurons in the surviving primary motor and premotor cortices, and markers of axonal and synaptic plasticity in the spinal cord. Compared to vehicle, EV treatment was associated with a greater density of cfos(+) pyramidal neurons in the deep layers of M1, greater density of cfos(+) inhibitory interneurons in premotor areas, and lower density of synapses on MAP2+ lower motor neurons in the cervical spinal cord. These data suggest that the anti-inflammatory effects of EVs may reduce injury-related upper motor neuron damage and hyperexcitability, as well as aberrant compensatory re-organization in the cervical spinal cord to improve motor function.

Neurology
Ghimire S, Cady NM, Lehman P, Peterson SR, Shahi SK, **Rashid F**, **Giri S**, and Mangalam AK. Dietary Isoflavones Alter Gut Microbiota and Lipopolysaccharide Biosynthesis to Reduce Inflammation. *Gut Microbes* 2022; 14(1):2127446. PMID: 36179318. Full Text

Department of Pathology University of Iowa Iowa City Iowa USA.
Department of Pathology Graduate Program University of Iowa Iowa City IA USA.
Graduate Program in Immunology University of Iowa Iowa City Iowa USA.
Department of Neurology Henry Ford Health System Detroit MI USA.

The etiopathogenesis of multiple sclerosis (MS) is strongly affected by environmental factors such as diet and the gut microbiota. An isoflavone-rich (ISO) diet was previously shown to reduce the severity of MS in the animal model experimental autoimmune encephalomyelitis (EAE). Translation of this concept to clinical trial where dietary isoflavones may be recommended for MS patients will require preliminary evidence that providing the isoflavone-rich diet to people with MS (PwMS) who lack phytoestrogen-metabolizing bacteria has beneficial effects. We have previously shown that the gut microbiota of PwMS resembles the gut microbiota of mice raised under a phytoestrogen-free (phyto-free) diet in that it lacks phytoestrogen-metabolizing bacteria. To investigate the effects of phytoestrogens on the microbiota inflammatory response and EAE disease severity we switched the diet of mice raised under a phyto-free (PF) diet to an isoflavone-rich diet. Microbiota analysis showed that the change in diet from one that is ISO to one that is PF reduces beneficial bacteria such as Bifidobacterium species. In addition we observed functional differences in lipopolysaccharide (LPS) biosynthesis pathways. Moreover LPS extracted from feces of mice fed an ISO diet induced increased production of anti-inflammatory cytokines from bone marrow-derived macrophages relative to fecal-LPS isolated from mice fed a PF diet. Eventually mice whose diet was switched from a PF diet to an ISO diet trended toward reduced EAE severity and mortality. Overall we show that an isoflavone-rich diet specifically modulates LPS biosynthesis of the gut microbiota imparts an anti-inflammatory response and decreases disease severity.

Neurosurgery
Lawless MH, Tong D, Claus CF, Hanson C, Li C, Park P, **Chang VW**, **Abdulhak MM**, Houseman CM, Bono PL, Carr DA, Richards BF, Kelkar PS, and Soo TM. The Effect of Preoperative Symptom Duration on Patient-Reported Outcomes After Anterior Cervical Discectomy and Fusion in Nonmyelopathic Patients: Analyses From the Michigan Spine Surgery Improvement Collaborative (MSSIC). *Neurosurgery* 2022; Epub ahead of print. PMID: 36524819. Full Text

Division of Neurosurgery, Ascension Providence Hospital, Michigan State University, College of Human Medicine, Southfield, Michigan, USA.
Department of Epidemiology and Biostatistics, Michigan State University, East Lansing, Michigan, USA.
Department of Neurosurgery, University of Michigan, Ann Arbor, Michigan, USA.
Department of Neurosurgery, Henry Ford Hospital, Detroit, Michigan, USA.

BACKGROUND: The effect of preoperative symptom duration (PSD) on patient-reported outcomes (PROs) in anterior cervical discectomy and fusion (ACDF) for radiculopathy is unclear. OBJECTIVE: To determine whether PSD is a predictor for PRO after ACDF for radiculopathy. METHODS: The Michigan Spine Surgery Improvement Collaborative registry was queried between March, 2014, and July, 2019, for patients who underwent ACDF without myelopathy and PROs (baseline, 90 days, 1 year, 2 years). PROs were measured by numerical rating scales for neck/arm pain, Patient-Reported Outcomes Measurement Information System Short Form-Physical Function (PROMIS-PF), EuroQol-5D (EQ5D), and North American Spine Society satisfaction. Univariate analyses were used to evaluate the proportion of patients reaching minimal clinically important differences (MCID). PSD was <3 months, 3 month-1 year, or >1 years. Multiple logistic regression models were used to estimate the association between PSD and PRO reaching MCID. The discriminative ability of the model was evaluated by receiver operating characteristic curve. RESULTS: We included 2233 patients who underwent ACDF with PSD <3 months (278, 12.4%), 3 month-1 year (669, 30%), and >1 years (1286, 57.6%). Univariate analyses demonstrated a greater proportion of patients achieving MCID in <3-month cohort for arm numerical rating scales, PROMIS-PF, EQ5D, and North American Spine Society Satisfaction. Multivariable analyses demonstrated using <3 months PSD as a reference, PSD >1 years was associated with decreased odds of achieving MCID for EQ5D (odds ratio 0.5, CI 0.32-0.80, P = .004). Private insurance and increased baseline PRO were associated with significantly higher odds for achieving PROMIS-PF MCID and EQ5D-MCID. CONCLUSION: Preoperative symptom duration greater than 1 year in patients who underwent ACDF for radiculopathy was associated with worse odds of achieving MCID for multiple PROs.

Neurosurgery
Squires M, **Schultz L**, **Schwalb J**, Park P, **Chang V**, **Nerenz D**, Perez-Cruet M, **Abdulhak M**, Khalil J, and Aleem I. Correlation of mJOA, PROMIS Physical Function, and Patient Satisfaction in Patients with Cervical Myelopathy: An Analysis of the Michigan Spine Surgery Improvement Collaborative (MSSIC) Database. *Spine J* 2022; Epub ahead of print. PMID: 36567055. Full Text

Department of Orthopedic Surgery, University of Michigan, 1500 E Medical Center Dr, Ann Arbor, MI 48109, USA. Electronic address: mdsquire@med.umich.edu.
Henry Ford Health System, 1 Ford Place, Detroit, MI 48202, USA. Electronic address: LSCHULT1@hfhs.org.
Henry Ford Health System, 1 Ford Place, Detroit, MI 48202, USA. Electronic address: JSCHWAL1@hfhs.org.
Department of Neurosurgery, University of Michigan, 1500 E Medical Center Dr, Ann Arbor, MI 48109, USA. Electronic address: ppark@med.umich.edu.
Henry Ford Health System, 1 Ford Place, Detroit, MI 48202, USA. Electronic address: VCHANG1@hfhs.org.
Henry Ford Health System, 1 Ford Place, Detroit, MI 48202, USA. Electronic address: DNERENZ1@hfhs.org.
Beaumont Health System, 3601 W. 13 Mile Rd., Royal Oak, MI 48073, USA. Electronic address: Miguelangelo.Perez-Cruet@beaumont.edu.
Henry Ford Health System, 1 Ford Place, Detroit, MI 48202, USA. Electronic address: MABDULH1@hfhs.org.

Beaumont Health System, 3601 W. 13 Mile Rd., Royal Oak, MI 48073, USA. Electronic address: Jad.Khalil@beaumont.org.
Department of Orthopedic Surgery, University of Michigan, 1500 E Medical Center Dr, Ann Arbor, MI 48109, USA. Electronic address: ialeem@med.umich.edu.

BACKGROUND CONTEXT: Patient-reported outcomes (PROs) are increasingly utilized to evaluate the efficacy and value of spinal procedures. Among patients with cervical myelopathy, the modified Japanese Orthopaedic Association (mJOA) remains the standard instrument, with Patient-Reported Outcomes Measurement Information System (PROMIS) physical function (PF) and patient satisfaction also frequently assessed. These outcomes have not all been directly compared using a large spine registry at 2 years follow-up for cervical myelopathic patients undergoing surgery. PURPOSE: To determine the correlation and association of PROMIS PF, mJOA, and patient satisfaction outcomes in patients undergoing surgery for cervical myelopathy. STUDY DESIGN/SETTING: Retrospective review of a multi-center spine registry database. PATIENT SAMPLE: Adult patients with cervical myelopathy who underwent cervical spine surgery between 2/26/2018 and 4/17/2021. OUTCOME MEASURES: PROMIS PF, mJOA, and North American Spine Society (NASS) patient satisfaction index. METHODS: The MSSIC database was accessed to gather pre- and postoperative outcome data on patients with cervical myelopathy. Spearman's correlation coefficients relating mJOA and PROMIS PF were quantified up to 2 years postoperatively. The effect sizes of the relationship between patient satisfaction with mJOA and PROMIS were determined. Kappa statistics were used to evaluate for agreement between those reaching the minimum clinically important difference (MCID) for mJOA and PROMIS PF. Odds ratios were calculated to determine the association between patient satisfaction and those reaching MCID for mJOA and PROMIS PF. Support for MSSIC is provided by BCBSM and Blue Care Network as part of the BCBSM Value Partnerships program. RESULTS: Data from 2023 patients were included. Moderate to strong correlations were found between mJOA and PROMIS PF at all time points ($p<0.001$). These outcomes had fair agreement at all postoperative time points when comparing those who reached MCID. Satisfaction was strongly related to changes from baseline for both mJOA and PROMIS PF at all time points ($p<0.001$). Odds ratios associating satisfaction with PROMIS PF MCID were higher at all time points compared to mJOA, although the differences were not significant. CONCLUSIONS: PROMIS PF has a strong positive correlation with mJOA up to 2 years postoperatively in patients undergoing surgery for cervical myelopathy, with similar odds of achieving MCID with both instruments. Patient satisfaction is predicted similarly by these outcome measures by 2 years postoperatively. These results affirm the validity of PROMIS PF in the cervical myelopathic population. Given its generalizability and ease of use, PROMIS PF may be a more practical outcome measure for clinical use compared to mJOA.

Obstetrics, Gynecology and Women's Health Services

Briskin RS, **Etta P**, **Luck AM**, **Raffee S**, and **Atiemo HO**. Comparison of Urinary Tract Infection Incidence Following Intradetrusor OnabotulinumtoxinA in Office Versus Operating Room Settings. *Urogynecology (Hagerstown)* 2022; 28(12):842-847. PMID: 36409641. Request Article

From the Division of Female Pelvic Medicine and Reconstructive Surgery, Department of Obstetrics and Gynecology.
Department of Urology, Henry Ford Health System/Wayne State University School of Medicine, Detroit, MI.

IMPORTANCE: Urinary tract infection (UTI) is a known complication of intradetrusor onabotulinumtoxinA (BTX) injection. However, whether administering intradetrusor BTX in different clinical settings affects the risk of postprocedural UTI has not been investigated. OBJECTIVES: The objective of this study was to assess differences in the incidence of postprocedural UTI in women who received intradetrusor BTX in an outpatient office versus an operating room (OR). STUDY DESIGN: We performed a retrospective chart review of intradetrusor BTX procedures at a single institution between 2013 and 2020. Demographic data, comorbidities, and perioperative data were abstracted. The primary outcome was UTI defined as initiation of antibiotics within 30 days following BTX administration based on clinician assessment of symptoms and/or urine culture results. Univariate analysis of patients with and without UTI was performed. RESULTS: A total of 446 intradetrusor BTX procedures performed on female patients either in an outpatient office (n = 160 [35.9%]) or in an OR (n = 286 [64.1%]) were included in the analysis. Within 30

days of BTX administration, UTI was diagnosed after 14 BTX procedures (8.8%) in the office group and 29 BTX procedures (10.1%) in the OR group (P = 0.633). De novo postprocedural urinary retention occurred in more women who were treated in the office than in the OR (13 [9.6%] vs 3 [1.3%], P < 0.001). CONCLUSIONS: Selecting the appropriate setting for BTX administration is dependent on multiple factors. However, the clinical setting in which intradetrusor BTX is administered may not be an important factor in the development of postprocedural UTI, and further research is warranted.

Obstetrics, Gynecology and Women's Health Services

Condon M, **Smith N**, **Ayyash M**, and **Goyert G**. The impact of COVID-19 vaccinations on stillbirth rates among pregnant women in the Metro-Detroit area. *J Natl Med Assoc* 2022; Epub ahead of print. PMID: 36581519. Full Text

Department of Clinical Quality and Safety, Henry Ford Health System, Detroit, MI, United States.
Department of Women's Health, Henry Ford Hospital, Detroit, MI, United States. Electronic address: NSmith22@hfhs.org.
Department of Women's Health, Henry Ford Hospital, Detroit, MI, United States.
Department of Maternal Fetal Medicine, Henry Ford Hospital, Detroit, MI, United States.

Infection by COVID-19 increases maternal morbidity and mortality prompting both the American College of Obstetrics and Gynecology and the Society of Maternal Fetal Medicine to strongly recommend vaccination during pregnancy. Limited data exist assessing the risk of intrauterine fetal death (IUFD) associated with COVID vaccination during pregnancy. This was a retrospective chart review at a large multisite hospital system in Metro Detroit which reviewed data from 13,368 pregnancies. We compared IUFD rates between vaccinated and unvaccinated patients. The rate of stillbirths among unvaccinated women (0.75%) was not statistically different from those who were vaccinated (0.60%). Individuals with government insurance were less likely to be vaccinated and more likely to have IUFD in comparison to patients with private insurance. The rate of stillbirths among Black women was significantly higher than among White women at a rate of 1.1% compared to 0.53% (p=0.008) with no difference in stillbirth rates among vaccinated vs unvaccinated racial distribution. Lastly, it is worth noting that the overall vaccination rate at our healthcare system in pregnancy was very poor (0.26%). In conclusion, this is a large population of highly diverse patients which indicates that COVID-19 vaccination does not lead to IUFD. We plan to use this data to help drive an educational vaccination campaign to try to increase our COVID-19 vaccination rate in our pregnant patients. Systemic racism and social determinants of health have played a large factor in COVID-19 outcomes, and our data highlights that this is the case for IUFD in Black women. Improvements must be made to identify barriers for these women to allow for better pregnancy outcomes. We acknowledge that individuals with government insurance may also have other barriers to healthcare or face healthcare inequity which leaves room for improvement on getting these individuals vaccinated and getting the resources they need to have better pregnancy outcomes.

Ophthalmology and Eye Care Services

Jackson ML, Virgili G, Shepherd JD, Di Nome MA, Fletcher DC, Kaleem MA, Lam LA, Lawrence LM, Sunness JS, and **Riddering AT**. Vision Rehabilitation Preferred Practice Pattern®. *Ophthalmology* 2022; Epub ahead of print. PMID: 36543605. Full Text

Department of Ophthalmology, University of British Columbia, Vancouver, Canada.
Department of NEUROFARBA, Eye Clinic, Careggi University Hospital, University of Florence, Florence, Italy; and Centre for Public Health, Queen's University Belfast, Belfast, United Kingdom.
Weigel Williamson Center for Visual Rehabilitation, Department of Ophthalmology & Visual Sciences, University of Nebraska Medical Center, Omaha, Nebraska.
Departments of Ophthalmology, Neurosurgery, Mayo Clinic, Phoenix, Arizona.
University of Kansas Medical Center, Department of Ophthalmology and KU Eye Center, Kansas City, Kansas and Retina Consultants of Southwest Florida, Ft. Myers, Florida, Envision, Wichita, Kansas.
Wilmer Eye Institute, Johns Hopkins School of Medicine, Baltimore, Maryland.
USC Roski Eye Institute, University of Southern California (USC) Keck School of Medicine, Los Angeles, California.
Private Practice, Salina, Kansas.

Hoover Low Vision Rehabilitation Services and Department of Ophthalmology, Greater Baltimore Medical Center, Towson, Maryland; and Ophthalmology, University of Maryland School of Medicine, Baltimore, Maryland.
Henry Ford Health, Department of Ophthalmology, Detroit, Michigan.

Orthopedics/Bone and Joint Center
Castle JP, Jildeh TR, **Chaudhry F**, **Turner EH**, **Abbas MJ**, Mahmoud O, **Hengy M**, Okoroha KR, and **Lynch TS**. Machine learning model identifies preoperative opioid use, male sex, and elevated BMI as predictive factors for of prolonged opioid consumption following arthroscopic meniscal surgery. *Arthroscopy* 2022; Epub ahead of print. PMID: 36586470. Full Text

Henry Ford Hospital, Department of Orthopaedic Surgery, 2799 W. Grand Blvd, Detroit, MI 48202. Electronic address: jcastle1@hfhs.org.
The Steadman Clinic, 180 S Frontage Rd E, Vail, CO 81657.
Detroit Medical Center, Department of General Surgery, 4201 St Antoine, Detroit, MI 48201.
Henry Ford Hospital, Department of Orthopaedic Surgery, 2799 W. Grand Blvd, Detroit, MI 48202.
Wayne State University School of Medicine, 540 E. Canfield Ave. Detroit, MI 48201.
Mayo Clinic Department of Orthopedic Surgery, 600 Hennepin Ave, Suite 310 Minneapolis, MN 55403.

PURPOSE: To develop a predictive machine learning model to identify prognostic factors for continued opioid prescriptions after arthroscopic meniscus surgery. METHODS: Patients undergoing arthroscopic meniscal surgery, such as meniscus debridement, repair, or revision at a single institution from 2013 to 2017 were retrospectively followed up to 1 year postoperatively. Procedural details were recorded, including concomitant procedures, primary versus revision, and whether a partial debridement or a repair was performed. Intraoperative arthritis severity was measured using the Outerbridge Classification. The number of opioid prescriptions in each month were recorded. Primary analysis used was multivariate Cox-Regression model. We then created a naïve Bayesian model, a machine learning classifier that utilizes Bayes' theorem with an assumption of independence between variables. RESULTS: A total of 581 patients were reviewed. Postoperative opioid refills occurred in 98 patients (16.9%). Using multivariate logistic modeling, independent risk factors for opioid refills included male sex, larger BMI, chronic preoperative opioid use while meniscus resection demonstrated decreased likelihood of refills. Concomitant procedures, revision procedures, and presence of arthritis graded by the Outerbridge classification were not significant predictors of postoperative opioid refills. The Naïve Bayesian model for extended postoperative opioid use demonstrated good fit with our cohort with an area under the curve of 0.79, sensitivity of 94.5%, positive predictive value (PPV) of 83%, and a detection rate of 78.2%. The two most important features in the model were preoperative opioid use and male sex. CONCLUSION: After arthroscopic meniscus surgery, preoperative opioid consumption and male sex were the most significant predictors for sustained opioid use beyond 1 month postoperatively. Intraoperative arthritis was not an independent risk factor for continued refills. A machine learning algorithm performed with high accuracy, although with a high false positive rate, to function as a screening tool to identify patients filling additional narcotic prescriptions after surgery.

Orthopedics/Bone and Joint Center
Elhage KG, **Yedulla NR**, **Cross AG**, Mehta N, Guo EW, Bernstein DN, and **Makhni E**. Forearm Flexor Tendon Injury in Adolescent Athletes: Risk Factors, Treatment, and Prevention. *Curr Sports Med Rep* 2022; 21(12):443-447. PMID: 36508600. Full Text

Department of Orthopaedic Surgery, Henry Ford Health, Detroit, MI.
Department of Orthopaedic Surgery, Rush University Medical Center, Chicago, IL.
Department of Orthopaedic Surgery, University of Michigan Medicine, Ann Arbor, MI.
Harvard Combined Orthopaedic Residency Program, Boston, MA.

Injury to the flexor pronator mass is a common condition that is especially prevalent in overhead throwing athletes. The increasing incidence of these injuries has promoted considerable efforts in research to better understand the pathology, risk factors, and potential mechanisms to prevent injury in these athletes. While there are numerous intrinsic and extrinsic factors associated with injury, a common theme

involves chronic overuse and microtrauma with inadequate resting intervals between performances. The purpose of this review is to discuss medial elbow injuries in young athletes with a particular focus on the flexor pronator mass.

Orthopedics/Bone and Joint Center
Tramer JS, **Castle JP**, **Gaudiani MA**, **Lizzio VA**, **McGee A**, Freehill MT, and **Lynch TS**. Upper extremity injuries have the poorest return to play and most time lost in professional baseball: a Systematic Review of injuries in major league baseball. *Arthroscopy* 2022; Epub ahead of print. PMID: 36587750. Full Text

Stanford University, Department of Orthopedic Surgery, 450 Broadway, MC 6342, Redwood City, CA, 94063. Electronic address: joe.tramer@gmail.com.
Henry Ford Hospital, Department of Orthopaedic Surgery, 2799 W. Grand Blvd, Detroit, MI 48202.
Stanford University, Department of Orthopedic Surgery, 450 Broadway, MC 6342, Redwood City, CA, 94063.

PURPOSE: The aim of this systematic review is to summarize the incidence of injuries occurring in professional baseball and compare player outcomes reported in the literature METHODS: We conducted a systematic review utilizing the PRISMA (Preferred Reporting Items for Systematic Reviews and Meta-Analyses) guidelines across three databases (PubMed, MEDLINE, Embase). Inclusion criteria were studies of injury incidences and/or injury outcomes on active MLB athletes and studies published in the English language. Exclusion criteria was non-MLB players, case series and case report studies with a cohort of < 3 players, and/or review articles. RESULTS: A total of 477 articles were identified from the initial search of three databases with 105 studies meeting inclusion criteria. Amongst these articles, the most common injuries studied were elbow (38%), shoulder (14%), hip/groin (11%), hand/wrist (7%), head/face (7%), knee (7%), spine (5%), and foot/ankle (3%). Injuries with the highest incidence included hand/wrist (150.3 per year), hamstring (7.8-73.5 per year), ulnar collateral ligament tears (0.23-26.8 per year), gastrocnemius strains (24.2 per year), and concussions (3.6-20.5 per year). Lowest rates of return to play were seen following shoulder labral tears (40-72.5%), rotator cuff tears (33.3-87%), and UCL tears (51-87.9%). The injuries leading to most time away from sport included elbow UCL tears (average 90.3 days treated non-operatively to 622.8 days following revision reconstruction), shoulder labral tears (average 315-492 days) and ACL tears (average 156.2-417.5 days). Following ACL tears, rotator cuff tears, shoulder labral tears, and hip femoroacetabular impingement (FAI) requiring arthroscopy, athletes had a significantly lower workloads compared to prior to injury upon return to play. CONCLUSION: Most published investigations focus on elbow injuries of the UCL, with variable RTP and mixed performance following surgery. Ulnar collateral ligament tears, shoulder labral tears, and anterior cruciate ligament tears result in the most missed time. Upper extremity injury such as shoulder labral tears, rotator cuff tears, and UCL tears had the poorest RTP rates. Workload was most affected following ACL reconstruction, rotator cuff repair, shoulder labral repair, and hip arthroscopy for FAI.

Otolaryngology – Head and Neck Surgery
Calderón-Garcidueñas L, Kulesza R, Greenough GP, García-Rojas E, Revueltas-Ficachi P, Rico-Villanueva A, Flores-Vázquez JO, Brito-Aguilar R, Ramírez-Sánchez S, Vacaseydel-Aceves N, Cortes-Flores AP, **Mansour Y**, Torres-Jardón R, Villarreal-Ríos R, Koseoglu E, Stommel EW, and Mukherjee PS. Fall Risk, Sleep Behavior, and Sleep-Related Movement Disorders in Young Urbanites Exposed to Air Pollution. *J Alzheimers Dis* 2022; Epub ahead of print. PMID: 36502327. Request Article

The University of Montana, Missoula, MT, USA.
Universidad del Valle de México, Mexico City, México.
Auditory Research Center, Lake Erie College of Osteopathic Medicine, Erie, PA, USA.
Department of Neurology, Geisel School of Medicine at Dartmouth, Hanover NH, USA.
Emergency Department, Hospital San Angel Inn Sur, Mexico City, Mexico.
Department of Otolaryngology -Head and Neck Surgery, Henry Ford Macomb Hospital, Clinton Township, MI, USA.
Instituto de Ciencias de la Atmósfera y Cambio Climático, Universidad Nacional, Autónoma de México, México.
Universidad Autónoma de Piedras Negras, Piedras Negras, Coahuila, México.

Neurology Department, Erciyes University, Kayseri, Turkey.
Interdisciplinary Statistical Research Unit, Indian Statistical Institute, Kolkata, India.

BACKGROUND: Quadruple aberrant hyperphosphorylated tau, amyloid-β, α-synuclein, and TDP-43 pathology had been documented in 202/203 forensic autopsies in Metropolitan Mexico City ≤40-year-olds with high exposures to ultrafine particulate matter and engineered nanoparticles. Cognition deficits, gait, equilibrium abnormalities, and MRI frontal, temporal, caudate, and cerebellar atrophy are documented in young adults. OBJECTIVE: This study aimed to identify an association between falls, probable Rapid Eye Movement Sleep Behavior Disorder (pRBD), restless leg syndrome (RLS), and insomnia in 2,466 Mexican, college-educated volunteers (32.5±12.4 years). METHODS: The anonymous, online study applied the pRBD and RLS Single-Questions and self-reported night-time sleep duration, excessive daytime sleepiness, insomnia, and falls. RESULTS: Fall risk was strongly associated with pRBD and RLS. Subjects who fell at least once in the last year have an OR=1.8137 [1.5352, 2.1426] of answering yes to pRBD and/or RLS questions, documented in 29% and 24% of volunteers, respectively. Subjects fell mostly outdoors (12:01 pm to 6:00 pm), 43% complained of early wake up hours, and 35% complained of sleep onset insomnia (EOI). EOI individuals have an OR of 2.5971 [2.1408, 3.1506] of answering yes to the RLS question. CONCLUSION: There is a robust association between falls, pRBD, and RLS, strongly suggesting misfolded proteinopathies involving critical brainstem arousal and motor hubs might play a crucial role. Nanoparticles are likely a significant risk for falls, sleep disorders, insomnia, and preventable neurodegenerative lethal diseases, thus characterizing air particulate pollutants' chemical composition, emission sources, and cumulative exposure concentrations are strongly recommended.

Otolaryngology – Head and Neck Surgery

Contrera KJ, **Tam S**, Pytynia K, Diaz EM, Jr., Hessel AC, Goepfert RP, Lango M, Su SY, Myers JN, Weber RS, Eguia A, Pisters PWT, Adair DK, Nair AS, Rosenthal DI, Mayo L, Chronowski GM, Zafereo ME, and Shah SJ. Impact of Cancer Care Regionalization on Patient Volume. *Ann Surg Oncol* 2022; Epub ahead of print. PMID: 36581726. Full Text

Department of Head and Neck Surgery, The University of Texas MD Anderson Cancer Center, Houston, TX, USA.
Department of Otolaryngology-Head and Neck Surgery, Henry Ford Health System, Detroit, MI, USA.
Department of Otorhinolaryngology-Head and Neck Surgery, McGovern Medical School, University of Texas Health Science Center, Houston, TX, USA.
The University of Texas MD Anderson Cancer Center, Houston, TX, USA.
Department of Global Business Development, The University of Texas MD Anderson Cancer Center, Houston, TX, USA.
Department of Radiation Oncology, The University of Texas MD Anderson Cancer Center, Houston, TX, USA.
Department of Head and Neck Surgery, The University of Texas MD Anderson Cancer Center, Houston, TX, USA. mzafereo@mdanderson.org.

BACKGROUND: Cancer centers are regionalizing care to expand patient access, but the effects on patient volume are unknown. This study aimed to compare patient volumes before and after the establishment of head and neck regional care centers (HNRCCs). METHODS: This study analyzed 35,394 unique new patient visits at MD Anderson Cancer Center (MDACC) before and after the creation of HNRCCs. Univariate regression estimated the rate of increase in new patient appointments. Geospatial analysis evaluated patient origin and distribution. RESULTS: The mean new patients per year in 2006-2011 versus 2012-2017 was 2735 ± 156 patients versus 3155 ± 207 patients, including 464 ± 78 patients at HNRCCs, reflecting a 38.4 % increase in overall patient volumes. The rate of increase in new patient appointments did not differ significantly before and after HNRCCs (121.9 vs 95.8 patients/year; P = 0.519). The patients from counties near HNRCCs, showed a 210.8 % increase in appointments overall, 33.8 % of which were at an HNRCC. At the main campus exclusively, the shift in regional patients to HNRCCs coincided with a lower rate of increase in patients from the MDACC service area (33.7 vs. 11.0 patients/year; P = 0.035), but the trend was toward a greater increase in out-of-state patients (25.7 vs. 40.3 patients/year; P = 0.299). CONCLUSIONS: The creation of HNRCCs coincided with stable increases

in new patient volume, and a sizeable minority of patients sought care at regional centers. Regional patients shifted to the HNRCCs, and out-of-state patient volume increased at the main campus, optimizing access for both local and out-of-state patients.

Otolaryngology – Head and Neck Surgery

Howell R, Tang A, Allen J, Altaye M, Amin M, Bayan S, Belafsky P, Cervenka B, deSilva B, Dion G, Ekbom D, Friedman A, Fritz M, Giliberto JP, Guardiani E, Harmon J, Kasperbauer JL, Khosla S, Kim B, Kuhn M, Kwak P, Ma Y, Madden L, Matrka L, **Mayerhoff R**, **Piraka C**, Rosen C, Tabangin ME, Wahab SA, Wilson K, Wright SC, Young V, Yuen S, and Postma GN. Killian Jamieson Diverticulum, the Great Mimicker: A Case Series and Contemporary Review. *Laryngoscope* 2022; Epub ahead of print. PMID: 36453465. Full Text

Department of Otolaryngology-Head and Neck Surgery, University of Cincinnati, Cincinnati, Ohio, USA.
Department of Surgery, University of Auckland, Auckland, New Zealand.
Division of Biostatistics and Epidemiology, Cincinnati Children's Hospital Medical Center, Cincinnati, Ohio, USA.
Department of Otolaryngology-Head and Neck Surgery, New York University, New York, New York, USA.
Department of Otolaryngology-Head and Neck Surgery, Mayo Clinic, Rochester, Minnesota, USA.
Department of Otolaryngology-Head and Neck Surgery, University of California, Davis, Davis, California, USA.
Department of Otolaryngology-Head and Neck Surgery, Ohio State University, Columbus, Ohio, USA.
Department of Otolaryngology-Head and Neck Surgery, University of Kentucky, Lexington, Kentucky, USA.
Department of Otolaryngology-Head and Neck Surgery, University of Washington, Seattle, Washington, USA.
Department of Otolaryngology-Head and Neck Surgery, Wake Forest University, Winston-Salem, North Carolina, USA.
Department of Otolaryngology-Head and Neck Surgery, University of California - San Francisco, San Francisco, California, USA.
Department of Otolaryngology-Head and Neck Surgery, Henry Ford Health System, Detroit, Michigan, USA.
Department of Gastroenterology/Hepatology, Henry Ford Health System, Detroit, Michigan, USA.
Department of Radiology, University of Cincinnati, Cincinnati, Ohio, USA.
Department of Otolaryngology-Head and Neck Surgery, University of Maryland, Baltimore, Maryland, USA.
Department of Otolaryngology-Head and Neck Surgery, Medical College of Georgia at Augusta University Health, Augusta, Georgia, USA.

OBJECTIVE: To assess barium esophagram (BAS) as a diagnostic marker for patients with Killian Jamieson diverticula (KJD). METHODS: Prospective, multicenter cohort study of individuals enrolled in the Prospective OUtcomes of Cricopharyngeus Hypertonicity (POUCH) Collaborative. Patient demographics, comorbidities, radiographic imaging reports, laryngoscopy findings, patient-reported outcome measures (PROM), and operative reporting were abstracted from a REDCap database and summarized using means, medians, percentages, frequencies. Paired t-tests and Wilcoxon Signed Rank test were used to test pre- to post-operative differences in RSI, EAT-10, and VHI-10 scores. Diagnostic test evaluation including sensitivity, specificity, positive, and negative predictive value with 95% confidence intervals were calculated comparing BAS findings to operative report. RESULTS: A total of 287 persons were enrolled; 13 (4%) patients were identified with confirmed KJD on operative reports. 100% underwent open transcervical excision. BAS has a 46.2% (95% confidence interval [CI]: 23.2, 70.9) sensitivity and 97.8% (95% CI: 95.3, 99.0) specificity in detecting a KJD and 50% (95% CI: 25.4, 74.6) positive predictive value but 97.4% (95%CI: 94.8, 98.7) negative predictive value. Preoperatively, patients reported mean (SD) RSI and EAT-10 of 19.4 (9) and 8.3 (7.5) accordingly. Postoperatively, patients reported mean (SD) RSI and EAT-10 as 5.4 (6.2) and 2.3 (3.3). Both changes in RSI and EAT-10 were statistically significant ($p = 0.008$, $p = 0.03$). CONCLUSION: KJD are rare and represent <5% of hypopharyngeal diverticula undergoing surgical intervention. Open transcervical surgery significantly

improves symptoms of dysphagia. BAS has high specificity but low sensitivity in detecting KJD. LEVEL OF EVIDENCE: Level 4 Laryngoscope, 2022.

Pathology and Laboratory Medicine
Al-Obaidy KI, Magers MJ, and Idrees MT. Testicular Cancer: Contemporary Updates in Staging. *Surg Pathol Clin* 2022; 15(4):745-757. PMID: 36344187. Full Text

Department of Pathology and Laboratory Medicine, Henry Ford Health, Detroit, MI 48202, USA.
IHA Pathology and Laboratory Medicine, Ann Arbor, MI 48106, USA.
Department of Pathology, Indiana University School of Medicine, Indianapolis, IN 46202, USA. Electronic address: midrees@iupui.edu.

Testicular tumors are the most common solid tumors in young men, the vast majority of which are of germ cell origin. The staging of human cancers is paramount to correct patient management. Staging systems have passed through several developments leading to the release of the most recent 8th edition of the American Joint Committee for Cancer (AJCC) staging manual, which is based on the current understanding of tumor behavior and spread. In this review, the authors summarize the current AJCC staging of the germ cell tumors, highlight essential concepts, and provide insight into the most important parameters of testicular tumors.

Pathology and Laboratory Medicine
Sangoi AR, **Al-Obaidy KI**, Cheng L, Kao CS, Chan E, **Sadasivan S**, **Levin AM**, Alvarado-Cabrero I, Kunju LP, Mehra R, Mannan R, Wang X, Dhillon J, Tretiakova M, Smith SC, Hes O, and Williamson SR. Clear Cell Renal Cell Carcinoma with Focal Psammomatous Calcifications: A Rare Occurrence Mimicking Translocation Carcinoma. *Histopathology* 2022; Epub ahead of print. PMID: 36564980. Full Text

El Camino Hospital, Mountain View, CA.
Henry Ford Health System, Detroit, MI.
Brown University Warren Albert Medical School, Providence, RI.
Stanford Medicine/Stanford University, Stanford, CA.
University of California, San Francisco, San Francisco, CA.
Mexican Oncology Hospital SXXI, IMSS, Mexico City, Mexico.
University of Michigan, Ann Arbor, MI.
H. Lee Moffitt Cancer Center & Research Institute, Tampa, FL.
University of Washington, Seattle, WA.
VCU School of Medicine, Richmond, VA.
Biopticka laboratory., Plzen, Czech Republic.
Cleveland Clinic, Cleveland, OH.

AIMS: Renal cell carcinoma (RCC) with clear cells and psammoma-like calcifications would often raise suspicion for MITF family translocation RCC. However, we have rarely encountered tumors consistent with clear cell RCC that contain focal psammomatous calcifications. METHODS & RESULTS: We identified clear cell RCCs with psammomatous calcifications from multiple institutions and performed immunohistochemistry and fluorescence and RNA in situ hybridization (FISH and RNA ISH). Twenty-one tumors were identified: 12 men, 9 women, ages 45 to 83 years. Tumor size was 2.3 to 14.0 cm (median 6.75 cm). Nucleolar grade was 3 (n=14), 2 (n=4), or 4 (n=3). In addition to clear cell pattern, morphology included eosinophilic (n=12), syncytial giant cell (n=4), rhabdoid (n=2), branched glandular (n=1), early spindle cell (n=1), and poorly differentiated components (n=1). Labeling for CA9 was usually 80-100% of the tumor cells (n=17/21) but was sometimes decreased in areas of eosinophilic cells (n=4). All (19/19) were positive for CD10. Most (19/20) were positive for AMACR (variable staining, 20-100%). Staining was negative for keratin 7, although 4 showed rare positive cells (4/20). Results were negative for cathepsin K (0/19), melan A (0/17), HMB45 (0/17), TFE3 (0/5), TRIM63 RNA-ISH (0/13), and TFE3 (0/19) and TFEB rearrangements (0/12). Seven of 19 (37%) showed chromosome 3p deletion. One (1/19) showed trisomy 7 and 17 without papillary features. CONCLUSIONS: Psammomatous calcifications in RCC with a clear cell pattern suggests a diagnosis of MITF family translocation RCC; however, psammomatous calcifications can rarely be found in true clear cell RCC.

Pathology and Laboratory Medicine

Thangaiah JJ, McHugh KE, **Yuan L**, Reynolds JP, Cruise MW, and Policarpio-Nicolas MLC. Revisiting the cytologic features of autoimmune pancreatitis: An institutional experience. *Cancer Cytopathol* 2022; Epub ahead of print. PMID: 36574153. Full Text

Department of Laboratory Medicine and Pathology, Mayo Clinic Rochester, Rochester, Minnesota, USA.
Department of Pathology, Mayo Clinic Arizona, Phoenix, Arizona, USA.
Department of Pathology, Henry Ford Hospital, Detroit, Michigan, USA.
Department of Pathology, Mayo Clinic Florida, Jacksonville, Florida, USA.
Department of Pathology and Laboratory Medicine, Cleveland Clinic, Cleveland, Ohio, USA.

BACKGROUND: Autoimmune pancreatitis (AIP) is a known mimicker of pancreatic ductal adenocarcinoma both clinically and radiologically. In this study, the authors present their institutional experience in diagnosing AIP on cytology and correlate results with the histologic findings. METHODS: A 14-year computerized search for patients who had histologically confirmed AIP with concurrent or prior cytology was performed. Clinical data, cytology findings, and surgical pathology results were reviewed for analysis. RESULTS: Eighteen patients were identified. The patients showed a male predominance, with a mean age of 59 years. Jaundice, weight loss, and abdominal pain were the most common clinical presentation. Five of 12 patients who were tested for serum immunoglobulin G4 had elevated levels. Cytologic findings of 16 cases that were available for review showed markedly inflamed fibrous stroma (54%) and cytologic atypia (50%). The final cytologic diagnoses were suspicious for adenocarcinoma (n = 1), atypical (n = 8), and benign/negative (n = 9). The corresponding surgical pathology diagnoses were classified as type 1 (n = 10), type 2 (n = 6), and AIP, not otherwise specified (n = 2). All type 2 AIP cases had at least atypical cytologic diagnoses, with one called suspicious for adenocarcinoma and another called adenocarcinoma at the time of rapid on-site evaluation. In contrast, eight of 10 type 1 AIP cases were negative/benign, and two of 10 were atypical. In these two atypical cases, the possibility of AIP was raised because of the presence of inflamed stroma.

Pharmacy

Lucas SR, **Pollak E**, and **Makowski C**. A failure in the medication delivery system-how disclosure and systems investigation improve patient safety. *J Healthc Risk Manag* 2022; Epub ahead of print. PMID: 36463558. Full Text

Biomedical Engineering Forensic Services, Jensen Hughes, Baltimore, Maryland, USA.
Quality and Performance Excellence, Anesthesiology and Perioperative Medicine, Henry Ford Health, Detroit, Michigan, USA.
Department of Pharmacy Services, Henry Ford Health, Detroit, Michigan, USA.

A recent medication error at Vanderbilt University Medical Center contributed to the death of a patient. The ensuing criminal indictment of the administering nurse has shaken the medical community. This has led to clinical staff questioning whether they can disclose patient safety incidents without fear of criminal prosecution. However, because of the publicity of this case, hospitals can benefit from the lessons learned and mitigate the risk of this and similar events at their facilities. To uncover the most impactful and relevant safety recommendations, the Vanderbilt case is examined from a systems investigation perspective using the available public information gathered from media reports, the Tennessee Bureau of Investigation report, and Vanderbilt's corrective action plan submitted to CMS. We present an example of how hospitals can benefit from disclosure: Henry Ford Health used the Vanderbilt case study as part of its medication safety continuous improvement initiatives, which are underpinned by available medication safety recommendations from the Institute for Safe Medication Practices. Using this experience and the lessons learned from the Vanderbilt case, a proactive action plan is presented for hospitals nationwide to prevent the recurrence of this medication error. Without disclosure, these analyses and safety recommendations would not have been possible.

Pharmacy

Palmer S, **Patel A**, Wang C, Patel B, Zeidner J, Foster M, Muluneh B, and Buhlinger K. Outpatient initiation of venetoclax in patients with acute myeloid leukemia. *J Oncol Pharm Pract* 2022; Epub ahead of print. PMID: 36474407. Full Text

6684Department of Pharmacy, Oregon Health and Sciences University Hospital, Portland, OR, USA.
2971Department of Pharmacy, Henry Ford Health, Detroit, MI, USA.
Department of Pharmacy, MD Anderson Cancer Center, Houston, TX, USA.
Department of Medicine for Foster and Zeidner, Department of Pharmacy for Buhlinger and Patel and Muluneh, University of North Carolina Medical Center, Chapel Hill, NC, USA.
Lineberger Comprehensive Cancer Center, Chapel Hill, NC, USA.
15521Eshelman School of Pharmacy, University of North Carolina, Chapel Hill, NC, USA.

INTRODUCTION: Venetoclax is a treatment option in patients with acute myeloid leukemia (AML) in both the front-line and relapsed/refractory settings. Initiation of therapy has been previously restricted to the inpatient setting at some institutions due to a risk of tumor lysis syndrome (TLS) and limitations in medication access efficiency given the high cost of therapy. METHODS: We assessed the safety of initiating venetoclax in the outpatient setting through a single-arm, retrospective study of adult AML patients between April 1, 2019 and June 30, 2020. RESULTS: Eighty-two patients started venetoclax during this time, with 47 (57%) patients initiated in the outpatient setting. Fifty-five percent of patients received venetoclax as first-line treatment for AML (n = 45) and 45% of patients received venetoclax for relapsed/refractory AML (n = 37). Successful initiation, defined as no hospitalizations secondary to TLS within seven days of therapy initiation, occurred in 98% of patients. The rate of TLS was 2.1% (n = 1) following venetoclax initiation. TLS symptoms were managed during hospitalization, requiring only one day of missed AML therapy. Median turnaround time for medication access was three days. Hospitalizations within seven days occurred in 17% of patients (n = 8), with the majority due to febrile neutropenia. CONCLUSIONS: The results of our study provide further evidence for the safety and feasibility of initiating venetoclax in the outpatient setting with a pharmacist-led interdisciplinary protocol.

Public Health Sciences

Abouelella DK, Canick JE, Barnes JM, Rohde RL, Watts TL, **Adjei Boakye E**, and Osazuwa-Peters N. Human papillomavirus vaccine uptake among teens before and during the COVID-19 pandemic in the United States. *Hum Vaccin Immunother* 2022; 18(7):2148825. PMID: 36484115. Full Text

Department of Head and Neck Surgery & Communication Sciences, Duke University School of Medicine, Durham, NC, USA.
Duke University School of Medicine, Durham, NC, USA.
Department of Radiation Oncology, Washington University School of Medicine in St Louis, St Louis, MO, USA.
Department of Otolaryngology & Communication Sciences, Medical College of Wisconsin, Milwaukee, WI, USA.
Duke Cancer Institute, Duke University, Durham, NC, USA.
Department of Public Health Sciences, Henry Ford Health System, Detroit, MI, USA.
Department of Otolaryngology-Head and Neck Surgery, Henry Ford Health System, Detroit, MI, USA.
Department of Population Health Sciences, School of Medicine, Duke University, Durham, NC, USA.

It is unclear how the COVID-19 pandemic impacted human papillomavirus (HPV) vaccine uptake and which sociodemographic groups may have been most impacted. We aimed to assess differences in HPV vaccine uptake (initiation and completion) before and during the pandemic in the United States. We conducted a cross-sectional study using data from the 2019 to 2020 National Immunization Surveys - Teen (NIS-Teen), comparing vaccine initiation and completion rates in 2019 vs. 2020, based on confirmed reports by a healthcare provider. Weighted logistic regression analysis estimated odds of vaccine initiation and completion for both adolescent and parental characteristics. There were 18,788 adolescents in 2019 and 20,162 in 2020. There was 3.6% increase in HPV vaccine initiation (71.5% vs. 75.1%) and a 4.4% in completion (54.2% vs. 58.6%) rates from 2019 to 2020. In 2020, Non-Hispanic White teens were significantly less likely to initiate (aOR = 0.62, 95% CI: 0.49, 0.79) and complete

(aOR = 0.71, 95% CI: 0.58, 0.86) vaccine uptake compared with non-Hispanic Black teens. Additionally, teens who lived above the poverty line were also less likely to initiate HPV vaccination (aOR = 0.63, 95% CI: 0.49, 0.80) or complete them (aOR = 0.73, 95% CI: 0.60, 0.90), compared to those who lived below the poverty line. During the COVID-19 pandemic in 2020, some historically advantaged socioeconomic groups such as those living above the poverty line were less likely to receive HPV vaccine. The impact of the pandemic on HPV vaccine uptake may transcend traditional access to care factors.

Public Health Sciences

Adjei Boakye E, McKinney SL, Whittington KD, Boyer VE, Franca MC, Lee M, McKinnies RC, Collins SK, and Gerend MA. Association between Sexual Activity and Human Papillomavirus (HPV) Vaccine Initiation and Completion among College Students. *Vaccines (Basel)* 2022; 10(12). PMID: 36560489. Full Text

Department of Otolaryngology-Head and Neck Surgery, Henry Ford Health System, One Ford Place, Detroit, MI 48202, USA.
Department of Public Health Sciences, Henry Ford Health System, One Ford Place, Detroit, MI 48202, USA.
Department of Dental Hygiene, School of Health Sciences, Southern Illinois University, 1263 Lincoln Dr, Carbondale, IL 62901, USA.
Department of Nursing, School of Health Sciences, Southern Illinois University, 1263 Lincoln Dr, Carbondale, IL 62901, USA.
Department of Communication Disorders and Sciences, School of Health Sciences, Southern Illinois University, 1263 Lincoln Dr, Carbondale, IL 62901, USA.
Department of Population Science and Policy, Southern Illinois University School of Medicine, 201 E. Madison Street, Springfield, IL 62794, USA.
Department of Radiologic Sciences, School of Health Sciences, Southern Illinois University, 1263 Lincoln Dr, Carbondale, IL 62901, USA.
Department of Health Care Management, School of Health Sciences, Southern Illinois University, 1263 Lincoln Dr, Carbondale, IL 62901, USA.
Department of Behavioral Sciences and Social Medicine, Florida State University College of Medicine, 1115 West Call Street, Tallahassee, FL 32306, USA.

HPV vaccination is most effective if received before initiation of sexual activity. Previous studies suggested that young adult women who were not sexually active were not interested in receiving the vaccine because they did not think it was necessary. Whether this misperception is still prevalent today-and also shared by men-is unknown. This study examined whether sexual activity was associated with HPV vaccine uptake (initiation and completion) among university students. A cross-sectional study was conducted between February and May 2021 among students (n = 951) at a public Midwestern University. Sexual activity was categorized as "never" or "ever" had oral and/or vaginal sex. Outcome variables were HPV vaccine initiation, defined as receipt of ≥1 dose, and completion, defined as receipt of ≥3 doses. Multivariable logistic regression models estimated the association between sexual activity and HPV vaccine uptake, adjusting for sociodemographic factors. Approximately 18% of students reported never engaging in sexual activity. Overall, 45.5% initiated the HPV vaccine, and 16.5% completed the vaccine series. After adjusting for covariates, compared to students that reported never engaging in sexual activity, those that had ever engaged in sexual activity were more likely to have initiated the vaccine series (aOR = 2.06, 95% CI: 1.34-3.17); however, no difference was observed for completion. HPV vaccination was low; sexually naïve students were less likely to initiate the HPV vaccine. Since sexually naïve students may benefit from receiving the HPV vaccination, targeted interventions should be implemented towards this population to help increase vaccination rates and prevent HPV-associated diseases.

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, Zhu Y, **Joseph CLM**, Singh AM, Hartert T, Cacho F, Karagas MR, North-Reid T, Lester BM, Kelly NR, Ganiban JM, Chu SH, O'Connor TG, Fry RC, Norman G, Trasande L, Restrepo B, James P, and Oken E. Associations of Neighborhood Opportunity and Social Vulnerability With Trajectories of Childhood Body Mass Index and Obesity Among US Children. *JAMA Netw Open* 2022; 5(12):e2247957. PMID: 36547983. Full Text

Division of Chronic Disease Research Across the Lifecourse, Department of Population Medicine, Harvard Medical School and Harvard Pilgrim Health Care Institute, Boston, Massachusetts.
Department of Epidemiology, Colorado School of Public Health, University of Colorado Anschutz Medical Campus, Aurora.
Lifecourse Epidemiology of Adiposity and Diabetes (LEAD) Center, University of Colorado Anschutz Medical Campus, Aurora.
Department of Pediatrics, University of Colorado Anschutz Medical Campus, Aurora.
Department of Obstetrics, Gynecology and Reproductive Sciences, University of California, San Francisco, San Francisco.
Department of Civil and Environmental Engineering, Northeastern University, Boston, Massachusetts.
UPR Medical Sciences Campus, University of Puerto Rico Graduate School of Public Health, San Juan.
Department of Pediatrics, Hackensack Meridian School of Medicine, Nutley, New Jersey.
Department of Pediatrics, Albert Einstein College of Medicine, New York, New York.
Department of Epidemiology, Harvard T.H. Chan School of Public Health, Boston, Massachusetts.
Channing Division of Network Medicine, Brigham and Women's Hospital, Harvard Medical School, Boston, Massachusetts.
Department of Emergency Medicine, Massachusetts General Hospital, Boston.
Department of Psychiatry, Columbia University and New York State Psychiatric Institute, New York, New York.
Department of Gynecology and Obstetrics, Emory University School of Medicine, Atlanta, Georgia.
Avera Research Institute, Sioux Falls, South Dakota.
Department of Pediatrics, University of South Dakota School of Medicine, Sioux Falls.
Division of Research, Kaiser Permanente Northern California, Oakland.
Department of Public Health Sciences, Henry Ford Health System, Detroit, Michigan.
Division of Allergy, Immunology and Rheumatology, University of Wisconsin-Madison, Madison.
Department of Medicine, Vanderbilt University Medical Center, Nashville, Tennessee.
Department of Pediatrics, Vanderbilt University Medical Center, Nashville, Tennessee.
Department of Epidemiology, Dartmouth Geisel School of Medicine, Hanover, New Hampshire.
Department of Pediatrics, Warren Alpert Medical School of Brown University, Providence, Rhode Island.
Department of Counseling Psychology and Human Services, Prevention Science Institute, University of Oregon, Eugene.
Department of Psychological and Brain Sciences, George Washington University, Washington, District of Columbia.
Department of Psychiatry, University of Rochester, Rochester, New York.
Department of Environmental Sciences and Engineering, Gillings School of Global Public Health, University of North Carolina, Chapel Hill.
Institute for Environmental Health Sciences, Wayne State University School of Medicine, Detroit, Michigan.
Department of Obstetrics and Gynecology, Wayne State University School of Medicine, Detroit, Michigan.
Department of Pediatrics, New York University Grossman School of Medicine, New York.
Department of Pediatrics, University of California Davis School of Medicine, Sacramento.
MIND Institute, University of California Davis, Sacramento, California.
Department of Environmental Health, Harvard T.H. Chan School of Public Health, Boston, Massachusetts.
Department of Nutrition, Harvard T.H. Chan School of Public Health, Boston, Massachusetts.

IMPORTANCE: Physical and social neighborhood attributes may have implications for children's growth and development patterns. The extent to which these attributes are associated with body mass index

(BMI) trajectories and obesity risk from childhood to adolescence remains understudied. OBJECTIVE: To examine associations of neighborhood-level measures of opportunity and social vulnerability with trajectories of BMI and obesity risk from birth to adolescence. DESIGN, SETTING, AND PARTICIPANTS: This cohort study used data from 54 cohorts (20 677 children) participating in the Environmental Influences on Child Health Outcomes (ECHO) program from January 1, 1995, to January 1, 2022. Participant inclusion required at least 1 geocoded residential address and anthropometric measure (taken at the same time or after the address date) from birth through adolescence. Data were analyzed from February 1 to June 30, 2022. EXPOSURES: Census tract-level Child Opportunity Index (COI) and Social Vulnerability Index (SVI) linked to geocoded residential addresses at birth and in infancy (age range, 0.5-1.5 years), early childhood (age range, 2.0-4.8 years), and mid-childhood (age range, 5.0-9.8 years). MAIN OUTCOMES AND MEASURES: BMI (calculated as weight in kilograms divided by length [if aged <2 years] or height in meters squared) and obesity (age- and sex-specific BMI ≥95th percentile). Based on nationwide distributions of the COI and SVI, Census tract rankings were grouped into 5 categories: very low (<20th percentile), low (20th percentile to <40th percentile), moderate (40th percentile to <60th percentile), high (60th percentile to <80th percentile), or very high (≥80th percentile) opportunity (COI) or vulnerability (SVI). RESULTS: Among 20 677 children, 10 747 (52.0%) were male; 12 463 of 20 105 (62.0%) were White, and 16 036 of 20 333 (78.9%) were non-Hispanic. (Some data for race and ethnicity were missing.) Overall, 29.9% of children in the ECHO program resided in areas with the most advantageous characteristics. For example, at birth, 26.7% of children lived in areas with very high COI, and 25.3% lived in areas with very low SVI; in mid-childhood, 30.6% lived in areas with very high COI and 28.4% lived in areas with very low SVI. Linear mixed-effects models revealed that at every life stage, children who resided in areas with higher COI (vs very low COI) had lower mean BMI trajectories and lower risk of obesity from childhood to adolescence, independent of family sociodemographic and prenatal characteristics. For example, among children with obesity at age 10 years, the risk ratio was 0.21 (95% CI, 0.12-0.34) for very high COI at birth, 0.31 (95% CI, 0.20-0.51) for high COI at birth, 0.46 (95% CI, 0.28-0.74) for moderate COI at birth, and 0.53 (95% CI, 0.32-0.86) for low COI at birth. Similar patterns of findings were observed for children who resided in areas with lower SVI (vs very high SVI). For example, among children with obesity at age 10 years, the risk ratio was 0.17 (95% CI, 0.10-0.30) for very low SVI at birth, 0.20 (95% CI, 0.11-0.35) for low SVI at birth, 0.42 (95% CI, 0.24-0.75) for moderate SVI at birth, and 0.43 (95% CI, 0.24-0.76) for high SVI at birth. For both indices, effect estimates for mean BMI difference and obesity risk were larger at an older age of outcome measurement. In addition, exposure to COI or SVI at birth was associated with the most substantial difference in subsequent mean BMI and risk of obesity compared with exposure at later life stages. CONCLUSIONS AND RELEVANCE: In this cohort study, residing in higher-opportunity and lower-vulnerability neighborhoods in early life, especially at birth, was associated with a lower mean BMI trajectory and a lower risk of obesity from childhood to adolescence. Future research should clarify whether initiatives or policies that alter specific components of neighborhood environment would be beneficial in preventing excess weight in children.

Public Health Sciences

Canick JE, Bhardwaj A, Patel A, Kuziez D, Larsen R, Misra S, Pearson B, Smith BD, Rohde RL, **Adjei Boakye E**, Kahmke RR, and Osazuwa-Peters N. Sociodemographic Differences in Patient-Reported Pain and Pain Management of Patients With Head and Neck Cancer in a Community Oncology Setting. *JCO Oncol Pract* 2022; Epub ahead of print. PMID: 36480772. Full Text

Duke University School of Medicine, Department of Head and Neck Surgery & Communication Sciences, Durham, NC.
Navigating Cancer, Seattle, WA.
Wake Forest School of Medicine, Department of Surgery, Winston-Salem, NC.
Medical College of Wisconsin, Department of Otolaryngology & Communication Sciences, Milwaukee, WI.
Henry Ford Health System, Department of Otolaryngology-Head & Neck Surgery, Detroit, MI.
Henry Ford Health System, Department of Population Health Sciences, Detroit, MI.
Duke Cancer Institute, Durham, NC.
Duke University School of Medicine, Department of Population Health Sciences, Durham, NC.

PURPOSE: While pain is prevalent among survivors of head and neck cancer (HNC), there is a lack of data on pain management in the community oncology setting. We described sociodemographic correlates

and disparities associated with patient-reported pain among patients with HNC. METHODS: We used the 2017-2021 nationwide community oncology data set from Navigating Cancer, which included electronic patient-reported outcomes. We identified a retrospective cohort of patients diagnosed with HNC (N = 25,572), with ≥ 1 patient-reported pain event. We adjusted for demographic (sex, age, smoking history, marital status) and clinical (cancer site) factors associated with pain reporting and pain resolution by new pain prescription on the basis of race (White v non-White patients), using multivariate logistic regression models. RESULTS: Our analytic cohort included 2,331 patients, 90.58% White, 58.62% married, with an average age of 66.47 years. Of these, 857 patients (36.76%) reported ≥ 1 pain event during study period. Mean resolution time (in minutes) for pain incidents was significantly longer for White patients than non-White patients (99.6 ± 3.2 v 74.9 ± 7.2, P < .05). After adjusting for covariates, smoking was associated with a 25% increased odds of reporting pain incidents (adjusted odds ratio [aOR], 1.25; 95% CI, 1.03 to 1.52). There was no statistically significant difference in odds of pain reporting between White versus non-White patients (aOR, 0.97; 95% CI, 0.73 to 1.30). However, White patients were significantly more likely to receive new prescription for pain than non-White patients (aOR, 2.52; 95% CI, 1.09 to 5.86). CONCLUSION: We found racial differences in patient-reported pain management, with White patients significantly more likely to receive new pain prescriptions. As pain management is a mainstay in cancer care, equity in pain management is critical to optimize quality of life for patients with HNC.

Public Health Sciences

Drake CL, **Kalmbach DA**, **Cheng P**, **Ahmedani BK**, **Peterson EL**, **Joseph CLM**, **Roth T**, Kidwell KM, and **Sagong C**. Sleep to Reduce Incident Depression Effectively (STRIDE): study protocol for a randomized controlled trial comparing stepped-care cognitive-behavioral therapy for insomnia versus sleep education control to prevent major depression. *Trials* 2022; 23(1):967. PMID: 36457045. Full Text

Thomas Roth Sleep Disorders & Research Center, Henry Ford Health, Detroit, MI, 48202, USA. cdrake1@hfhs.org.
Thomas Roth Sleep Disorders & Research Center, Henry Ford Health, Detroit, MI, 48202, USA.
Center for Health Policy & Health Services Research, Henry Ford Health, Detroit, MI, 48202, USA.
Department of Public Health Services, Henry Ford Health, Detroit, MI, 48202, USA.
Department of Biostatistics, University of Michigan, Ann Arbor, MI, 48109, USA.

BACKGROUND: Prevention of major depressive disorder (MDD) is a public health priority. Strategies targeting individuals at elevated risk for MDD may guide effective preventive care. Insomnia is a reliable precursor to depression, preceding half of all incident and relapse cases. Thus, insomnia may serve as a useful entry point for preventing MDD. Cognitive-behavioral therapy for insomnia (CBT-I) is recommended as the first-line treatment for insomnia, but widespread implementation is limited by a shortage of trained specialists. Innovative stepped-care approaches rooted in primary care can increase access to CBT-I and reduce rates of MDD. METHODS/DESIGN: We propose a large-scale stepped-care clinical trial in the primary care setting that utilizes a sequential, multiple assignment, randomized trial (SMART) design to determine the effectiveness of dCBT-I alone and in combination with clinician-led CBT-I for insomnia and the prevention of MDD incidence and relapse. Specifically, our care model uses digital CBT-I (dCBT-I) as a first-line intervention to increase care access and reduce the need for specialist resources. Our proposal also adds clinician-led CBT-I for patients who do not remit with first-line intervention and need a more personalized approach from specialty care. We will evaluate negative repetitive thinking as a potential treatment mechanism by which dCBT-I and CBT-I benefit insomnia and depression outcomes. DISCUSSION: This project will test a highly scalable model of sleep care in a large primary care system to determine the potential for wide dissemination and implementation to address the high volume of population need for safe and effective insomnia treatment and associated prevention of depression. TRIAL REGISTRATION: ClinicalTrials.gov NCT03322774. Registered on October 26, 2017.

Public Health Sciences

Maxwell DL, **Bryson TD**, **Taube D**, **Xu J**, **Peterson E**, and **Harding P**. Deleterious effects of cardiomyocyte-specific prostaglandin E2 EP3 receptor overexpression on cardiac function after myocardial infarction. *Life Sci* 2022; 313:121277. PMID: 36521546. Full Text

Department of Physiology, Wayne State University School of Medicine, USA; Hypertension and Vascular Research Division, Department of Internal Medicine, Henry Ford Health, Detroit, MI, USA.
Hypertension and Vascular Research Division, Department of Internal Medicine, Henry Ford Health, Detroit, MI, USA.
Department of Public Health Sciences, Henry Ford Health, Detroit, MI, USA.
Department of Physiology, Wayne State University School of Medicine, USA; Hypertension and Vascular Research Division, Department of Internal Medicine, Henry Ford Health, Detroit, MI, USA. Electronic address: phardin1@hfhs.org.

AIMS: Prostaglandin E2 (PGE2) is a lipid hormone that signals through 4 different G-protein coupled receptor subtypes which act to regulate key physiological processes. Our laboratory has previously reported that PGE2 through its EP3 receptor reduces cardiac contractility at the level of isolated cardiomyocytes and in the isolated working heart preparation. We therefore hypothesized that cardiomyocyte specific overexpression of the PGE2 EP3 receptor further decreases cardiac function in a mouse model of heart failure produced by myocardial infarction. MAIN METHODS: Our study tested this hypothesis using EP3 transgenic mice (EP3 TG), which overexpress the porcine analogue of human EP3 in the cardiomyocytes, and their wildtype (WT) littermates. Mice were analyzed 2 wks after myocardial infarction (MI) or sham operation by echocardiography, RT-PCR, immunohistochemistry, and histology. KEY FINDINGS: We found that the EP3 TG sham controls had a reduced ejection fraction, reduced fractional shortening, and an increased left ventricular dimension at systole and diastole compared to the WT sham controls. Moreover, there was a further reduction in the EP3 TG mice after myocardial infarction. Additionally, single-cell analysis of cardiomyocytes isolated from EP3 TG mice showed reduced contractility under basal conditions. Overexpression of EP3 significantly increased cardiac hypertrophy, interstitial collagen fraction, macrophage, and T-cell infiltration in the sham operated group. Interestingly, after MI, there were no changes in hypertrophy but there were changes in collagen fraction, and inflammatory cell infiltration. SIGNIFICANCE: Overexpression of EP3 reduces cardiac function under basal conditions and this is exacerbated after myocardial infarction.

Public Health Sciences

Patel OP, Quist A, Martin CL, **Wegienka G**, Baird DD, Wise LA, and Vines AI. Life-Course Mobility in Socioeconomic Position and High Depressive Symptoms Among Young Black Women: The SELF Study. *Womens Health Issues* 2022; Epub ahead of print. PMID: 36588050. Full Text

Department of Epidemiology, UNC Gillings School of Global Public Health, Chapel Hill, North Carolina.
Department of Public Health Sciences, Henry Ford Health System, Detroit, Michigan.
Epidemiology Branch, National Institute of Environmental Health Sciences, National Institutes of Health, Research Triangle Park, North Carolina.
Department of Epidemiology, Boston University School of Public Health, Boston, Massachusetts.
Department of Epidemiology, UNC Gillings School of Global Public Health, Chapel Hill, North Carolina. Electronic address: avines@email.unc.edu.

BACKGROUND: Current literature on the association between mobility in socioeconomic position (SEP) and depression demonstrates mixed findings, with variation in the benefits of upward SEP by racial group and ethnic background. No study has examined life-course SEP mobility and depressive symptoms among Black women in the United States. METHODS: Our cohort included 1,612 Black women enrolled in the Study of Environment, Lifestyle and Fibroids between 2010 and 2012 and followed for 5 years. We used data on socioeconomic indicators at childhood and adulthood and used latent class analysis to create a life-course SEP mobility measure (persistently low, downward, upward, and persistently high). Using the 11-item Center for Epidemiologic Studies Depression Scale (CES-D), we assessed high (≥9) versus low depressive symptoms. Multivariable log risk models were used to produce risk ratios (RRs) and 95% confidence intervals (CIs). RESULTS: Of the participants, 37% had high depressive symptoms. Persistently low (RR, 1.56; 95% CI, 1.31-1.86) and downward (RR, 1.36; 95% CI, 1.14-1.63) SEP mobility was associated with high depressive symptoms after adjustment for age, adult social support, and marital status. There was evidence of an effect measure modification by adult social support, with a stronger association among those who reported high adult social support compared with low adult social support. CONCLUSIONS: These findings suggest directing mental health resources to people experiencing low

SEP at any stage in life, especially those with low SEP in adulthood, to aid in the management of depressive symptoms.

Public Health Sciences
Pati S, Baid U, **Luo B**, **Poisson L**, **Wen N**, et al. Federated learning enables big data for rare cancer boundary detection. *Nat Commun* 2022; 13(1):7346. PMID: 36470898. Full Text

Although machine learning (ML) has shown promise across disciplines, out-of-sample generalizability is concerning. This is currently addressed by sharing multi-site data, but such centralization is challenging/infeasible to scale due to various limitations. Federated ML (FL) provides an alternative paradigm for accurate and generalizable ML, by only sharing numerical model updates. Here we present the largest FL study to-date, involving data from 71 sites across 6 continents, to generate an automatic tumor boundary detector for the rare disease of glioblastoma, reporting the largest such dataset in the literature (n = 6, 314). We demonstrate a 33% delineation improvement for the surgically targetable tumor, and 23% for the complete tumor extent, over a publicly trained model. We anticipate our study to: 1) enable more healthcare studies informed by large diverse data, ensuring meaningful results for rare diseases and underrepresented populations, 2) facilitate further analyses for glioblastoma by releasing our consensus model, and 3) demonstrate the FL effectiveness at such scale and task-complexity as a paradigm shift for multi-site collaborations, alleviating the need for data-sharing.

Public Health Sciences
Qiu S, **Divine G**, and **Rao SD**. Effect of vitamin D metabolites on bone histomorphometry in healthy black and white women: An attempt to unravel the so-called vitamin D paradox in blacks. *Bone Rep* 2023; 18:101650. PMID: 36588780. Full Text

Bone and Mineral Research Laboratory, Henry Ford Hospital, Detroit, MI, USA.
Department of Public Health Sciences, Henry Ford Hospital, Detroit, MI, USA.
Division of Endocrinology, Diabetes, and Bone & Mineral Disorders, Henry Ford Hospital, Detroit, MI, USA.

An apparent vitamin D paradox, characterized by lower serum 25-hydroxyvitamin D (25(OH)D) levels and higher bone mineral density, is present in black population. In contrast, blacks have higher serum 1,25-dihydroxyvitamin D (1,25(OH)(2)D) levels. The effect of 1,25(OH)(2)D on the skeleton is not fully understood. We examined serum 25(OH)D, 1,25(OH)(2)D and bone histomorphometry in 50 black and white women (25 each) matched for age, menstrual status, and BMI. Histomorphometric indices related to bone structure, remodeling and mineralization were measured in cancellous bone in iliac bone biopsies. Data analyses led to the following results: 1) serum 25(OH)D was significantly lower and 1,25(OH)(2)D was significantly higher in black than in white women, but neither blacks nor whites revealed significant correlation between these two vitamin D metabolites. 2) there was no significant difference in PTH levels between blacks and whites. 3) except for greater trabecular thickness (Tb.Th) in blacks, there were no significant differences in other histomorphometric variables between the two ethnic groups. 4) osteoid surface (OS/BS), unlabeled osteoid surface (ulOS/BS), and osteoblast surface (ObS/BS) significantly correlated with serum 1,25(OH)(2)D levels. We conclude that lower serum 25(OH)D levels in blacks do not impair bone structure and remodeling, nor decrease bone mineralization. Higher serum 1,25(OH)(2)D levels in blacks may help preserve bone mass by stimulating bone formation via increasing osteoblast number and function, but moderately inhibit terminal bone mineralization as shown by higher ulOS/BS.

Public Health Sciences
Sangoi AR, **Al-Obaidy KI**, Cheng L, Kao CS, Chan E, **Sadasivan S**, **Levin AM**, Alvarado-Cabrero I, Kunju LP, Mehra R, Mannan R, Wang X, Dhillon J, Tretiakova M, Smith SC, Hes O, and Williamson SR. Clear Cell Renal Cell Carcinoma with Focal Psammomatous Calcifications: A Rare Occurrence Mimicking Translocation Carcinoma. *Histopathology* 2022; Epub ahead of print. PMID: 36564980. Full Text

El Camino Hospital, Mountain View, CA.
Henry Ford Health System, Detroit, MI.

Brown University Warren Albert Medical School, Providence, RI.
Stanford Medicine/Stanford University, Stanford, CA.
University of California, San Francisco, San Francisco, CA.
Mexican Oncology Hospital SXXI, IMSS, Mexico City, Mexico.
University of Michigan, Ann Arbor, MI.
H. Lee Moffitt Cancer Center & Research Institute, Tampa, FL.
University of Washington, Seattle, WA.
VCU School of Medicine, Richmond, VA.
Biopticka laboratory., Plzen, Czech Republic.
Cleveland Clinic, Cleveland, OH.

AIMS: Renal cell carcinoma (RCC) with clear cells and psammoma-like calcifications would often raise suspicion for MITF family translocation RCC. However, we have rarely encountered tumors consistent with clear cell RCC that contain focal psammomatous calcifications. METHODS & RESULTS: We identified clear cell RCCs with psammomatous calcifications from multiple institutions and performed immunohistochemistry and fluorescence and RNA in situ hybridization (FISH and RNA ISH). Twenty-one tumors were identified: 12 men, 9 women, ages 45 to 83 years. Tumor size was 2.3 to 14.0 cm (median 6.75 cm). Nucleolar grade was 3 (n=14), 2 (n=4), or 4 (n=3). In addition to clear cell pattern, morphology included eosinophilic (n=12), syncytial giant cell (n=4), rhabdoid (n=2), branched glandular (n=1), early spindle cell (n=1), and poorly differentiated components (n=1). Labeling for CA9 was usually 80-100% of the tumor cells (n=17/21) but was sometimes decreased in areas of eosinophilic cells (n=4). All (19/19) were positive for CD10. Most (19/20) were positive for AMACR (variable staining, 20-100%). Staining was negative for keratin 7, although 4 showed rare positive cells (4/20). Results were negative for cathepsin K (0/19), melan A (0/17), HMB45 (0/17), TFE3 (0/5), TRIM63 RNA-ISH (0/13), and TFE3 (0/19) and TFEB rearrangements (0/12). Seven of 19 (37%) showed chromosome 3p deletion. One (1/19) showed trisomy 7 and 17 without papillary features. CONCLUSIONS: Psammomatous calcifications in RCC with a clear cell pattern suggests a diagnosis of MITF family translocation RCC; however, psammomatous calcifications can rarely be found in true clear cell RCC.

Public Health Sciences

Squires M, **Schultz L**, **Schwalb J**, Park P, **Chang V**, **Nerenz D**, Perez-Cruet M, **Abdulhak M**, Khalil J, and Aleem I. Correlation of mJOA, PROMIS Physical Function, and Patient Satisfaction in Patients with Cervical Myelopathy: An Analysis of the Michigan Spine Surgery Improvement Collaborative (MSSIC) Database. *Spine J* 2022; Epub ahead of print. PMID: 36567055. Full Text

Department of Orthopedic Surgery, University of Michigan, 1500 E Medical Center Dr, Ann Arbor, MI 48109, USA. Electronic address: mdsquire@med.umich.edu.
Henry Ford Health System, 1 Ford Place, Detroit, MI 48202, USA. Electronic address: LSCHULT1@hfhs.org.
Henry Ford Health System, 1 Ford Place, Detroit, MI 48202, USA. Electronic address: JSCHWAL1@hfhs.org.
Department of Neurosurgery, University of Michigan, 1500 E Medical Center Dr, Ann Arbor, MI 48109, USA. Electronic address: ppark@med.umich.edu.
Henry Ford Health System, 1 Ford Place, Detroit, MI 48202, USA. Electronic address: VCHANG1@hfhs.org.
Henry Ford Health System, 1 Ford Place, Detroit, MI 48202, USA. Electronic address: DNERENZ1@hfhs.org.
Beaumont Health System, 3601 W. 13 Mile Rd., Royal Oak, MI 48073, USA. Electronic address: Miguelangelo.Perez-Cruet@beaumont.edu.
Henry Ford Health System, 1 Ford Place, Detroit, MI 48202, USA. Electronic address: MABDULH1@hfhs.org.
Beaumont Health System, 3601 W. 13 Mile Rd., Royal Oak, MI 48073, USA. Electronic address: Jad.Khalil@beaumont.org.
Department of Orthopedic Surgery, University of Michigan, 1500 E Medical Center Dr, Ann Arbor, MI 48109, USA. Electronic address: ialeem@med.umich.edu.

BACKGROUND CONTEXT: Patient-reported outcomes (PROs) are increasingly utilized to evaluate the efficacy and value of spinal procedures. Among patients with cervical myelopathy, the modified Japanese Orthopaedic Association (mJOA) remains the standard instrument, with Patient-Reported Outcomes Measurement Information System (PROMIS) physical function (PF) and patient satisfaction also frequently assessed. These outcomes have not all been directly compared using a large spine registry at 2 years follow-up for cervical myelopathic patients undergoing surgery. PURPOSE: To determine the correlation and association of PROMIS PF, mJOA, and patient satisfaction outcomes in patients undergoing surgery for cervical myelopathy. STUDY DESIGN/SETTING: Retrospective review of a multi-center spine registry database. PATIENT SAMPLE: Adult patients with cervical myelopathy who underwent cervical spine surgery between 2/26/2018 and 4/17/2021. OUTCOME MEASURES: PROMIS PF, mJOA, and North American Spine Society (NASS) patient satisfaction index. METHODS: The MSSIC database was accessed to gather pre- and postoperative outcome data on patients with cervical myelopathy. Spearman's correlation coefficients relating mJOA and PROMIS PF were quantified up to 2 years postoperatively. The effect sizes of the relationship between patient satisfaction with mJOA and PROMIS were determined. Kappa statistics were used to evaluate for agreement between those reaching the minimum clinically important difference (MCID) for mJOA and PROMIS PF. Odds ratios were calculated to determine the association between patient satisfaction and those reaching MCID for mJOA and PROMIS PF. Support for MSSIC is provided by BCBSM and Blue Care Network as part of the BCBSM Value Partnerships program. RESULTS: Data from 2023 patients were included. Moderate to strong correlations were found between mJOA and PROMIS PF at all time points ($p<0.001$). These outcomes had fair agreement at all postoperative time points when comparing those who reached MCID. Satisfaction was strongly related to changes from baseline for both mJOA and PROMIS PF at all time points ($p<0.001$). Odds ratios associating satisfaction with PROMIS PF MCID were higher at all time points compared to mJOA, although the differences were not significant. CONCLUSIONS: PROMIS PF has a strong positive correlation with mJOA up to 2 years postoperatively in patients undergoing surgery for cervical myelopathy, with similar odds of achieving MCID with both instruments. Patient satisfaction is predicted similarly by these outcome measures by 2 years postoperatively. These results affirm the validity of PROMIS PF in the cervical myelopathic population. Given its generalizability and ease of use, PROMIS PF may be a more practical outcome measure for clinical use compared to mJOA.

Public Health Sciences

Vachani A, Carroll NM, **Simoff MJ**, **Neslund-Dudas C**, Honda S, Greenlee RT, Rendle KA, Burnett-Hartman A, and Ritzwoller DP. Stage Migration and Lung Cancer Incidence After Initiation of Low-Dose Computed Tomography Screening. *J Thorac Oncol* 2022; 17(12):1355-1364. PMID: 36087860. Full Text

Perelman School of Medicine, University of Pennsylvania, Philadelphia, Pennsylvania. Electronic address: avachani@pennmedicine.upenn.edu.
Institute for Health Research, Kaiser Permanente Colorado, Aurora, Colorado.
Henry Ford Health System and Henry Ford Cancer Institute, Detroit, Michigan.
Center for Integrated Healthcare Research, Kaiser Permanente Hawaii, Oahu, Hawaii.
Marshfield Clinic Research Institute, Marshfield, Wisconsin.
Perelman School of Medicine, University of Pennsylvania, Philadelphia, Pennsylvania.

INTRODUCTION: Despite evidence from clinical trials of favorable shifts in cancer stage and improvements in lung cancer-specific mortality, the effectiveness of lung cancer screening (LCS) in clinical practice has not been clearly revealed. METHODS: We performed a multicenter cohort study of patients diagnosed with a primary lung cancer between January 1, 2014, and September 30, 2019, at one of four U.S. health care systems. The primary outcome variables were cancer stage distribution and annual age-adjusted lung cancer incidence. The primary exposure variable was receipt of at least one low-dose computed tomography for LCS before cancer diagnosis. RESULTS: A total of 3678 individuals were diagnosed with an incident lung cancer during the study period; 404 (11%) of these patients were diagnosed after initiation of LCS. As screening volume increased, the proportion of patients diagnosed with lung cancer after LCS initiation also rose from 0% in the first quartile of 2014 to 20% in the third quartile of 2019. LCS did not result in a significant change in the overall incidence of lung cancer (average annual percentage change [AAPC]: -0.8 [95% confidence interval (CI): -4.7 to 3.2]) between 2014 and 2018. Stage-specific incidence rates increased for stage I cancer (AAPC = 8.0 [95% CI: 0.8-

15.7]) and declined for stage IV disease (AAPC = -6.0 [95% CI: -11.2 to -0.5]). CONCLUSIONS: Implementation of LCS at four diverse health care systems has resulted in a favorable shift to a higher incidence of stage I cancer with an associated decline in stage IV disease. Overall lung cancer incidence did not increase, suggesting a limited impact of overdiagnosis.

Pulmonary and Critical Care Medicine

Vachani A, Carroll NM, **Simoff MJ**, **Neslund-Dudas C**, Honda S, Greenlee RT, Rendle KA, Burnett-Hartman A, and Ritzwoller DP. Stage Migration and Lung Cancer Incidence After Initiation of Low-Dose Computed Tomography Screening. *J Thorac Oncol* 2022; 17(12):1355-1364. PMID: 36087860. Full Text

Perelman School of Medicine, University of Pennsylvania, Philadelphia, Pennsylvania. Electronic address: avachani@pennmedicine.upenn.edu.
Institute for Health Research, Kaiser Permanente Colorado, Aurora, Colorado.
Henry Ford Health System and Henry Ford Cancer Institute, Detroit, Michigan.
Center for Integrated Healthcare Research, Kaiser Permanente Hawaii, Oahu, Hawaii.
Marshfield Clinic Research Institute, Marshfield, Wisconsin.
Perelman School of Medicine, University of Pennsylvania, Philadelphia, Pennsylvania.

INTRODUCTION: Despite evidence from clinical trials of favorable shifts in cancer stage and improvements in lung cancer-specific mortality, the effectiveness of lung cancer screening (LCS) in clinical practice has not been clearly revealed. METHODS: We performed a multicenter cohort study of patients diagnosed with a primary lung cancer between January 1, 2014, and September 30, 2019, at one of four U.S. health care systems. The primary outcome variables were cancer stage distribution and annual age-adjusted lung cancer incidence. The primary exposure variable was receipt of at least one low-dose computed tomography for LCS before cancer diagnosis. RESULTS: A total of 3678 individuals were diagnosed with an incident lung cancer during the study period; 404 (11%) of these patients were diagnosed after initiation of LCS. As screening volume increased, the proportion of patients diagnosed with lung cancer after LCS initiation also rose from 0% in the first quartile of 2014 to 20% in the third quartile of 2019. LCS did not result in a significant change in the overall incidence of lung cancer (average annual percentage change [AAPC]: -0.8 [95% confidence interval (CI): -4.7 to 3.2]) between 2014 and 2018. Stage-specific incidence rates increased for stage I cancer (AAPC = 8.0 [95% CI: 0.8-15.7]) and declined for stage IV disease (AAPC = -6.0 [95% CI: -11.2 to -0.5]). CONCLUSIONS: Implementation of LCS at four diverse health care systems has resulted in a favorable shift to a higher incidence of stage I cancer with an associated decline in stage IV disease. Overall lung cancer incidence did not increase, suggesting a limited impact of overdiagnosis.

Radiation Oncology

Matrosic CK, Dess K, Boike T, Dominello MM, Dryden DA, **Fraser C**, Grubb M, Hayman JA, Jarema D, Marsh R, Paximadis PA, Torolski K, Wilson ML, Jolly S, and Matuszak M. Knowledge Based Quality Assurance and Model Maintenance in Lung Cancer Radiotherapy in a Statewide Quality Consortium of Academic and Community Practice Centers. *Pract Radiat Oncol* 2022; Epub ahead of print. PMID: 36526245. Full Text

University of Michigan, Medical School, Radiation Oncology, Ann Arbor, Michigan. Electronic address: matrosic@med.umich.edu.
University of Michigan, Medical School, Radiation Oncology, Ann Arbor, Michigan.
GenesisCare, Farmington Hills, Michigan.
Barbara Ann Karmanos Cancer Institute, Wayne State University, Detroit, Michigan.
Covenant HealthCare, Saginaw, Michigan.
Henry Ford Health System, Detroit, Michigan.
Spectrum Health Lakeland, St. Joseph, Michigan.

PURPOSE/OBJECTIVES: Locally-advanced lung cancer (LALC) treatment planning is often complex due to challenging tradeoffs related to large targets near organs at risk, making the judgement of plan quality difficult. The purpose of this work was to update and maintain a multi-institutional knowledge-based planning (KBP) model developed by a statewide consortium of academic and community practices for

use as a plan quality assurance (QA) tool. MATERIALS/METHODS: Sixty LALC volumetric-modulated arc therapy (VMAT) plans from 2021 were collected from twenty-four institutions. Plan quality was scored, with high-quality clinical (HQC) plans selected to update a KBP model originally developed in 2017. The model was validated via automated KBP planning with twenty cases excluded from the model. Differences in dose-volume histogram metrics in the clinical plans, 2017 KBP model plans, and 2022 KBP model plans were compared. Twenty recent clinical cases not meeting consortium quality metrics were replanned with the 2022 model to investigate potential plan quality improvements. RESULTS: Forty-seven plans were included in the final KBP model. Compared to the clinical plans, the 2022 model validation plans improved 60%, 65%, and 65% of the lung V20Gy, mean heart dose, and spinal canal D0.3cc metrics, respectively. The 2022 model showed improvements from the 2017 model in hot spot management at the cost of higher lung doses. Of the twenty recent cases not meeting quality metrics, 40% of the KBP model-replanned cases resulted in acceptable plans, suggesting potential clinical plan improvements. CONCLUSIONS: A multi-institutional KBP model was updated using plans from a statewide consortium. Multi-disciplinary plan review resulted in HQC model training plans and model validation resulted in acceptable quality plans. The model proved to be effective at identifying potential plan quality improvements. Work is ongoing to develop web-based training plan review tools and vendor-agnostic platforms to provide the model as a QA tool statewide.

Radiation Oncology
Pati S, Baid U, **Luo B**, **Poisson L**, **Wen N**, et al. Federated learning enables big data for rare cancer boundary detection. *Nat Commun* 2022; 13(1):7346. PMID: 36470898. Full Text

Although machine learning (ML) has shown promise across disciplines, out-of-sample generalizability is concerning. This is currently addressed by sharing multi-site data, but such centralization is challenging/infeasible to scale due to various limitations. Federated ML (FL) provides an alternative paradigm for accurate and generalizable ML, by only sharing numerical model updates. Here we present the largest FL study to-date, involving data from 71 sites across 6 continents, to generate an automatic tumor boundary detector for the rare disease of glioblastoma, reporting the largest such dataset in the literature (n = 6, 314). We demonstrate a 33% delineation improvement for the surgically targetable tumor, and 23% for the complete tumor extent, over a publicly trained model. We anticipate our study to: 1) enable more healthcare studies informed by large diverse data, ensuring meaningful results for rare diseases and underrepresented populations, 2) facilitate further analyses for glioblastoma by releasing our consensus model, and 3) demonstrate the FL effectiveness at such scale and task-complexity as a paradigm shift for multi-site collaborations, alleviating the need for data-sharing.

Radiation Oncology
Sriramulu S, **Thoidingjam S**, **Brown SL**, **Siddiqui F**, **Movsas B**, and **Nyati S**. Molecular targets that sensitize cancer to radiation killing: From the bench to the bedside. *Biomed Pharmacother* 2022; 158:114126. PMID: 36521246. Full Text

Department of Radiation Oncology, Henry Ford Health, Detroit, MI 48202, USA.
Department of Radiation Oncology, Henry Ford Health, Detroit, MI 48202, USA. Electronic address: snyati1@hfhs.org.

Radiotherapy is a standard cytotoxic therapy against solid cancers. It uses ionizing radiation to kill tumor cells through damage to DNA, either directly or indirectly. Radioresistance is often associated with dysregulated DNA damage repair processes. Most radiosensitizers enhance radiation-mediated DNA damage and reduce the rate of DNA repair ultimately leading to accumulation of DNA damages, cell-cycle arrest, and cell death. Recently, agents targeting key signals in DNA damage response such as DNA repair pathways and cell-cycle have been developed. This new class of molecularly targeted radiosensitizing agents is being evaluated in preclinical and clinical studies to monitor their activity in potentiating radiation cytotoxicity of tumors and reducing normal tissue toxicity. The molecular pathways of DNA damage response are reviewed with a focus on the repair mechanisms, therapeutic targets under current clinical evaluation including ATM, ATR, CDK1, CDK4/6, CHK1, DNA-PKcs, PARP-1, Wee1, & MPS1/TTK and potential new targets (BUB1, and DNA LIG4) for radiation sensitization.

Radiation Oncology

Zong W, **Carver E**, **Zhu S**, **Schaff E**, **Chapman D**, Lee J, **Bagher-Ebadian H**, **Movsas B**, Wen W, Alafif T, and Zong X. Prostate cancer malignancy detection and localization from mpMRI using auto-deep learning as one step closer to clinical utilization. *Sci Rep* 2022; 12(1):22430. PMID: 36575209. Full Text

WeCare.WeTeach, Troy, MI, 48098, USA. mandyzong.research@gmail.com.
Henry Ford Health System, Detroit, MI, 48202, USA.
Trinity Health, Minot, ND, 58701, USA.
Department of Radiology, Michigan State University, East Lansing, MI, 48824, USA.
Department of Osteophytic, Michigan State University, East Lansing, MI, 48824, USA.
Department of Physics, Oakland University, Rochester, MI, 48309, USA.
SJTU-Ruijing-UIH Institute for Medical Imaging Technology, Shanghai, 200241, China.
Department of Radiology, Ruijin Hospital Shanghai Jiaotong University School of Medicine, Shanghai, 200031, China.
The Global Institute of Future Technology, Shanghai Jiaotong University, Shanghai, 200240, China.
Umm Al-Qura University, Jamoum, 25375, Saudi Arabia.
Shanghai JiaoTong University Affiliated Sixth People's Hospital, Shanghai, 200233, China.

Automatic diagnosis of malignant prostate cancer patients from mpMRI has been studied heavily in the past years. Model interpretation and domain drift have been the main road blocks for clinical utilization. As an extension from our previous work we trained on a public cohort with 201 patients and the cropped 2.5D slices of the prostate glands were used as the input, and the optimal model were searched in the model space using autoKeras. As an innovative move, peripheral zone (PZ) and central gland (CG) were trained and tested separately, the PZ detector and CG detector were demonstrated effective in highlighting the most suspicious slices out of a sequence, hopefully to greatly ease the workload for the physicians.

Sleep Medicine

Drake CL, **Kalmbach DA**, **Cheng P**, **Ahmedani BK**, **Peterson EL**, **Joseph CLM**, **Roth T**, Kidwell KM, and **Sagong C**. Sleep to Reduce Incident Depression Effectively (STRIDE): study protocol for a randomized controlled trial comparing stepped-care cognitive-behavioral therapy for insomnia versus sleep education control to prevent major depression. *Trials* 2022; 23(1):967. PMID: 36457045. Full Text

Thomas Roth Sleep Disorders & Research Center, Henry Ford Health, Detroit, MI, 48202, USA. cdrake1@hfhs.org.
Thomas Roth Sleep Disorders & Research Center, Henry Ford Health, Detroit, MI, 48202, USA.
Center for Health Policy & Health Services Research, Henry Ford Health, Detroit, MI, 48202, USA.
Department of Public Health Services, Henry Ford Health, Detroit, MI, 48202, USA.
Department of Biostatistics, University of Michigan, Ann Arbor, MI, 48109, USA.

BACKGROUND: Prevention of major depressive disorder (MDD) is a public health priority. Strategies targeting individuals at elevated risk for MDD may guide effective preventive care. Insomnia is a reliable precursor to depression, preceding half of all incident and relapse cases. Thus, insomnia may serve as a useful entry point for preventing MDD. Cognitive-behavioral therapy for insomnia (CBT-I) is recommended as the first-line treatment for insomnia, but widespread implementation is limited by a shortage of trained specialists. Innovative stepped-care approaches rooted in primary care can increase access to CBT-I and reduce rates of MDD. METHODS/DESIGN: We propose a large-scale stepped-care clinical trial in the primary care setting that utilizes a sequential, multiple assignment, randomized trial (SMART) design to determine the effectiveness of dCBT-I alone and in combination with clinician-led CBT-I for insomnia and the prevention of MDD incidence and relapse. Specifically, our care model uses digital CBT-I (dCBT-I) as a first-line intervention to increase care access and reduce the need for specialist resources. Our proposal also adds clinician-led CBT-I for patients who do not remit with first-line intervention and need a more personalized approach from specialty care. We will evaluate negative repetitive thinking as a potential treatment mechanism by which dCBT-I and CBT-I benefit insomnia and depression outcomes. DISCUSSION: This project will test a highly scalable model of sleep care in a large primary care system

to determine the potential for wide dissemination and implementation to address the high volume of population need for safe and effective insomnia treatment and associated prevention of depression. TRIAL REGISTRATION: ClinicalTrials.gov NCT03322774. Registered on October 26, 2017.

Sleep Medicine
Kalmbach DA, and **Cheng P**. Embracing telemedicine and digital delivery of cognitive behavioral therapy for insomnia: Where do we come from and where are we going? *Sleep* 2022; Epub ahead of print. PMID: 36455233. Full Text

Thomas Roth Sleep Disorders & Research Center, Henry Ford Health, Detroit, MI 48202 USA.
Department of Obstetrics, Gynecology, and Reproductive Biology, Michigan State University College of Human Medicine, Grand Rapids, MI 49503 USA.
Department of Medicine, Michigan State University College of Human Medicine, Grand Rapids, MI 49503 USA.

Sleep Medicine
Kalmbach DA, Fernandez-Mendoza J, and **Drake CL**. Stress and sleep reactivity increase risk for insomnia: Highlighting the dynamic interplay between sleep-wake regulation and stress responsivity. *Sleep* 2022; Epub ahead of print. PMID: 36507774. Full Text

Thomas Roth Sleep Disorders & Research Center, Henry Ford Health, 1 Ford Place, Detroit, MI 48202 USA.
Department of Obstetrics, Gynecology, and Reproductive Biology, Michigan State University College of Human Medicine, 15 Michigan St NE, Grand Rapids, MI 49503 USA.
Sleep Research and Treatment Center, Department of Psychiatry and Behavioral Health, College of Medicine, Penn State University, Hershey, PA 17033 USA.

Sleep Medicine
Rogers J, Gong X, Byars-Winston A, McDaniels M, Thayer-Hart N, **Cheng P**, Diggs-Andrews K, Martínez-Hernández KJ, and Pfund C. Comparing the Outcomes of Face-to-Face and Synchronous Online Research Mentor Training Using Propensity Score Matching. *CBE Life Sci Educ* 2022; 21(4):ar62. PMID: 36112621. Full Text

Wisconsin Center for Education Research, University of Wisconsin-Madison, Madison, WI 53706.
Department of Educational Leadership and Policy Analysis, University of Wisconsin-Madison, Madison, WI 53706.
Department of Medicine, University of Wisconsin-Madison, Madison, WI 53715.
Center for Women's Health Research, University of Wisconsin-Madison, Madison, WI 53715.
Thomas Roth Sleep Disorders and Research Center, Henry Ford Health, Detroit, MI 48202.
Diggs-Andrews Consulting LLC, Ashburn, VA 20147.
Chemistry Department, St. John Fisher University, Rochester, NY 14618.
Institute for Clinical and Translational Research, University of Wisconsin-Madison, Madison, WI 53705.

In this study, propensity score matching (PSM) was conducted to examine differences in the effectiveness of research mentor training (RMT) implemented using two modes-face-to-face or synchronous online training. This study investigated each training mode and assessed participants' perceived gains in mentoring skills, ability to meet mentees' expectations, and overall quality of mentoring, as well as intention to make changes to their mentoring practices. Additional factors that may contribute to participant outcomes were also examined. In total, 152 mentors trained using a synchronous online platform and 655 mentors trained in in-person workshops were analyzed using the PSM method. Mentors were matched based on similar characteristics, including mentee's career stage, mentor's title, mentor's prior mentoring experience, mentor's race/ethnicity and sex, and mentor's years of experience; results show that both face-to-face and synchronous online modes of RMT are effective. Findings indicated that the training mode did not significantly impact the mentors' perceived training outcomes. Factors associated with the reported training outcomes included dosage (hours of training), facilitator effectiveness, race/ethnicity, and previous mentoring experience. The results of this study demonstrate

that mentors' perceived training outcomes are comparable regardless of the training modality used-online versus face-to-face.

Surgery

Carlin AM, **Varban OA**, Ehlers AP, Bonham AJ, Ghaferi AA, and Finks JF. Independent predictors and timing of portomesenteric vein thrombosis after bariatric surgery. *Surg Obes Relat Dis* 2022; 18(12):1385-1391. PMID: 36198496. Full Text

Department of Surgery, Henry Ford Health, Detroit, Michigan; Michigan Bariatric Surgery Collaborative, Ann Arbor, Michigan. Electronic address: acarlin1@hfhs.org.
Department of Surgery, Henry Ford Health, Detroit, Michigan; Michigan Bariatric Surgery Collaborative, Ann Arbor, Michigan.
Department of Surgery, Michigan Medicine, Ann Arbor, Michigan; Center for Healthcare Outcomes and Policy, Ann Arbor, Michigan.
Michigan Bariatric Surgery Collaborative, Ann Arbor, Michigan.
Michigan Bariatric Surgery Collaborative, Ann Arbor, Michigan; Department of Surgery, Michigan Medicine, Ann Arbor, Michigan; Center for Healthcare Outcomes and Policy, Ann Arbor, Michigan.
Michigan Bariatric Surgery Collaborative, Ann Arbor, Michigan; Department of Surgery, Michigan Medicine, Ann Arbor, Michigan.

BACKGROUND: Portomesenteric vein thrombosis (PVT) is a rare complication following bariatric surgery but can result in severe morbidity as well as death. OBJECTIVE: Identification of risk factors for PVT to facilitate targeted management strategies to reduce incidence. SETTING: Prospective, statewide bariatric-specific clinical registry. METHODS: We identified all patients who underwent primary bariatric surgery between June 2006 and November 2021 (n = 102,869). Patient characteristics, procedure type, operative details, and 30-day postoperative complications were analyzed with multivariable logistic regression to evaluate for independent predictors of PVT. RESULTS: A total of 117 patients (.11%) developed a postoperative PVT, with 6 (5.1%) associated deaths. The majority of PVTs occurred in patients who underwent sleeve gastrectomy (109 patients; 93.2%), and the PVT occurred most commonly during the second (37%), third (31%), and fourth weeks (23%) after surgery. Independent risk factors for PVT included a prior history of venous thromboembolism (odds ratio [OR] = 3.1; 95% confidence interval [CI]: 1.64-5.98; P = .0005), liver disorder (OR = 2.3; 95% CI: 1.36-4.00; P = .0021), undergoing sleeve gastrectomy (OR = 12.4; 95% CI: 4.98-30.69; P < .0001), and postoperative complications including obstruction (OR = 12.5; 95% CI: 4.65-33.77; P < .0001), leak (OR = 7.9; 95% CI: 2.76-22.64; P = .0001), and hemorrhage (OR = 7.6; 95% CI: 3.57-16.06; P < .0001). CONCLUSIONS: Independent predictors of PVT include a prior history of venous thromboembolism, liver disease, undergoing sleeve gastrectomy, and experiencing a serious postoperative complication. Given that the incidence of PVT is most common within the first month after surgery, extending postdischarge chemoprophylaxis during this time frame is advised for patients with increased risk.

Surgery

Hecht LM, Schruff MA, Young J, **Carlin AM**, and **Miller-Matero LR**. Psychometric Evaluation of a Measure of Health Numeracy Among Individuals Seeking Bariatric Surgery. *Obes Surg* 2022; Epub ahead of print. PMID: 36562961. Full Text

Center for Health Policy and Health Services Research, Henry Ford Health, Detroit, MI, 48202, USA. lhecht1@hawk.iit.edu.
Department of Psychology, University of Mississippi, University, Oxford, MS, 38677, USA.
Department of Surgery, Henry Ford Health, Detroit, MI, 48202, USA.
Center for Health Policy and Health Services Research, Henry Ford Health, Detroit, MI, 48202, USA.
Behavioral Health, Henry Ford Health, Detroit, MI, 48202, USA.

Surgery

Ivanics T, Wallace D, Claasen M, Patel MS, Brahmbhatt R, Shwaartz C, Prachalias A, Srinivasan P, Jassem W, Heaton N, Cattral MS, Selzner N, Ghanekar A, Morgenshtern G, Mehta N, Massie AB, van der Meulen J, Segev DL, and Sapisochin G. Low utilization of adult-to-adult LDLT in Western countries despite excellent outcomes: International multicenter analysis of the US, the UK, and Canada. *J Hepatol* 2022; 77(6):1607-1618. PMID: 36170900. Full Text

Multi-Organ Transplant Program, University Health Network Toronto, Ontario, Canada; Department of Surgery, Henry Ford Hospital, Detroit, Michigan, USA; Department of Surgical Sciences, Akademiska Sjukhuset, Uppsala University, Uppsala, Sweden; Deparment of Epidemiology, Johns Hopkins Bloomberg School of Public Health, Baltimore, Maryland, USA.
Department of Health Services Research and Policy, London School of Hygiene and Tropical Medicine, London, UK; Institute of Liver Studies, Kings College Hospital, Denmark Hill, London, UK.
Multi-Organ Transplant Program, University Health Network Toronto, Ontario, Canada; Department of Surgery, Erasmus MC, University Medical Center Rotterdam, Rotterdam, the Netherlands.
Division of Surgical Transplantation, Department of Surgery, University of Texas Southwestern Medical Center, Dallas, Texas, USA.
Division of General Surgery, University Health Network, Toronto, Ontario, Canada.
Multi-Organ Transplant Program, University Health Network Toronto, Ontario, Canada; Division of General Surgery, University Health Network, Toronto, Ontario, Canada.
Institute of Liver Studies, Kings College Hospital, Denmark Hill, London, UK.
Multi-Organ Transplant Program, University Health Network Toronto, Ontario, Canada.
Department of Computer Science, University of Toronto, Ontario, Canada; Genetics & Genome Biology, The Hospital for Sick Children, Toronto, ON, Canada; Vector Institute, Toronto, Ontario, Canada.
Division of Gastroenterology, Department of Medicine, University of California, San Francisco, CA, USA.
Deparment of Epidemiology, Johns Hopkins Bloomberg School of Public Health, Baltimore, Maryland, USA; Department of Surgery, Johns Hopkins University School of Medicine, Baltimore, Maryland, USA; Department of Surgery, NYU Grossman School of Medicine, New York, NY, USA.
Department of Health Services Research and Policy, London School of Hygiene and Tropical Medicine, London, UK.
Multi-Organ Transplant Program, University Health Network Toronto, Ontario, Canada; Division of General Surgery, University Health Network, Toronto, Ontario, Canada. Electronic address: Gonzalo.sapisochin@uhn.ca.

BACKGROUND & AIMS: Adult-to-adult living donor liver transplantation (LDLT) offers an opportunity to decrease the liver transplant waitlist and reduce waitlist mortality. We sought to compare donor and recipient characteristics and post-transplant outcomes after LDLT in the US, the UK, and Canada. METHODS: This is a retrospective multicenter cohort-study of adults (≥18-years) who underwent primary LDLT between Jan-2008 and Dec-2018 from three national liver transplantation registries: United Network for Organ Sharing (US), National Health Service Blood and Transplantation (UK), and the Canadian Organ Replacement Registry (Canada). Patients undergoing retransplantation or multi-organ transplantation were excluded. Post-transplant survival was evaluated using the Kaplan-Meier method, and multivariable adjustments were performed using Cox proportional-hazards models with mixed-effect modeling. RESULTS: A total of 2,954 living donor liver transplants were performed (US: n = 2,328; Canada: n = 529; UK: n = 97). Canada has maintained the highest proportion of LDLT utilization over time (proportion of LDLT in 2008 - US: 3.3%; Canada: 19.5%; UK: 1.7%; p <0.001 - in 2018 - US: 5.0%; Canada: 13.6%; UK: 0.4%; p <0.001). The 1-, 5-, and 10-year patient survival was 92.6%, 82.8%, and 70.0% in the US vs. 96.1%, 89.9%, and 82.2% in Canada vs. 91.4%, 85.4%, and 66.7% in the UK. After adjustment for characteristics of donors, recipients, transplant year, and treating transplant center as a random effect, all countries had a non-statistically significantly different mortality hazard post-LDLT (Ref US: Canada hazard ratio 0.53, 95% CI 0.28-1.01, p = 0.05; UK hazard ratio 1.09, 95% CI 0.59-2.02, p = 0.78). CONCLUSIONS: The use of LDLT has remained low in the US, the UK and Canada. Despite this, long-term survival is excellent. Continued efforts to increase LDLT utilization in these countries may be warranted due to the growing waitlist and differences in allocation that may disadvantage patients currently awaiting liver transplantation. LAY SUMMARY: This multicenter international comparative analysis of living donor liver transplantation in the United States, the United Kingdom, and Canada

demonstrates that despite low use of the procedure, the long-term outcomes are excellent. In addition, the mortality risk is not statistically significantly different between the evaluated countries. However, the incidence and risk of retransplantation differs between the countries, being the highest in the United Kingdom and lowest in the United States.

Surgery

Mehra MR, Nayak A, Morris AA, **Lanfear DE**, **Nemeh H**, Desai S, Bansal A, Guerrero-Miranda C, Hall S, Cleveland JC, Jr., Goldstein DJ, Uriel N, Chen L, Bailey S, Anyanwu A, Heatley G, Chuang J, and Estep JD. Prediction of Survival After Implantation of a Fully Magnetically Levitated Left Ventricular Assist Device. *JACC Heart Fail* 2022; 10(12):948-959. PMID: 36456068. Full Text

Brigham and Women's Hospital, Boston, Massachusetts, USA. Electronic address: mmehra@bwh.harvard.edu.
Emory University, Atlanta, Georgia, USA.
Henry Ford Hospital, Detroit, Michigan, USA.
Ochsner Medical Center, New Orleans, Louisiana, USA.
Baylor University Medical Center, Dallas, Texas, USA.
University of Colorado School of Medicine, Aurora, Colorado, USA.
Montefiore Einstein Center for Heart and Vascular Care, New York, New York, USA.
NewYork-Presbyterian Hospital, Columbia University College of Physicians and Surgeons, New York, New York, USA.
University of Rochester Medical Center, Rochester, New York, USA.
Allegheny Health Network, Pittsburgh, Pennsylvania.
Icahn School of Medicine at Mount Sinai, New York, New York, USA.
Abbott, Abbott Park, Illinois, USA.
Cleveland Clinic Florida, Weston, Florida, USA.

BACKGROUND: Clinical trials inform on average efficacy, but individualized risk assessments for outcome prediction are important in guiding treatment implementation. OBJECTIVES: The authors developed and validated a patient-specific risk score to predict survival at 1 and 2 years after HeartMate 3 (HM3) left ventricular assist device (LVAD) implantation. METHODS: The MOMENTUM 3 (Multicenter Study of MagLev Technology in Patients Undergoing Mechanical Circulatory Support Therapy with HeartMate 3) trial includes 2,200 HM3 LVAD patients in the pivotal trial and Continued Access Protocol study (2014-2018). The authors randomly assigned all patients to a derivation cohort (n = 1,540) or validation cohort (n = 660). Univariate mortality predictors were screened for potential model inclusion, stepwise selection was used to build the multivariable Cox proportional hazards regression model, and performance (discrimination and calibration) was evaluated. RESULTS: Age, prior cardiac surgery (coronary artery bypass grafting [CABG] or valve procedure), lower serum sodium, higher blood urea nitrogen (BUN), small left ventricular size, and right atrial pressure-to-pulmonary capillary wedge pressure (RAP/PCWP) ratio >0.6 were significant risk factors for mortality. Receiver-operating characteristic (ROC) analysis in the validation cohort demonstrated an area under the curve (AUC) of 0.76 (95% CI: 0.70-0.81) at 1 year and 0.71 (95% CI: 0.66-0.77) at 2 years. Calibration between predicted and observed survival of the risk quintiles was high, with Pearson correlation coefficients of 0.986 and 0.994 at 1 and 2 years, respectively. Patients were successfully stratified into tertiles with higher-than-average, average, and lower-than-average survival, and observed mortality risk increased by 2-fold from one tertile to the next. CONCLUSIONS: A practical, easy-to-use HM3 Survival Risk Score with 6 components was developed to accurately predict 1- and 2-year survival after HM3 LVAD implantation. The survival risk score can be used to provide individual survival estimates to facilitate shared decision making when considering HM3 LVAD therapy. (MOMENTUM 3 Trial Portfolio; NCT02224755, NCT02892955).

Surgery

Rajendran L, Choi WJ, Muaddi H, **Ivanics T**, Feld JJ, Claasen MPAW, Castelo M, and Sapisochin G. Association of Viral Hepatitis Status and Post-hepatectomy Outcomes in the Era of Direct-Acting Antivirals. *Ann Surg Oncol* 2022; Epub ahead of print. PMID: 36515750. Full Text

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

Institute of Health Policy, Management and Evaluation, Dalla Lana School of Public Health, University of Toronto, Toronto, Ontario, Canada.
Multi-Organ Transplant Program, University Health Network, Toronto, Ontario, Canada.
Department of Surgery, Henry Ford Hospital, Detroit, Michigan, USA.
Department of Surgical Sciences, Akademiska Sjukhuset, Uppsala University, Uppsala, Sweden.
Toronto Centre for Liver Disease, University Health Network, Toronto, Ontario, Canada.
Department of Surgery, Division of HPB and Transplant Surgery, Erasmus MC Transplant Institute, University Medical Centre Rotterdam, Rotterdam, The Netherlands.
Department of Surgery, Division of General Surgery, University of Toronto, Toronto, Ontario, Canada.
Gonzalo.sapisochin@uhn.ca.
Multi-Organ Transplant Program, University Health Network, Toronto, Ontario, Canada.
Gonzalo.sapisochin@uhn.ca.

BACKGROUND: The role of viral hepatitis status in post-hepatectomy outcomes has yet to be delineated. This large, multicentred contemporary study aimed to evaluate the effect of viral hepatitis status on 30-day post-hepatectomy complications in patients treated for hepatocellular carcinoma (HCC). METHODS: Patients from the National Surgical Quality Improvement Program (NSQIP) database with known viral hepatitis status, who underwent hepatectomy for HCC between 2014 and 2018, were included. Patients were classified as HBV-only, HCV-only, HBV and HCV co-infection (HBV/HCV), or no viral hepatitis (NV). Multivariable models were used to assess outcomes of interest. The primary outcome was any 30-day post-hepatectomy complication. The secondary outcomes were major complications and post-hepatectomy liver failure (PHLF). Subgroup analyses were performed for cirrhotic and noncirrhotic patients. RESULTS: A total of 3234 patients were included. The 30-day complication rate was 207/663 (31.2%) HBV, 356/1077 (33.1%) HCV, 29/81 (35.8%) HBV/HCV, and 534/1413 (37.8%) NV (p = 0.01). On adjusted analysis, viral hepatitis status was not associated with occurrence of any 30-day post-hepatectomy complications (ref: NV, HBV odds ratio (OR) 0.89 [95% confidence interval (CI): 0.71-1.12]; HCV OR 0.91 [95% CI: 0.75-1.10]; HBV/HCV OR 1.17 [95% CI: 0.71-1.93]). Similar results were found in cirrhotic and noncirrhotic subgroups, and for secondary outcomes: occurrence of any major complications and PHLF. CONCLUSIONS: In patients with HCC managed with resection, viral hepatitis status is not associated with 30-day post-hepatectomy complications, major complications, or PHLF compared with NV. This suggests that clinical decisions and prognostication of 30-day outcomes in this population likely should not be made based on viral hepatitis status.

Surgery
Shimada S, **Shamaa T**, **Ivanics T**, **Kitajima T**, **Adhnan M**, **Collins K**, **Rizzari M**, **Yoshida A**, **Abouljoud M**, **Salgia R**, and **Nagai S**. ASO Visual Abstract: Multiple Pretransplant Treatments for Patients Without Pathological Complete Response may Worsen Posttransplant Outcomes in Patients With Hepatocellular Carcinoma. *Ann Surg Oncol* 2022; Epub ahead of print. PMID: 36496492. Full Text

Division of Transplant and Hepatobiliary Surgery, Henry Ford Health System, Detroit, MI, USA.
Division of Gastroenterology and Hepatology, Henry Ford Health System, Detroit, MI, USA.
Division of Transplant and Hepatobiliary Surgery, Henry Ford Health System, Detroit, MI, USA.
snagai1@hfhs.org.

Surgery
Taber DJ, Gordon EJ, **Jesse MT**, Myaskovsky L, Peipert JD, Jaure A, George R, and Fitzsimmons W. A viewpoint describing the American Society of Transplantation rationale to conduct a comprehensive patient survey assessing unmet immunosuppressive therapy needs. *Clin Transplant* 2022; Epub ahead of print. PMID: 36465024. Full Text

Department of Surgery, Medical University of South Carolina, Charleston, South Carolina, USA.
Department of Surgery, Vanderbilt University Medical Center, Nashville, Tennessee, USA.
Henry Ford Transplant Institute, Internal Medicine, Henry Ford Health, Detroit, Michigan, USA.
Center for Healthcare Equity in Kidney Disease and Department of Internal Medicine, University of New Mexico, Health Sciences Center, Albuquerque, New Mexico, USA.

Department of Medical Social, Sciences & Northwestern University Transplant Outcomes Research Collaboration, Northwestern University Feinberg School of Medicine, Chicago, Illinois, USA.
Sydney School of Public Health, The University of Sydney, Camperdown, Sydney, Australia.
Emory University and Children's Healthcare of Atlanta, Atlanta, Georgia.
Colleges of Pharmacy and Medicine, University of Illinois at Chicago, Chicago, Illinois, USA.

This viewpoint aims to "set the stage" and provide the rationale for the proposed development of a large-scale, comprehensive survey assessing transplant patients' perceived unmet immunosuppressive therapy needs. Research in organ transplantation has historically focused on reducing the incidence and impact of rejection on allograft survival and minimizing or eliminating the need for chronic immunosuppressive therapies. There has been less emphasis and investment in therapies to improve patient-reported outcomes including health-related quality of life and side-effects. Patient-focused drug development (PFDD) is a new and important emphasis of the Food and Drug Administration (FDA) that provides a guiding philosophy for incorporating the patient experience into drug development and evaluation. The American Society of Transplantation (AST) Board of Directors commissioned this working group to prepare for the conduct of a comprehensive patient survey assessing unmet immunosuppressive therapy needs. This paper aims to describe the basis for why it is important to conduct this survey and briefly outline the plan for broad stakeholder engagement to ensure the information gained is diverse, inclusive, and relevant for advancing PFDD in organ transplant recipients.

Urology
Briskin RS, **Etta P**, **Luck AM**, **Raffee S**, and **Atiemo HO**. Comparison of Urinary Tract Infection Incidence Following Intradetrusor OnabotulinumtoxinA in Office Versus Operating Room Settings. *Urogynecology (Hagerstown)* 2022; 28(12):842-847. PMID: 36409641. Request Article

From the Division of Female Pelvic Medicine and Reconstructive Surgery, Department of Obstetrics and Gynecology.
Department of Urology, Henry Ford Health System/Wayne State University School of Medicine, Detroit, MI.

IMPORTANCE: Urinary tract infection (UTI) is a known complication of intradetrusor onabotulinumtoxinA (BTX) injection. However, whether administering intradetrusor BTX in different clinical settings affects the risk of postprocedural UTI has not been investigated. OBJECTIVES: The objective of this study was to assess differences in the incidence of postprocedural UTI in women who received intradetrusor BTX in an outpatient office versus an operating room (OR). STUDY DESIGN: We performed a retrospective chart review of intradetrusor BTX procedures at a single institution between 2013 and 2020. Demographic data, comorbidities, and perioperative data were abstracted. The primary outcome was UTI defined as initiation of antibiotics within 30 days following BTX administration based on clinician assessment of symptoms and/or urine culture results. Univariate analysis of patients with and without UTI was performed. RESULTS: A total of 446 intradetrusor BTX procedures performed on female patients either in an outpatient office (n = 160 [35.9%]) or in an OR (n = 286 [64.1%]) were included in the analysis. Within 30 days of BTX administration, UTI was diagnosed after 14 BTX procedures (8.8%) in the office group and 29 BTX procedures (10.1%) in the OR group (P = 0.633). De novo postprocedural urinary retention occurred in more women who were treated in the office than in the OR (13 [9.6%] vs 3 [1.3%], P < 0.001). CONCLUSIONS: Selecting the appropriate setting for BTX administration is dependent on multiple factors. However, the clinical setting in which intradetrusor BTX is administered may not be an important factor in the development of postprocedural UTI, and further research is warranted.

Urology
Corsi NJ, Messing EM, **Sood A**, **Keeley J**, **Bronkema C**, **Rakic N**, **Jamil M**, **Dalela D**, **Arora S**, **Piontkowski AJ**, **Majdalany SE**, **Butaney M**, **Rakic I**, **Li P**, **Menon M**, **Rogers CG**, and **Abdollah F**. Risk-Based Assessment Of the Impact Of Intravesical Therapy on Recurrence-Free Survival Rate Following Resection of Suspected Low-grade, Non-muscle-invasive Bladder Cancer (NMIBC): A Southwest Oncology Groups (SWOG) S0337 Posthoc Analysis. *Clin Genitourin Cancer* 2022; 20(6):e498-e505. PMID: 35871040. Full Text

Vattikuti Urology Institute Center for Outcomes Research, Analytics and Evaluation (VCORE), Henry Ford Hospital, Detroit, MI; Wayne State University School of Medicine, Detroit, MI.
Department of Urology, University of Rochester, Rochester, NY.
Vattikuti Urology Institute Center for Outcomes Research, Analytics and Evaluation (VCORE), Henry Ford Hospital, Detroit, MI; Department of Urology, University of Texas MD Anderson Cancer Center, Houston, TX.
Vattikuti Urology Institute Center for Outcomes Research, Analytics and Evaluation (VCORE), Henry Ford Hospital, Detroit, MI.
Vattikuti Urology Institute Center for Outcomes Research, Analytics and Evaluation (VCORE), Henry Ford Hospital, Detroit, MI; Department of Urology, Massachusetts General Hospital, Harvard Medical School, Boston, MA.
Vattikuti Urology Institute Center for Outcomes Research, Analytics and Evaluation (VCORE), Henry Ford Hospital, Detroit, MI; Department of Urology, Baylor College of Medicine, Houston, TX.
Vattikuti Urology Institute Center for Outcomes Research, Analytics and Evaluation (VCORE), Henry Ford Hospital, Detroit, MI; Vattikuti Urology Institute, Henry Ford Hospital, Detroit, MI.
Vattikuti Urology Institute Center for Outcomes Research, Analytics and Evaluation (VCORE), Henry Ford Hospital, Detroit, MI; Department of Urology, Icahn School of Medicine at Mount Sinai Hospital, New York, NY.
Vattikuti Urology Institute Center for Outcomes Research, Analytics and Evaluation (VCORE), Henry Ford Hospital, Detroit, MI; Vattikuti Urology Institute, Henry Ford Hospital, Detroit, MI. Electronic address: fabdoll1@hfhs.org.

BACKGROUND: Nonmuscle invasive bladder cancer (NMIBC) has an elevated risk of recurrence, and immediate postresection intravesical instillation of chemotherapy (IVC) significantly reduces the risk of recurrence. Questions remain about which subpopulation may maximally benefit from IVC. Our aim was to develop risk groups based on recurrence risk in NMIBC, and then evaluate the impact of a single, postoperative instillation of IVC on the subsequent risk of recurrence for each risk group. MATERIAL AND METHODS: Using the SWOG S0337 trial cohort, we performed a posthoc analysis of 345 patients who were diagnosed with suspected low-grade NMIBC, underwent transurethral resection of the bladder tumor (TURBT), and received post-operative IVC (gemcitabine vs. saline). Using regression tree analysis, the regression tree stratified patients based on their risk of recurrence into low-risk - single tumor and aged < 57 years, intermediate-risk - single tumor and aged ≥ 57 years, and high-risk - multiple tumors. We used Cox proportional hazard models to test the impact of recurrence-free rate, and after adjustment to available covariates. RESULTS: Median age of the cohort was 66.5 (IQR: 59.7-75.8 years) with 85% of patients being males. Median overall follow-up time was 3.07 years (IQR: 0.75-4.01 years). When testing the impact of treatment in each risk group separately, we found that patients in the intermediate-risk treated with gemcitabine had a 24-month recurrence free rate of 77% (95% CI: 68%-86%) vs. 59% (95% CI: 49%-70%) in the saline group. This survival difference was confirmed on multivariable analysis (hazard ratio: 0.39, 95% CI: 23%-66%, P < 0.001). This group represented 53% of our cohort. Conversely, we did not observe a significant difference in recurrence-free survival among patients in the low- (P = 0.7) and high-risk (P = 0.4) groups. CONCLUSION: Our findings indicate that older patients with a single tumor of suspected low-grade NMIBC at TURBT maximally benefit from immediate postresection IVC (gemcitabine).

Urology
Pallauf M, D'Andrea D, König F, Laukthina E, Yanagisawa T, Rouprêt M, Daneshmand S, Djaladat H, Ghoreifi A, Soria F, Fujita K, Boorjian SA, Potretzke AM, Mari A, Roumiguié M, Antonelli A, Bianchi A, Khene ZE, Sfakianos JP, **Jamil M**, Boormans JL, Raman JD, Grossmann NC, Breda A, Heidenreich A, Del Giudice F, Singla N, Shariat SF, and Pradere B. Diagnostic Accuracy of Clinical Lymph Node Staging for Upper Tract Urothelial Cancer Patients - A Multicenter, Retrospective, Observational Study. *J Urol* 2022; Epub ahead of print. PMID: 36475808. Full Text

Department of Urology, Comprehensive Cancer Center, Medical University of Vienna, Vienna, Austria.
Department of Urology, Paracelsus Medical University Salzburg, University Hospital Salzburg, Salzburg, Austria.
Department of Urology, University Medical Center Hamburg-Eppendorf, Hamburg, Germany.

Department of Urology, The Jikei University School of Medicine, Tokyo, Japan.
Urology Department, GRC n°5, Predictive Onco-Uro, AP-HP, Pitié-Salpêtrière Hospital, Sorbonne University, Paris, France.
Department of Urology, USC/Norris Comprehensive Cancer Center, University of Southern California, Los Angeles, California.
Division of Urology, Department of Surgical Sciences, San Giovanni Battista Hospital, University of Studies of Torino, Turin, Italy.
Department of Urology, Kindai University Faculty of Medicine, Osaka, Japan.
Department of Urology, Mayo Clinic, Rochester, Minnesota.
Department of Experimental and Clinical Medicine, University of Florence, Unit of Urological Oncologic Minimally-Invasive Robotic Surgery and Andrology, Careggi Hospital, Florence, Italy.
Department of Urology, CHU Toulouse, Toulouse, France.
Department of Urology, University of Verona, Verona, Italy.
Department of Urology, University of Rennes, Rennes, France.
Department of Urology, Icahn School of Medicine at Mount Sinai, New York, New York.
Department of Urology, Henry Ford Cancer Institute, Detroit, Michigan.
Department of Urology, Erasmus MC Cancer Institute, University Medical Center Rotterdam, Rotterdam, The Netherlands.
Department of Urology, Penn State Health, Hershey, Pennsylvania.
Department of Urology, University Hospital Zurich, Zurich, Switzerland.
Department of Urology, Luzerner Kantonsspital, Lucerne, Switzerland.
Department of Urology, Fundació Puigvert, Autonomous University of Barcelona, Barcelona, Spain.
Department of Urology, Faculty of Medicine and University Hospital of Cologne, Cologne, Germany.
Department of Maternal-Infant and Urologic Sciences, "Sapienza" University of Rome, Policlinico Umberto I Hospital, Rome, Italy.
Departments of Urology and Oncology, the James Buchanan Brady Urological Institute, The Johns Hopkins University School of Medicine, Baltimore, Maryland.
Hourani Center for Applied Scientific Research, Al-Ahliyya Amman University, Amman, Jordan.
Karl Landsteiner Institute of Urology and Andrology, Vienna, Austria.
Department of Urology, Weill Cornell Medical College, New York, New York.
Department of Urology, University of Texas Southwestern, Dallas, Texas.
Department of Urology, Second Faculty of Medicine, Charles University, Prague, Czech Republic.
Department of Urology UROSUD, La Croix du Sud Hospital, Quint-Fonsegrives, France.

PURPOSE: Treatment options for the management of upper tract urothelial cancer (UTUC) are based on accurate staging. However, the performance of conventional cross-sectional imaging (CCI) for clinical lymph node staging (N-staging) remains poorly investigated. This study aims to evaluate the diagnostic accuracy of CCI for UTUC N-staging. MATERIALS AND METHODS: This study was a multicenter, retrospective, observational study. We included 865 non-metastatic (M0) UTUC patients treated with curative intended surgery and lymph node dissection (LND) who had been staged with CCI before surgery. We compared clinical (c) and pathologic (p) N-staging results to evaluate the concordance of node-positive (N+) and node-negative (N0) disease and calculate cN-staging's diagnostic accuracy. RESULTS: CCI categorized 750 patients cN0 and 115 cN+. LND categorized 641 patients pN0 and 224 pN+. The cN-stage was pathologically downstaged in 6.8% of patients, upstaged in 19%, and found concordant in 74%. The sensitivity and specificity of cN-staging were 25% (95% Confidence Interval [CI] 20; 31) and 91% (95% CI 88; 93). Positive and negative likelihood ratios were 2.7 (95% CI 2.0; 3.8) and 0.83 (95% CI 0.76; 0.89). The area under the receiver operating characteristics curve (0.58, 95% CI 0.55; 0.61) revealed low diagnostic accuracy. CONCLUSIONS: CCI had low sensitivity in detecting UTUC pN + disease. However, cN + increased the likelihood of pN + by almost three-fold. Thus, CCI is a rule-in but not a rule-out test. LND should remain the standard during extirpative UTUC surgery to obtain accurate N-staging. cN + could be a strong argument for early systemic treatment.

Urology

Tzou DT, Stern KL, Duty BD, Hsi RS, Canvasser NE, De S, Wong AC, Royal CR, Sloss ML, Ziemba JB, Harper JD, Bechis SK, Zampini AM, Borofsky MS, Bell JR, Friedlander JI, **Leavitt DA**, Nevo A, Patel ND, Patel RM, Okeke Z, Rivera ME, Hsu CH, Chi T, Vedantam G, and Lainhart WD. Heterogeneity in stone culture protocols and endourologist practice patterns: a multi-institutional survey. *Urolithiasis* 2022; 51(1):15. PMID: 36507964. Full Text

Department of Urology, University of Arizona College of Medicine, 1501 N. Campbell Ave, PO Box 245077, Tucson, AZ, 85724, USA. dtzou@urology.arizona.edu.
Department of Urology, Mayo Clinic Arizona, 5777 E. Mayo Blvd, Phoenix, AZ, 85054, USA.
Department of Urology, Oregon Health and Science University, 3303 SW Bond Ave, CH10U, Portland, OR, 97239, USA.
Department of Urology, Vanderbilt University Medical Center, A-1302 Medical Center North, Nashville, TN, 37232, USA.
Department of Urology, University of California Davis, 4860 Y Street, Suite 3500, Sacramento, CA, 95817, USA.
Department of Urology, Cleveland Clinic, 9500 Euclid Ave, Cleveland, OH, 44195, USA.
Department of Urology, University of Arizona College of Medicine, 1501 N. Campbell Ave, PO Box 245077, Tucson, AZ, 85724, USA.
Division of Urology, University of Pennsylvania, 3PCAM West, 3400 Civic Center Blvd, Philadelphia, PA, 19104, USA.
Department of Urology, University of Washington, 1959 NE Pacifica St, Seattle, WA, 98195, USA.
Department of Urology, University of California San Diego, 200 W. Arbor Drive #8897, San Diego, CA, 92103, USA.
Department of Urology, University of Minnesota, 420 Delaware St SE, Box 394 Mayo, Minneapolis, MN, 55455, USA.
Department of Urology, University of Kentucky, MS 277 Medical Science Bldg., Lexington, KY, 40536, USA.
Temple Health/Fox Chase Cancer Center, 2705 Dekalb Pike, Medical Arts Pavilion, Suite 310, East Norriton, PA, 19041, USA.
Vattikui Urology Institute, Henry Ford Hospital, 2799 W. Grand Blvd, Detroit, MI, 48202, USA.
Department of Urology, Case Western Reserve University, 11100 Euclid Ave, Cleveland, OH, 44106, USA.
Department of Urology, University of Virginia, 500 Ray C. Hunt Drive, Charlottesville, VA, 22903, USA.
Department of Urology, University of California, Irvine. 333 City Blvd. West, Suite 2100, Orange, CA, 92868, USA.
Donald and Barbara Zucker School of Medicine at Hofstra/Northwell, 450 Lakeville Road, Suite M41, Lake Success, NY, 11042, USA.
Indiana University, Methodist Prof Bldg MPC1 220. 1801 N. Senate Blvd, Indianapolis, IN, 46202, USA.
College of Public Health, University of Arizona, Roy P. Drachman Hall, Rm. A232, Tucson, AZ, 85721, USA.
Department of Urology, University of California San Francisco, 400 Parnassus Ave, San Francisco, CA, 94122, USA.
College of Animal Sciences, University of Arizona. Animal and Comparative Bio Sci, Rm 227, Tucson, AZ, 85721, USA.
Departments of Pathology and Medicine, University of Arizona College of Medicine, 1501 N. Campbell Ave, Tucson, AZ, 85724, USA.

Kidney stone cultures can be beneficial in identifying bacteria not detected in urine, yet how stone cultures are performed among endourologists, under what conditions, and by what laboratory methods remain largely unknown. Stone cultures are not addressed by current clinical guidelines. A comprehensive REDCap electronic survey sought responses from directed (n = 20) and listserv elicited (n = 108) endourologists specializing in kidney stone disease. Questions included which clinical scenarios prompt a stone culture order, how results influence post-operative antibiotics, and what microbiology lab protocols exist at each institution with respect to processing and resulting stone cultures. Logistic regression statistical analysis determined what factors were associated with performing stone cultures. Of

128 unique responses, 11% identified as female and the mean years of practicing was 16 (range 1-46). A specific 'stone culture' order was available to only 50% (64/128) of those surveyed, while 32% (41/128) reported culturing stone by placing a urine culture order. The duration of antibiotics given for a positive stone culture varied, with 4-7 days (46%) and 8-14 days (21%) the most reported. More years in practice was associated with fewer stone cultures ordered, while higher annual volume of percutaneous nephrolithotomy was associated with ordering more stone cultures ($p < 0.01$). Endourologists have differing practice patterns with respect to ordering stone cultures and utilizing the results to guide post-operative antibiotics. With inconsistent microbiology lab stone culture protocols across multiple institutions, more uniform processing is needed for future studies to assess the clinical benefit of stone cultures and direct future guidelines.

Urology

Wright HC, Gheordunescu G, O'Laughlin K, Sun A, Fulla J, **Kachroo N**, and De S. Ergonomics in the OR: An Electromyographic Evaluation of Common Muscle Groups Used During Simulated Flexible Ureteroscopy - a Pilot Study. *Urology* 2022; 170:66-72. PMID: 36057324. Full Text

Northwestern Medicine, Department of Urology, Chicago, IL. Electronic address: henry.wright@nm.org.
Case Western Reserve University School of Medicine, Cleveland, OH.
Lerner Research Institute, Cleveland Clinic, Cleveland, OH.
Hospital Clinico San Borja Arriarán, Santiago, Chile.
Henry Ford Health System, Wyandotte, MI.
Glickman Urological and Kidney Institute, Cleveland Clinic, Cleveland, OH.

OBJECTIVE: To assess the effects of different surgeon positions and ureteroscope types on muscle activation as measured by surface electromyography (sEMG) during simulated ureteroscopy in an endourology box-trainer model and the kidney phantom. METHODS: For this exploratory study, sEMG was used to quantify muscle activation of 3 endourology fellows during various ureteroscopic tasks. Electrodes were placed on the ureteroscope-holding side of the following muscles: thenar, forearm flexor, forearm extensor, biceps, triceps, deltoid, and trapezius. Subjects wore fitted lead aprons in an operating room and used a cystoscopy table with surgical drapes and an endoscopic video tower. Trials were completed with a disposable and reusable ureteroscope, both in the standing and sitting positions. Each subject performed an identical set of tasks in a phantom silicone kidney and ureteroscopy box trainer to recreate the procedural components of basketing, navigating a renal collecting system, and dusting. Raw EMG data for each task was processed and normalized as a percent of each subject's maximum voluntary contraction to allow comparison. RESULTS: The forearm extensor was the most heavily utilized muscle. The trapezius and deltoid muscles were activated more during sitting whereas the forearm flexors had increased activity during standing. The heavier reusable ureteroscope had increased forearm extensor activation compared to the disposable ureteroscope. CONCLUSION: Preliminary data show measurable differences in muscle activation based on both surgical posture and type of ureteroscope used. This highlights the need for more extensive EMG studies to identify techniques and equipment to optimize ergonomics and potentially minimize injury during flexible ureteroscopy.

Otolaryngology – Head and Neck Surgery

Mell LK, Torres-Saavedra P, Wong S, **Chang S**, Kish JA, Minn AJ, Jordan R, Liu T, Truong MT, Winquist E, Wise-Draper T, Rodriguez CP, Musaddiq A, Beadle BM, Henson C, Narayan S, Spencer SA, Harris J, and Yom SS. Radiotherapy with Durvalumab vs. Cetuximab in Patients with Locoregionally Advanced Head and Neck Cancer and a Contraindication to Cisplatin: Phase II Results of NRG-HN004. *Int J Radiat Oncol Biol Phys* 2022; 114(5):1058. Full Text

L.K. Mell, Department of Radiation Medicine and Applied Sciences, University of California San Diego, La Jolla, CA

Purpose/Objective(s): The optimal treatment for patients with locoregionally advanced head and neck squamous cell carcinoma (HNSCC) and contraindication to cisplatin is uncertain. This trial (NCT03258554) tested the primary hypothesis that radiation therapy (RT) with concurrent and adjuvant durvalumab, a PD-L1 inhibitor, improves progression-free survival (PFS) compared to standard RT with cetuximab. Materials/Methods: This phase II/III randomized trial enrolled patients ≥ 18 years of age who had previously untreated AJCC 8th stage III-IVB SCC of the larynx, hypopharynx, oral cavity, p16-oropharynx/unknown primary (OPC/UP) or stage III and selected stage I-II p16+ OPC/UP, with a contraindication to cisplatin: ECOG performance status (PS) 2; renal or hearing impairment; peripheral neuropathy; age ≥ 70 with moderate/severe comorbidity; age < 70 with severe comorbidity. Favorable-risk p16+ HNSCC, PS >2, inadequate end-organ function, or active autoimmune disease were exclusion criteria. Patients were randomized 2:1 to RT (70 Gy, 35 fractions, 7 weeks) plus either: (arm A) durvalumab 1500 mg IV q4 weeks starting 2 weeks before RT (7 cycles) or (arm B) cetuximab 400 mg/m2 IV 1 week prior to RT then 250 mg/m2 weekly (8 cycles). The primary phase II endpoint was PFS with planned sample size of 234 randomized patients (69 PFS events, hazard ratio 0.65, 80% power, 1-sided alpha 0.20). The difference in PFS between arms was tested using a log-rank test. Results: This study enrolled 190 patients (186 randomized; 123 arm A; 63 arm B) from Mar 2019-Jul 2021. Following planned interim futility analysis, the trial was temporarily closed to accrual, pending analysis based on total required phase II PFS events (met in Jun 2022). Median age was 72 years (59% ≥ 70). 95% had ≥ 3 comorbidities (median 5); 58% had T3-4; 49% had N2-3; 47% had p16+ OPC/UP. 87% in arm A and 89% in arm B completed RT. 89%/63% completed concurrent/adjuvant durvalumab and 81% completed ≥ 7 cycles of cetuximab. At median follow-up of 1.2 years, PFS was not improved and locoregional failure (LRF) was higher with durvalumab (Table). Grade ≥ 3 adverse events were 69%/79% for arm A/B. Grade ≥ 3 dysphagia, mucositis, and dermatitis rates were 22%/30%, 11%/20%, and 5%/13% for arm A/B, respectively. Conclusion: Novel eligibility criteria and feasibility of accrual were established. However, RT with durvalumab did not show a signal toward improved PFS and led to significantly worse LRF, compared to RT with cetuximab in HNSCC pts with a contraindication to cisplatin. The trial will not move to phase III.

Radiation Oncology

Parikh PJ, Lee P, Low D, **Kim J**, Mittauer KE, Bassetti MF, Glide-Hurst C, Raldow A, Yang Y, Portelance L, Zaki B, Kim H, Mancias JD, Ng J, Pfeffer RM, Mueller A, Kelly P, Boldrini L, Fuss M, and Chuong MD. Stereotactic MR-Guided On-Table Adaptive Radiation Therapy (SMART) for Patients with Borderline or Locally Advanced Pancreatic Cancer: Primary Endpoint Outcomes of a Prospective Phase II Multi-Center International Trial. *Int J Radiat Oncol Biol Phys* 2022; 114(5):1062-1063. Full Text

P.J. Parikh, Department of Radiation Oncology, Henry Ford Cancer Institute, Detroit, MI, United States

Purpose/Objective(s): Retrospective studies demonstrate that ablative stereotactic MR-guided on-table adaptive radiation therapy (SMART) achieves favorable local control (LC) and overall survival (OS) with limited grade 3+ toxicity compared to historical non-ablative outcomes for locally advanced and borderline resectable pancreatic cancer (LAPC/BRPC). We conducted an international multi-center single-arm phase 2 trial of ablative 5-fraction SMART for LAPC/BRPC. Materials/Methods: Subjectswere required to have biopsy-confirmed adenocarcinoma, receive ≥3 months of chemotherapy, have no distant metastasis and CA19-9 ≤500 U/mL. SMART was delivered on a 0.35T MR-60Co or MR-linac system prescribed to

50 Gy in 5 fractions (biologically effective dose10 [BED10]=100 Gy) using continuous intrafraction cine-MRI, soft tissue tracking, and automatic beam gating. The original plan was recomputed onto the daily anatomy and if that plan would not have met constraints, on-table adaptive replanning using an isotoxicity approach was performed. The primary objective was to demonstrate <15.8% acute grade 3+ gastrointestinal (GI) toxicity definitely related to SMART measured through 90 days and evaluated according to Common Terminology Criteria for Adverse Events v5.0 (CTCAE). All patients have completed 90-day follow-up. Secondary objectives included OS, distant progression free survival (DPFS), and patient-reported quality of life. Results: 136 patients across 13 sites were enrolled between 2019-2021. Mean age was 65.7 years. Head of pancreas lesions were most common (66.9%; n=91). 43.4% (n=59) had BRPC, 56.6% (n=77) LAPC. Mean induction chemotherapy duration was 155.7 days, typically with FOLFIRINOX 65.4% (n=89) or gemcitabine doublet 16.9% (n=23). Mean CA19-9 after induction chemotherapy was 71.7 U/mL. On-table adaptive replanning was used for 93.1% of fractions. SMART was delivered in consecutive days (56.6%) or every other day (43.4%). Median follow-up was 16.4 months and 8.8 months from diagnosis and SMART, respectively. 31.6% (n=43) had surgery after SMART. The incidence of acute grade 3+ GI toxicity definitely and probably related to SMART were 0% and 2.2% (n=3), respectively. 1-year LC and DPFS from SMART were 82.9% and 50.6%, respectively. 1-year OS was 93.9% from diagnosis and 65.0% from SMART. Conclusion: This is the first prospective, multi-institutional study of ablative SMART with prescribed BED10 of 100 Gy delivered in 5 fractions for BRPC/LAPC. The primary objective was met, signaling that further prospective evaluation of ablative SMART for BRPC/LAPC is warranted with a focus on long-term LC and OS compared to chemotherapy alone.

Sleep Medicine

Cheng P, Casement M, **Kalmbach D**, **Castelan AC**, and **Drake C**. Digital Cognitive Behavioral Therapy for Insomnia Promotes Resilience During the Coronavirus Disease 19 (COVID-19) Pandemic. *Sleep Med* 2022; 100:S114. Full Text

Introduction: Stressful life events contribute to insomnia, psychosocial functioning, and illness. Though individuals with a history of insomnia may be especially vulnerable during stressful life events, risk may be mitigated by prior intervention. This study evaluated the effect of prior digital cognitive-behavioral therapy for insomnia (dCBT-I) versus sleep education on resilience during the COVID-19 pandemic. Materials and Methods: COVID impact, insomnia, general- and COVID-related stress, depression, and global health were assessed in April 2020 in adults with a history of insomnia who completed a randomized controlled trial of dCBT-I (n = 102) versus sleep education control (n = 106) in 2016-2017. Regression analyses were used to evaluate the effect of intervention conditions on subsequent stress and health during the pandemic. Results: Insomnia symptoms were significantly associated with COVID-19 related disruptions, and those previously received dCBT-I reported less insomnia symptoms, less general stress and COVID-related cognitive intrusions, less depression, and better global health than those who received sleep education. Moreover, the odds for resurgent insomnia was 51% lower in the dCBT-I versus control condition. Similarly, odds of moderate to severe depression during COVID-19 was 57% lower in the dCBT-I condition. Conclusions: Those who received dCBT-I had increased resilience during the COVID-19 pandemic in adults with a history of insomnia and ongoing mild to moderate mental health symptoms. These data provide evidence that dCBT-I is a powerful tool to promote mental and physical health during stressors, including the COVID-19 pandemic. Acknowledgements: HLK23138166

Sleep Medicine

Dauvilliers Y, **Roth T**, Bogan R, Thorpy M, Morse AM, Roy A, Seiden D, Dubow J, and Gudeman J. Efficacy of Once-Nightly Sodium Oxybate (ON-SXB; FT218) By Narcolepsy Type: Post-hoc Analyses From the REST-ON Trial. *Sleep Med* 2022; 100:S157. Full Text

Introduction: In REST-ON (NCT02720744), once-nightly sodium oxybate (ON-SXB; FT218) treatment resulted in significant improvement vs placebo for the coprimary endpoints mean sleep latency on the Maintenance of Wakefulness test (MWT), Clinical Global Impression of Improvement (CGI-I) rating of “much” or “very much” improved, and weekly number of cataplexy attacks (NCA) overall (all P<0.001) and in post-hoc analyses of subgroups of narcolepsy type 1 or 2 (NT1/NT2) for MWT and CGI-I (all P<0.05). Secondary REST-ON endpoints included polysomnographic measures of sleep stage shifts and nocturnal

arousals (NAs) and patient-reported assessments of sleep quality and refreshing nature of sleep. Post-hoc analyses to investigate ON-SXB efficacy based on secondary REST-ON endpoints measuring effects on objective and subjective measures of disrupted nighttime sleep and daytime sleepiness in patient subgroups based on narcolepsy type were conducted. Materials and Methods: Individuals aged ≥16 years with NT1 or NT2 were randomized 1:1 to receive ON-SXB (1 week, 4.5 g; 2 weeks, 6 g; 5 weeks, 7.5 g; 5 weeks, 9 g) or placebo. P values for change from baseline vs placebo at weeks 3 (6 g), 8 (7.5 g), and 13 (9 g) in Epworth sleepiness scale (ESS) score, sleep shifts (ie, the number of shifts from stages N1, N2, N3 and rapid eye movement [REM] sleep to Wake and from N2, N3 and REM sleep to N1), nocturnal arousals (NA), and patient-reported outcomes of sleep quality and refreshing nature of sleep on a 100-point visual analog scale were calculated using a mixed-effects model for repeated measures. Results: Of the 190 participants in the modified intent-to-treat population, 145 had NT1 (ON-SXB, n=73; placebo, n=72) and 45 had NT2 (ON-SXB, n=24; placebo, n=21). Significant improvements with ON-SXB vs placebo were observed for both narcolepsy types for shifts to a lighter stage of sleep (NT1: 6, 7.5, and 9 g, all P<0.001; NT2: 6 and 7.5 g, both P<0.05, 9 g, P<0.001), NA (NT1, 6 g, P<0.05, 7.5 and 9 g, P<0.01; NT2, 7.5 and 9 g, P<0.05), and sleep quality (NT1, 6, 7.5, and 9 g, all P<0.001; NT2, 6, 7.5, and 9 g, all P<0.05). For both ESS and refreshing nature of sleep, significant improvements with ON-SXB vs placebo were observed for NT1 (6, 7.5, and 9 g, P≤0.001). The NT2 subgroup showed directional improvements for these endpoints but did not achieve statistical significance. Conclusions: Stratifying objective and subjective measures of disrupted nighttime sleep and daytime sleepiness by NT1 and NT2 allows for subgroup efficacy analyses. Lack of statistical significance on some endpoints for the NT2 subgroup may be due to underpowering. The results of these post-hoc analyses are generally consistent with the previously reported positive endpoints from REST-ON and provide further support for the efficacy of ON-SXB as a treatment for narcolepsy symptoms in adults with either NT1 or NT2. Acknowledgements: This study was funded by Avadel Pharmaceuticals.

Sleep Medicine

Drake C, Yardley J, Pinner K, Perdomo C, and Moline M. Evaluation of Long-term Perception of Medication Effectiveness: Results from Subjects Receiving Lemborexant for up to 12 Months. *Sleep Med* 2022; 100:S120. Full Text

Introduction: The Patient Global Impression–Insomnia version (PGI-I) is a self-report instrument used to evaluate patients' perceptions of the effects of their insomnia medication on their sleep relative to their sleep before the start of treatment. The PGI-I questionnaire includes 3 items related to the effects of medication (helped/worsened sleep; decreased/increased time to fall asleep; and increased/decreased total sleep; the choices for response include: 1=positive, 2=neutral, 3=negative) and 1 item related to perceived appropriateness of study medication strength (the choices for response include: 1=too strong, 2=just right, 3=too weak). In Study E2006-G000-303 (Study 303; SUNRISE-2; NCT02952820), the percentages of subjects who reported a positive impact of lemborexant (LEM) was significantly greater compared with placebo (PBO) at 1, 3, and 6mo for the PGI-I items related to the effects of medication. LEM is a dual orexin receptor antagonist approved in multiple countries, including the United States, Japan, Canada and Australia for the treatment of insomnia in adults. We present here the PGI-I results at 9 and 12mo for subjects that received continuous treatment with LEM for up to 12mo. Materials and Methods: Study 303 was a 12mo, randomized, double-blind, PBO-controlled (during the first 6mo [Period 1]), phase 3 study. Subjects were age ≥18 years with a diagnosis of insomnia disorder. During Period 1, subjects received PBO (n=318) or LEM (5mg, [LEM5], n=316; 10mg, [LEM10], n=315). During Period 2 (second 6mo), LEM subjects continued their assigned dose while PBO subjects were rerandomized to LEM5 or LEM10 (data for PBO subjects rerandomized to LEM in Period 2 reported separately). All subjects (LEM and PBO) were administered the PGI-I at 1, 3 and 6mo (previously presented). PGI-I was also administered at 9 and 12mo, and only subjects who had received LEM during Period 1 are summarized here. Results: At 9 and 12mo, the majority of LEM5 (9mo: n=241; 12mo: n=205) and LEM10 (9mo, n=211; 12mo, n=192) subjects reported that their study medication "helped" sleep at night (9mo: LEM5=73.4%; LEM10=76.3%; 12mo: LEM5=74.6%; LEM10=77.6%), reduced time to fall asleep (9mo: LEM5=79.3%, LEM10=78.2%; 12mo: LEM5=76.6%, LEM10=80.2%), and increased total sleep time (9mo: LEM5=62.2%, LEM10=73.0%; 12mo: LEM5=62.4%; LEM10=65.1%). Also, at both 9 and 12mo the majority of subjects in the LEM5 and LEM10 groups responded that their perception of the appropriateness of the strength of their treatment was "just right" (9mo: LEM5=60.6%, LEM10=62.1%;

12mo: LEM5=63.4%; LEM10=60.4%), which were higher percentages than reported “just right” at 1, 3 and 6mo (1mo: LEM5=43.7%, LEM10=43.4%; 3mo: LEM5=49.8%, LEM10=51.5%; 6mo: LEM5=55.6%; LEM10=53.4%). LEM was generally well tolerated. The majority of events were mild or moderate in severity. Conclusion: The majority of subjects receiving LEM5 or LEM10 reported a positive medication effect at both 9 and 12mo. These results are similar to positive effects for LEM achieved at earlier time points during the first 6mo of treatment in Study 303 and suggest that for the majority of subjects, a positive perception of their insomnia medication is sustained for up to 12mo. Acknowledgements: Supported by Eisai Inc.

Sleep Medicine
Jaziri M, **Palmer W**, and **Tovar M**. Positional therapy in a patient with refractory treatment-emergent central sleep apnea. *Sleep Med* 2022; 100:S266-S267. Full Text

Introduction: Treatment-emergent central sleep apnea (TE-CSA) is a condition characterized by central respiratory events that can arise with the use of positive airway pressure (PAP) therapy during treatment of obstructive sleep apnea (OSA). It is usually transient in nature and resolves after continuous PAP therapy most of the time. In cases of persistent TE-CSA, adaptive servo-ventilation (ASV) is a common treatment as it affords a backup respiratory rate to support central apneas, and studies have shown ASV’s ability to improve the apnea-hypopnea index (AHI) in patients with TE-CSA. While worsening sleep apnea in the supine position is a known phenomenon in OSA and central sleep apnea (CSA), worsening positional TE-CSA is rarely reported and to date poorly understood. Positional therapy is a strategy that has been shown to be effective in treating both OSA and central sleep apnea (CSA) but has not been established as a treatment option for TE-CSA. We are presenting a rare case of persistent positional TE-CSA that was refractory to standard treatments and only improved after adding positional therapy. Case report: This is the case of a 60-year-old woman with symptomatic moderate obstructive sleep apnea who experienced progression to treatment-emergent central sleep apnea (TE-CSA) after initial treatment with positive airway pressure (PAP) therapy. A prolonged trial with continuous PAP (CPAP) or bilevel PAP (BPAP) was not possible because the patient experienced periods of pressure intolerance and adaptive servo-ventilation (ASV) was pursued. However, ASV titration revealed a persistent and positional preference for central respiratory events. She was fitted for a mandibular advancement device and had serial home sleep studies with device adjustment that continued to reveal inadequate control of her apneic events. After having used CPAP for 72 days, BPAP for 26 days, ASV for 78 days, and a mandibular advancement device, the patient was evaluated for HGNS therapy. Her HGNS titration re-demonstrated persistent central events with a supine AHI of 43.4 and a lateral AHI of 2.9, indicating a strong positional component of her refractory TE-CSA. Positional therapy was initiated with good control of the patient’s apnea with HGNS use during lateral sleep and resolution of the patients reported sleep related symptoms. Conclusions: The final improvement in our case of TE-CSA resulted from positional therapy in concert with HGNS. The patient’s successful lateral sleep therapy for positionally exacerbated TE-CSA demonstrates the benefit of a well-known sleep apnea treatment for this rarely described condition. Positional therapy continues to be invaluable in treating various forms of sleep apnea and may be effective for patients with positional TE-CSA who are refractory to other common therapies.

Sleep Medicine
Kushida C, **Roth T**, Thorpy M, Seiden D, Dubow J, and Gudeman J. Efficacy of FT218, a Once-Nightly Sodium Oxybate Formulation, in Patients With Narcolepsy: Post-hoc Sensitivity Analyses From the REST-ON Trial. *Sleep Med* 2022; 100:S156-S157. Full Text

Introduction: In REST-ON (NCT02720744), once-nightly sodium oxybate (ON-SXB; FT218) treatment resulted in significant improvement vs placebo for coprimary endpoints mean sleep latency on the Maintenance of Wakefulness test (MWT), Clinical Global Impression of Improvement (CGI-I) rating of “much” or “very much” improved, and weekly number of cataplexy attacks (NCA) (all P<0.001). Post-hoc sensitivity analyses using different methods to handle missing data were conducted to support the robustness of the primary data. Materials and Methods: Individuals aged ≥16 years with narcolepsy type 1 or 2 were randomized 1:1 to receive ON-SXB (1 week, 4.5 g; 2 weeks, 6 g; 5 weeks, 7.5 g; 5 weeks, 9 g) or placebo. Sensitivity analyses included completer population; placebo-based multiple imputation (MI) with missing not at random assumption (missing values in both arms imputed from observed placebo-arm

values); analysis of covariance (ANCOVA); and tipping point-based MI of worsening values until P>0.05. For MWT and NCA, mean differences and P values were calculated. For CGI-I, odds ratios (OR) and P values were calculated for completers; mean differences (1–7-points; lower values indicate greater improvement) and P values were calculated using ANCOVA. Results: For completers (ON-SXB, n=69; placebo, n=79), significant improvement was observed with 6, 7.5, and 9 g ON-SXB vs placebo on all coprimary endpoints (all P<0.001); with 9-g dose, mean difference vs placebo on MWT was 6.0 min (95% CI: 3.3–8.7), CGI-I responder proportions for ON-SXB and placebo were 72.3% and 31.6% (OR, 5.7 [95% CI: 2.8–11.6]), and mean difference in NCA was –6.6 (95% CI: –9.6 to –3.6). With placebo-based MI, all ON-SXB doses were associated with significant improvement vs placebo on all coprimary endpoints (all P<0.001); with 9-g dose, mean difference vs placebo on MWT was 5.4 min (95% CI: 2.8–8.0), CGI-I responder proportions for ON-SXB and placebo were 63.0% and 28.5% (OR, 4.3 [95% CI: 2.3–8.0]), and mean difference in NCA was –6.4 (95% CI: –11.3 to –3.7). With ANCOVA, all ON-SXB doses were associated with significant improvement vs placebo on all coprimary endpoints (all P<0.001); for the 9-g dose, mean difference vs placebo on the MWT was 6.0 min (95% CI: 3.6–8.5), CGI-I rating difference was –1.0 (95% CI: –1.3 to –0.7), and mean NCA was –6.4 (95% CI: –9.0 to –3.8). With MWT tipping point MI, differences between ON-SXB and placebo lost significance with worsening of 7.0, 5.2, and 4.3 min from baseline for 6, 7.5, and 9 g, respectively, which was implausible for the 7.5- and 9-g doses as baseline MWT was 5 min. When participants who withdrew from the ON-SXB arm were imputed as “not improved,” CGI-I remained significant in favor of ON-SXB (all 3 doses, P<0.001). Mean NCA remained significant for all 3 ON-SXB doses vs placebo with worsening trajectories imputed; positive results could not be tipped over with plausible values. Conclusions: These post-hoc results are consistent with the coprimary endpoints and further confirm the efficacy of ON-SXB as a treatment for narcolepsy symptoms. Acknowledgements: This study was funded by Avadel Pharmaceuticals.

Sleep Medicine
Roth T, Yardley J, Pinner K, Kumar D, Cheng JY, and Moline M. The incidence of abnormal dreams and nightmares in adults with insomnia treated with lemborexant: results from two Phase 3 studies. *Sleep Med* 2022; 100:S142. Full Text

Introduction: Abnormal dreams and nightmares have been reported by patients with insomnia both before and after treatment with hypnotics. Since dual orexin receptor antagonists (DORAs) such as lemborexant (LEM) increase REM sleep, during which dream content is more likely to be recalled, we assessed the frequency of reports of nightmares/abnormal dreams in subjects treated with LEM during two Phase 3 studies. LEM is approved in multiple countries including the United States, Japan, Canada and Australia for the treatment of adults with insomnia. Materials and Methods: Study 303 (SUNRISE-2; NCT02952820) was a 12 month, randomized, double-blind, placebo (PBO)-controlled (first 6 month [Period 1]), phase 3 study that enrolled subjects aged ≥18 years with insomnia disorder and Insomnia Severity Index (ISI) scores ≥15. During Period 1, the safety analysis set (SAS) included: PBO, n=319; LEM 5 mg, (LEM5), n=314; LEM 10 mg (LEM10), n=314. Study 304 (SUNRISE-1; NCT02783729) was a 1 month, randomized, double-blind, PBO- and active-controlled (zolpidem tartrate extended-release 6.25 mg [ZOL-ER]) study of LEM5 and LEM10. The SAS included: PBO, n=209; ZOL-ER, n=263; LEM5, n=266; LEM10, n=268. Results: In Study 303 Period 1, 28/947 subjects (3.0%) reported nightmares (n=12; PBO, n=1; LEM5, n=4; LEM10, n=7) or abnormal dreams (n=17; PBO, n=6; LEM5, n=7; LEM10, n=4) as treatment-emergent adverse events (TEAEs). In Study 304, 12/1006 subjects (1.2%) reported nightmares (n=4; PBO, n=1; ZOL-ER, n=0; LEM5; n=2; LEM10, n=1) or abnormal dreams (n=8; PBO, n=1; ZOL-ER, n=3; LEM5, n=0; LEM10, n=4). 32/40 subjects (80.0%) reporting these events were female. In the LEM groups, 11/28 subjects (39.3%) reported the TEAE within 3 days of treatment initiation. There were 2 TEAEs of nightmare/abnormal dreams during the PBO run-in prior to randomization. Conclusions: Abnormal dreams/nightmares were not common events in either study. Incidence was slightly higher with LEM10 and higher in females, which was consistent with a greater proportion of females being enrolled in both studies. Acknowledgements: Supported by Eisai Inc.

Sleep Medicine
Roth T, Zammit G, Kumar D, Pappadopulos E, and Moline M. Lemborexant versus Zolpidem: An Assessment of Wake Bouts in Adults with Insomnia. *Sleep Med* 2022; 100:S128-S129. Full Text

Introduction: Dual orexin receptor antagonists (DORAs), including lemborexant (LEM), are thought to promote sleep by inhibiting orexin-mediated wakefulness. In Study 304 (SUNRISE-1; NCT02783729; ≥55 years with insomnia), LEM significantly improved sleep efficiency and wake after sleep onset (WASO) versus placebo (PBO) and zolpidem tartrate extended-release 6.25mg (ZOL). The precise effects of LEM on WASO dynamics were examined by evaluating the effect of LEM on frequency and duration of wake bouts. Materials and Methods: Study 304 was a 1 month, randomized, double-blind, PBO (n=208)- and active-controlled (ZOL; n=263) study of LEM 5mg (LEM5; n=266) and LEM 10mg (LEM10; n=269). Polysomnographic data from Night (NT) 2 and NT31 of treatment were analyzed to determine the number and total duration of all wake bouts (any duration), short (≤2 minutes) and long (>2 minutes) wake bouts. P-values are based on differences in least squares mean changes from baseline, in the number and total duration of all, short, and long wake bouts among treatment groups. Results: Wake bouts of any duration were more frequent in LEM-treated subjects during NT2, (LEM5, 35.1; LEM10, 37.8) versus PBO (32.7) or ZOL (31.5), and during NT31: 37.9, 40.3, 31.7, and 31.0, respectively. LEM-treated subjects spent fewer total minutes in wake bouts during NT2 (LEM5, 62.2; LEM10, 55.2) versus PBO (93.0) or ZOL (72.7) and during NT31: 66.4, 67.3, 92.4, and 79.7, respectively. LEM-treated subjects had more short wake bouts during NT2 (LEM5, 30.4; LEM10, 33.4) versus PBO (26.9) or ZOL (26.3) and during NT31: 32.8, 34.7, 26.1, and 25.9, respectively. LEM5- and LEM10-treated subjects spent significantly more minutes in short wake bouts than PBO- or ZOL-treated subjects during NT2 (LEM5, 22.0 [P<0.05 vs PBO and ZOL]; PBO, 20.1; and ZOL, 19.5; LEM10, 24.5 [P<0.0001 vs PBO and ZOL]). Findings were similar during NT31 (LEM5, 23.9; LEM10, 25.7 [both P<0.0001 vs PBO and ZOL]; PBO, 19.4; and ZOL, 19.3). ZOL was not significant versus PBO for total time spent in short wake bouts at either NT2 or NT31. LEM-treated subjects had fewer long wake bouts (LEM5, 4.7; LEM10, 4.4) versus PBO (5.9) or ZOL (5.2) during NT2 but were similar during NT31: 5.1, 5.6, 5.5, and 5.2, respectively. LEM5- and LEM10-treated subjects spent significantly fewer minutes in long wake bouts than PBO- or ZOL-treated subjects during NT2 (LEM5, 40.3; LEM10, 30.8 [both P<0.0001 vs PBO and ZOL]; PBO, 73.0; and ZOL, 53.2). Findings were similar during NT31: LEM5, 42.5; LEM10, 41.6 (both P<0.0001 vs PBO and ZOL); PBO, 73.0; and ZOL, 60.4. ZOL was significant versus PBO at NT2 and NT31 (both P<0.001). Conclusion: Relative to PBO and ZOL, WASO decreased with LEM, mediated by a decrease in the number and time spent in long wake bouts, and an increase in the number and time spent in short wake bouts. These findings are consistent with the effects of the DORA, suvorexant on WASO (Svetnik V, et al. SLEEP. 2018;41(1)) and reflect differences between hypnotics with different mechanisms of action. Acknowledgements: Supported by Eisai Inc.

Sleep Medicine

Thorpy M, Dauvilliers Y, **Roth T**, Morse AM, Roy A, Bogan R, Seiden D, Dubow J, and Gudeman J. Efficacy of Once-Nightly Sodium Oxybate (ON-SXB; FT218) Across Stimulant Use Subgroups: Post-hoc Analyses From the REST-ON Trial. *Sleep Med* 2022; 100:S157. Full Text

Introduction: In REST-ON (NCT02720744), once-nightly sodium oxybate (ON-SXB; FT218) resulted in significant improvement vs placebo for the coprimary endpoints of mean sleep latency on the Maintenance of Wakefulness test (MWT), Clinical Global Impression of Improvement (CGI-I) rating, and number of weekly cataplexy attacks (NCA) overall (P<0.001) and in subgroups based on concomitant stimulant use for MWT and CGI-I (all P<0.05). Post-hoc analyses to investigate ON-SXB efficacy on the secondary REST-ON endpoints of disturbed nocturnal sleep (DNS) and the Epworth Sleepiness Scale (ESS) score were similarly conducted. Materials and Methods: Individuals aged ≥16 years with narcolepsy type 1 or 2 were randomized 1:1 to receive ON-SXB (1 week, 4.5 g; 2 weeks, 6 g; 5 weeks, 7.5 g; 5 weeks, 9 g) or placebo. P values for change from baseline vs placebo at weeks 3 (6 g), 8 (7.5 g), and 13 (9 g) in ESS score, sleep shifts (ie, the number of shifts from stages N1, N2, N3 and rapid eye movement [REM] sleep to Wake and from N2, N3 and REM sleep to N1), nocturnal arousals (NA), and patient-reported outcomes of sleep quality and refreshing nature of sleep on a 100-point visual analog scale were calculated using a mixed-effects model for repeated measures. Results: Of the 190 participants in the modified intent-to-treat population, 119 were taking concomitant stimulants (ON-SXB, n=66; placebo, n=53) including modafinil (ON-SXB, 21.5%; placebo, 21.0%), armodafinil (ON-SXB, 12.1%; placebo, 6.7%), amphetamine (various; ON-SXB, 10.3%; placebo, 5.7%), and methylphenidate (ON-SXB, 10.3%; placebo, 6.7%), and 71 were not taking stimulants (ON-SXB, n=31; placebo, n=40). Improvements with ON-SXB vs placebo were observed regardless of stimulant-use subgroup for ESS

(stimulants: all doses, P≤0.01; no stimulants: 6 g, directional improvement; 7.5 g, P<0.01; 9 g, P<0.001), sleep shifts (stimulants: 6 g, P<0.01; 7.5 and 9 g, P<0.001; no stimulants: all doses, P<0.001), and NA (stimulants: directional improvement, 6 g; 7.5 g, P<0.01; 9 g, P=0.001; no stimulants: 6 and 7.5 g, P<0.05; 9 g, P=0.01). Improvements with ON-SXB vs placebo were also observed on the patient-reported outcomes of sleep quality (stimulants: 6 and 7.5 g, P<0.01; 9 g, P<0.05; no stimulants: all doses P<0.001) and refreshing nature of sleep (stimulants: 6 and 9 g, P<0.05; 7.5 g, P<0.001; no stimulants: 6 and 7.5 g, P<0.01; 9 g, P=0.001). Conclusions: The results of these post-hoc analyses were consistent with the previously reported statistically significant coprimary endpoint results from REST-ON. These data support the efficacy of ON-SXB for EDS and DNS in adults, as measured by objective and subjective endpoints, regardless of concurrent stimulant use. Acknowledgements: This study was funded by Avadel Pharmaceuticals.

Sleep Medicine
Thorpy M, **Roth T**, Kushida C, Seiden D, Dubow J, and Gudeman J. Efficacy of Once-nightly Sodium Oxybate (ON-SXB; FT218) for Excessive Daytime Sleepiness and Cataplexy: Post-hoc Number Needed to Treat and Effect Size Analyses From REST-ON. *Sleep Med* 2022; 100:S157-S158. Full Text

Introduction: Narcolepsy is a chronic neurologic disease; symptoms include excessive daytime sleepiness (EDS) and cataplexy. FT218 is an extended-release, once-nightly formulation of sodium oxybate (ON-SXB) that is in development for treatment of adults with narcolepsy. Treatment with ON-SXB resulted in significant improvement vs placebo (6 g, 7.5 g, and 9 g, all P<0.001) for the coprimary endpoints of mean sleep latency on the Maintenance of Wakefulness test (MWT), Clinical Global Impression of Improvement rating, and number of weekly cataplexy episodes, as well as the secondary endpoint Epworth sleepiness scale (ESS) score, in the phase 3 REST-ON clinical trial (NCT02720744). Post-hoc analyses of numbers needed to treat (NNT) and effect sizes were performed to provide further context into the effectiveness of ON-SXB. Materials and Methods: Individuals aged ≥16 years with narcolepsy type 1 or 2 were randomized 1:1 to receive ON-SXB (1 week, 4.5 g; 2 weeks, 6 g; 5 weeks, 7.5 g; 5 weeks, 9 g) or placebo. For the post-hoc analyses, response on the MWT was defined as ≥5 min increase from baseline in mean sleep latency, response on the ESS was defined as a score ≤10, and cataplexy response was defined as ≥50% reduction from baseline in the mean number of weekly. Results:In total, 222 participants were randomized and 190 comprised the modified intent-to-treat population (ON-SXB, n=97 [NT1, n=73]; placebo, n=93 [NT1, n= 72]). For MWT response, all doses of ON-SXB (6 g at week 3, 7.5 g at week 8, and 9 g at week 13) had NNTs of 3 and effect sizes ranging from 0.7–0.9. For ESS response, NNTs ranged from 3 to 6, with a dose-response effect. As a decrease signifies response, effect sizes were between –0.5 to –0.7 for the 3 doses. For cataplexy response, NNT was 6 for the 6-g dose and 3 for the 7.5-g and 9-g doses, and the effect sizes were between –0.7 to –0.8. Conclusions: NNTs provide a useful interpretation of the expected effectiveness of a medication. As defined by these measures, only 3–6 patients need to be treated with ON-SXB to achieve ≥5 minutes increased sleep latency on the MWT or an ESS of ≤10, with the same number needed to achieve a 50% or greater reduction in cataplexy. Effect size provides a useful interpretation, as this calculation relies upon the standard deviation; an effect size of 0.50 or more is generally regarded as a moderate effect and 0.80 as a large effect. These post-hoc analyses provide further confidence in the strength of ON-SXB efficacy and may be useful to clinicians in discussing treatment expectations. Acknowledgements: This study was funded by Avadel Pharmaceuticals.

Sleep Medicine
Zammit G, **Roth T**, Kumar D, Perdomo C, and Moline M. Impact of Lemborexant Versus Placebo and Zolpidem on REM Sleep Duration by Quarter-of-the-Night Intervals in Older Adults with Insomnia Disorder. *Sleep Med* 2022; 100:S123. Full Text

Introduction: Lemborexant (LEM) is a dual orexin receptor antagonist approved in multiple countries, including the United States, Japan, Canada and Australia for the treatment of adults with insomnia. The effects of LEM on sleep architecture in adults ≥55y with insomnia disorder were assessed in Study E2006-G000-304 (Study 304; SUNRISE-1; NCT02783729). These post hoc analyses examined the acute effect of LEM on REM pressure, as assessed by changes from baseline in REM latency and in REM sleep duration in 2-hour quarter-of-the-night (QoN) intervals. Materials and Methods: Study 304 was a 1

month, randomized, double-blind, placebo (PBO)- and active-controlled (zolpidem tartrate extended-release 6.25mg [ZOL]) study of LEM (5mg, LEM5; 10mg, LEM10). Subjects received PBO (n=208), ZOL (n=263), LEM5 (n=266), or LEM10 (n=269). Paired polysomnographic assessments were conducted at baseline, the first 2 (N1/2), and the last 2 (N29/30) nights of treatment; mean values from the paired assessments are reported. Results: Baseline REM latency (minutes) was similar across treatments (98.4-101.4). On N1/2, significant mean (SD) decreases from baseline in REM latency were observed for LEM5 (−42.6 [53.9]) and LEM10 (−49.6[52.9]) vs PBO (−6.9[54.5]) and vs ZOL (0.2[54.2]) (all P<0.0001). On N29/30, REM latency was also significantly decreased from baseline with LEM5 (−30.7[55.7]) and LEM10 (−37.7[56.2]) vs PBO (−7.7[62.3]) and vs ZOL (−4.0[56.4]) (all P<0.0001). No difference was observed for ZOL vs PBO at either N1/2 or N29/30. Within each QoN, baseline REM sleep duration (minutes) was similar across treatments. On N1/2, mean REM (minutes) across quarters ranged from 16.5-23.8 for LEM5, 19.7-26.1 for LEM10, 10.3-21.6 for PBO, and 8.5-22.8 for ZOL. On N29/30, mean REM values were 14.4-22.4 for LEM5, 16.9-24.1 for LEM10, 9.2-21.5 for PBO, and 8.3-22.3 for ZOL. In each QoN during N1/2, REM sleep duration (minutes) significantly increased from baseline with LEM10 vs PBO (all P<0.0001) and vs ZOL (all P<0.001). With LEM5 during N1/2, REM sleep significantly increased from baseline vs PBO during Q1, Q3, and Q4 (all P<0.05) and vs ZOL in Q1 and Q2 (both P<0.01). With ZOL, REM was significantly decreased vs PBO during Q1 (P<0.05) and significantly increased vs PBO during Q3 (P<0.05). On N29/30, REM sleep (minutes) significantly increased from baseline with LEM10 vs PBO in each QoN (all P<0.05) and vs ZOL in Q1, Q3, and Q4 (all P<0.05). With LEM5, REM sleep significantly increased from baseline vs PBO and vs ZOL in Q1 (both P<0.0001). No significant differences were observed for ZOL vs PBO in any QoN on N29/30. In each QoN, the increases in REM sleep were significantly greater on N1/2 than N29/30 with LEM5 (all P<0.05) and LEM10 (all P<0.0001). Conclusion: LEM, but not ZOL, acutely increases REM pressure as evidenced by REM latency and REM duration per QoN. In each QoN, increases in REM sleep were greater with LEM5 and LEM10 than with ZOL or PBO. Decreases in REM latency and increases in REM sleep per QoN with LEM were greater during N1/2 than N29/30. Acknowledgements: Supported by Eisai Inc.