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HENRY FORD HEALTH

Henry Ford Health Publication List – March 2025

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 biomedical databases PubMed, Embase, Web of Science, CINAHL, and PsycINFO, as well as Google Books during the month, and then imported into EndNote for formatting. There are 211 unique citations listed this month, including 132 articles and 79 conference abstracts.

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

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Articles

Conference Abstracts

Articles

Administration

Henry A, Mo X, Finan C, Chaffin MD, Speed D, Issa H, Denaxas S, Ware JS, Zheng SL, Malarstig A, Gratton J, Bond I, Roselli C, Miller D, Chopade S, Schmidt AF, Abner E, Adams L, Andersson C, Aragam KG, Ärnlöv J, Asselin G, Raja AA, Backman JD, Bartz TM, Biddinger KJ, Biggs ML, Bloom HL, Boersma E, Brandimarto J, Brown MR, Brunak S, Bruun MT, Buckbinder L, Bundgaard H, Carey DJ, Chasman DI, Chen X, Cook JP, Czuba T, de Denus S, Dehghan A, Delgado GE, Doney AS, Dörr M, Dowsett J, Dudley SC, Engström G, Erikstrup C, Esko T, Farber-Eger EH, Felix SB, Finer S, Ford I, Ghanbari M, Ghasemi S, Ghouse J, Giedraitis V, Giulianini F, Gottdiener JS, Gross S, Guðbjartsson DF, **Gui H**, Gutmann R, Hägg S, Haggerty CM, Hedman Å K, Helgadottir A, Hemingway H, Hillege H, Hyde CL, Aagaard Jensen B, Jukema JW, Kardys I, Karra R, Kavousi M, Kizer JR, Kleber ME, Køber L, Koekemoer A, Kuchenbaecker K, Lai YP, **Lanfear D**, Langenberg C, Lin H, Lind L, Lindgren CM, Liu PP, London B, Lowery BD, Luan J, Lubitz SA, Magnusson P, Margulies KB, Marston NA, Martin H, März W, Melander O, Mordi IR, Morley MP, Morris AP, Morrison AC, Morton L, Nagle MW, Nelson CP, Niessner A, Niiranen T, Noordam R, Nowak C, O'Donoghue ML, Ostrowski SR, Owens AT, Palmer CNA, Paré G, Pedersen OB, Perola M, Pigeyre M, Psaty BM, Rice KM, Ridker PM, Romaine SPR, Rotter JI, Ruff CT, Sabatine MS, Sallah N, Salomaa V, Sattar N, Shalaby AA, Shekhar A, Smelser DT, Smith NL, Sørensen E, Srinivasan S, Stefansson K, Sveinbjörnsson G, Svensson P, Tammesoo ML, Tardif JC, Teder-Laving M, Teumer A, Thorgeirsson G, Thorsteinsdottir U, Torp-Pedersen C, Tragante V, Trompet S, Uitterlinden AG, Ullum H, van der Harst P, van Heel D, van Setten J, van Vugt M, Veluchamy A, Verschuuren M, Verweij N, Vissing CR, Völker U, Voors AA, Wallentin L, Wang Y, Weeke PE, Wiggins KL, **Williams LK**, Yang Y, Yu B, Zannad F, Zheng C, Asselbergs FW, Cappola TP, Dubé MP, Dunn ME, Lang CC, Samani NJ, Shah S, Vasan RS, Smith JG, Holm H, Shah S, Ellinor PT, Hingorani AD, Wells Q, and Lumbers RT. Genome-wide association study meta-analysis provides insights into the etiology of heart failure and its subtypes. *Nat Genet* 2025; Epub ahead of print. PMID: 40038546. Full Text

Heart failure (HF) is a major contributor to global morbidity and mortality. While distinct clinical subtypes, defined by etiology and left ventricular ejection fraction, are well recognized, their genetic determinants remain inadequately understood. In this study, we report a genome-wide association study of HF and its subtypes in a sample of 1.9 million individuals. A total of 153,174 individuals had HF, of whom 44,012 had a nonischemic etiology (ni-HF). A subset of patients with ni-HF were stratified based on left ventricular systolic function, where data were available, identifying 5,406 individuals with reduced ejection fraction and 3,841 with preserved ejection fraction. We identify 66 genetic loci associated with HF and its subtypes, 37 of which have not previously been reported. Using functionally informed gene prioritization methods, we predict effector genes for each identified locus, and map these to etiologic disease clusters through phenome-wide association analysis, network analysis and colocalization. Through heritability enrichment analysis, we highlight the role of extracardiac tissues in disease etiology. We then examine the differential associations of upstream risk factors with HF subtypes using Mendelian randomization. These findings extend our understanding of the mechanisms underlying HF etiology and may inform future approaches to prevention and treatment.

Administration

Venkateswaran VR, **She R**, Gardell SJ, **Luzum JA**, **Gupta R**, **Zhang K**, **Williams LK**, **Sabbah HN**, and **Lanfear DE**. Association of plasma metabolites and cardiac mitochondrial function with heart failure progression. *ESC Heart Fail* 2025; Epub ahead of print. PMID: 40064034. Full Text

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AIMS: Plasma metabolites are prognostic in heart failure with reduced ejection fraction (HFrEF), with citric acid cycle metabolites linked to ejection fraction (EF) changes. We investigated these mechanisms in a canine chronic HFrEF model. We tested associations between changes in plasma metabolites, left ventricular (LV) end-diastolic volume and cardiomyocyte mitochondrial function. METHODS: Eighteen dogs underwent microembolization to induce moderate HFrEF (target LVEF 35%-40%). Plasma metabolites, LV size and mitochondrial function were assessed over 12 months. RESULTS: Plasma metabolite heatmap showed acylcarnitine changes, with early alterations in organic acids and amino acids predicting later adverse LV remodelling. Using either baseline or change over time, 13 metabolites correlated with 12 month LV enlargement. This is mostly often at 3 months (11 of 13), notably C18:2 ($r = -0.58$, $P = 0.003$) and cardiac anaplerotic substrates like glutamine ($r = -0.52$, $P = 0.009$) and 3-HBA ($r = -0.43$, $P = 0.035$). Impaired cardiomyocyte mitochondrial function correlated with LV enlargement (max ATP synthesis 12.7 vs. 19.9 nmol/min/mg, $P = 0.0036$; ADP-stimulated respiration 224 vs. 308 nAtom O/min/mg protein; $P = 0.0064$). Plasma metabolites correlated with mitochondrial parameters at 12 month, particularly with MAX ATP: malate ($r = -0.75$, $P < 0.001$), fumarate ($r = -0.6$, $P = 0.008$) and glutamine ($r = 0.51$, $P = 0.031$). CONCLUSIONS: In canine HFrEF, plasma acylcarnitines, citric acid cycle or anaplerotic metabolites predicted adverse LV remodelling. LV enlargement correlated with reduced cardiomyocyte mitochondrial function, which in turn was also associated with increased citric acid cycle metabolites. Together, these data suggest impaired cardiac energetic function drives plasma metabolite associations in HFrEF progression.

Allergy and Immunology

Miller RL, Schuh H, Chandran A, Habre R, Angal J, Aris IM, Aschner JL, Bendixsen CG, Blossom J, Bosquet-Enlow M, Breton CV, Camargo CA, Jr., Carroll KN, Commodore S, Croen LA, Dabelea DM, Deoni SCL, Ferrara A, Fry RC, Ganiban JM, Geiger SD, Gern JE, Gilliland FD, Gogcu S, Gold DR, Hare ME, Harte RN, Hartert TV, Hertz-Picciotto I, Hipwell AE, Jackson DJ, Karagas MK, Khurana Hershey GK, **Kim H**, Litonjua AA, Marsit CJ, McEvoy CT, Mendonça EA, Moore PE, Nguyen AP, Nkoy FL, O'Connor TG, Oken E, Ownby DR, Perzanowski M, Rivera-Spoljaric K, Sathyanarayana S, Singh AM, Stanford JB, Stroustrup A, Towe-Goodman N, Wang VA, Woodruff TJ, Wright RO, Wright RJ, Zanobetti A, **Zoratti EM**, and **Johnson CC**. Child Opportunity Index at Birth and Asthma with Recurrent Exacerbations in the U.S. ECHO Program. *J Allergy Clin Immunol* 2025; Epub ahead of print. PMID: 40089117. Full Text

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Icahn School of Medicine at Mount Sinai, New York.
Medical University of South Carolina, Charleston.
Division of Research, Kaiser Permanente Northern California, Oakland.
University of Colorado Anschutz Medical Campus and.
Bill & Melinda Gates Foundation, Seattle.
Gillings School of Global Public Health and the Frank Porter Graham Child Development Institute, University of North Carolina at Chapel Hill, Chapel Hill.
Department of Psychological & Brain Sciences, George Washington University, Washington, DC.
Department of Kinesiology and Community Health, University of Illinois, Champaign; Beckman Institute for Advanced Science and Technology, Urbana.
University of Wisconsin School of Medicine and Public Heath, Madison.
Wake Forest University School of Medicine, Salem.

Channing Division of Network Medicine, Brigham and Women's Hospital and Harvard Medical School, Boston; Department of Environmental Health, Harvard T.H. Chan School of Public Health, Boston.
University of Tennessee Health Science Center, Memphis.
Colorado School of Public Health, Aurora.
Departments of Medicine and Pediatrics, Vanderbilt University Medical Center, Nashville.
University of California Davis Health, Davis.
Department of Psychiatry, University of Pittsburgh, Pittsburgh.
Geisel School of Medicine at Dartmouth, Hanover.
University of Cincinnati and Cincinnati Children's Hospital Medical Center, Cincinnati.
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University of Rochester Medical Center, Golisano Children's Hospital, Rochester.
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University of Utah Health, Salt Lake City.
Division of Allergy and Immunology, Augusta University, Augusta.
Columbia University Mailman School of Public Health, New York.
Washington University, St Louis Children's Hospital, St. Louis.
University of Washington, Departments of Pediatrics and Environmental and Occupational Health Sciences, Epidemiology, Seattle.
Northwell Health, New York.
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BACKGROUND: Environmental exposures and social determinants likely influence specific childhood asthma phenotypes. OBJECTIVE: We hypothesized that the Child Opportunity Index (COI) at birth, measuring multiple neighborhood opportunities, influences incidence rates (IRs) for asthma with recurrent exacerbations (ARE). METHODS: We tested for COI associations with ARE incidence rates in 15,877 children born between 1990-2018 in the Environmental Influences on Child Health Outcomes (ECHO) program. Parent-reported race and ethnicity and other demographics were assessed as effect modifiers. RESULTS: The IR of ARE for children born in very low COI neighborhoods was higher (IR=10.98; 95% Confidence Intervals (CI) 9.71, 12.25) than for other COI categories. Rates for Non-Hispanic Black children (NHB) were significantly higher than Non-Hispanic White (NHW) children in every COI category. The ARE IRs for children born in very low COI neighborhoods were several-fold higher for NHB and Hispanic Black (HB) children (IR=15.30; 95% CI 13.10, 17.49; IR=18.48; 95% CI 8.80, 28.15 respectively) when compared to White children. Adjusting for individual-level characteristics, children born in very low COI neighborhoods demonstrated an ARE incidence rate ratio (IRR) of 1.26 (95% CI 0.99,1.59) with a higher incidence of cases among children ages 2-4 years and with a parental history of asthma. CONCLUSIONS: Rates of ARE were higher among children born in under-resourced communities and this relationship is strongest for young minoritized children with a parental history of asthma. Higher rates for NHB even in the highest COI categories suggest that risk associated with race persists regardless of social disadvantage.

Anesthesiology

Chou A, **Oye M**, **Modi K**, **Gupta K**, **Fram G**, **Dawdy J**, **Zweig B**, **Frisoli T**, **Gonzalez PE**, **Spinetto PV**, **O'Neill B**, **Szymanski T**, **Deporre A**, **Parikh S**, and **Lee J**. Safety of Transesophageal Echocardiography in Patients Referred for Tricuspid Valve Disease at a Center for Structural Heart Disease. *J Cardiothorac Vasc Anesth* 2025; Epub ahead of print. PMID: 40090789. Full Text

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OBJECTIVES: The aim of this study was to examine safety outcomes in patients referred for transesophageal echocardiograms (TEEs) for tricuspid valve disease. DESIGN: Retrospective

observational study. SETTING: Single quaternary referral center specializing in structural heart disease. PARTICIPANTS: One hundred five patients referred for TEE for tricuspid valve disease between July 2022 and June 2023. INTERVENTIONS: This study was not interventional, but assessed the safety of TEE. METHODS AND MAIN RESULTS: The primary outcome was a composite of hypotension (mean arterial pressure [MAP] < 60 mmHg); use of epinephrine, norepinephrine, or calcium chloride; aborted studies due to documented clinical instability; emergent intubation; hospitalization or escalation of care post-TEE; oropharyngeal or gastrointestinal injury; or cardiac arrest. Secondary outcomes were 30-day cardiovascular mortality, all vasopressor use, and time spent per TEE. The primary outcome was noted in 32 patients (30.5%). The rate of cardiac arrest was 2.9% (3/105). Hypotension (MAP < 60 mmHg) was noted in 30 patients, with 7 patients needing hospitalization after TEE. No patients had oropharyngeal or gastrointestinal injury. There was a greater prevalence of moderate to severe right ventricular (RV) dilation (77% vs 53%; p = 0.022) and moderately to severely decreased RV function (48% vs 25%; p = 0.023) in patients who met the primary outcome. Both RV fractional area change (37.9% vs 29.8%; p = 0.003) and tricuspid annular plane systolic excursion (1.84 cm vs 1.45 cm; p = 0.002) were lower on baseline transthoracic echocardiogram. CONCLUSIONS: Patients with severe tricuspid regurgitation had a high prevalence of adverse events when undergoing TEE. Further studies are needed to compare these outcomes with other groups undergoing diagnostic TEE and delineate what risk factors may place these patients at greater risk.

Anesthesiology
Muthukumar A, Lakda A, and **Allouch H**. Comment on 'Peri-operative and anaesthetic considerations for gender-affirming vocal surgery'. *Anaesth Rep* 2025; 13(1):e70004. PMID: 40046852. Full Text

Department of Anaesthesiology Henry Ford Hospitals Detroit Michigan USA.
Department of Anaesthesiology Cleveland Clinic Cleveland Ohio USA.

Anesthesiology
Siddiqui N, **Sanders J**, and Krishnan S. Angiotensin II in Vasoplegia: Expanding Frontiers in Hemodynamic Therapy. *J Cardiothorac Vasc Anesth* 2025; Epub ahead of print. PMID: 40057440. Full Text

Department of Anesthesiology, Wayne State University School of Medicine, Detroit, MI; Department of Anesthesiology, Trinity-Health Oakland, Pontiac, MI.
Department of Anesthesiology, Henry Ford Health, Detroit, MI.

Anesthesiology
Sun H, Harman AE, **Mitchell JD**, Gaiser RR, and Deiner SG. Anesthesiology Resident Demographics and the BASIC Examination Pass Rates. *Anesth Analg* 2025; Epub ahead of print. PMID: 40146634. Full Text

From the Assessment Services, The American Board of Anesthesiology, Raleigh, North Carolina.
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Department of Anesthesiology, Yale School of Medicine, New Haven, Connecticut.
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BACKGROUND: The BASIC Examination was added to the US examination system for anesthesiology certification in 2014. The American Board of Anesthesiology conducted retrospective analyses to assess whether resident demographics, program characteristics, and/or prior examination performance were associated with first-time BASIC pass rates. METHODS: Anesthesiology residents who took the BASIC Examination for the first time from July 2014 to November 2022 were eligible to participate, and they had at least 2 more attempts (or opportunities to attempt) through December 2023. First-time and eventual pass rates (ie, based on up to 3 attempts) were calculated for each demographic group. For those residents who had the clinical base year in-training examination (CBY ITE) scores available, demographic group performance differences on this examination were first examined. Mixed-effects logistical regression models assessed how resident demographics, program characteristics, and/or prior CBY ITE

scores were associated with the odds of passing the BASIC the first time. RESULTS: The analyses included 17,286 examination attempts from 15,789 residents. The majority of residents were male (65.8%), non-Hispanic or Latino (76.2%), White (47.8%), and US medical school graduates (87.4%). Differences in the first-attempt BASIC pass rates included male (92.7%) vs female (88.1%), non-Hispanic or Latino (92.0%) vs Hispanic or Latino (85.8%), Asian (92.6%) and White (92.4%) vs Black/African American (81.9%), respectively, and US (91.5%) vs international (88.6%) medical school graduates. Females had significantly lower odds of passing the BASIC the first time than males (odds ratio [OR] = 0.53, 95% confidence interval [CI], 0.47-0.60); Black/African American residents (OR = 0.41, 95% CI, 0.33-0.51) and Middle Eastern or North African residents (OR = 0.64, 95% CI, 0.46-0.91) had lower odds of passing the BASIC on first attempt than White residents; Hispanic or Latino residents had lower odds of passing the BASIC initially than non-Hispanic or Latino residents (OR = 0.52, 95% CI, 0.42-0.64). Nevertheless, all demographic subgroups' eventual pass rates were >99%.Male and White residents outperformed female and Black/African American residents, respectively, in CBY ITEs. The gender and race performance gaps in the first-time BASIC pass rates were attenuated but not eliminated after controlling for their CBY ITE scores-compared to male and White residents, respectively, the odds of passing the BASIC the first time changed from 46% to 56% for female residents, and from 41% to 53% for Black/African American residents. CONCLUSIONS: Female and nonwhite residents had lower first-time BASIC Examination pass rates. Almost all trainees passed by their up-to-third attempts. Future studies are needed to understand the basis of these differences and identify opportunities for improvement.

Behavioral Health Services/Psychiatry/Neuropsychology

Gui H, Lessard CJ, Liu J, Li M, and **Adrianto I**. Editorial: Integrative genetics and multi-omics of complex human disorders. *Front Genet* 2025; 16:1574431. PMID: 40061127. Full Text

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Behavioral Health Services/Psychiatry/Neuropsychology

Haley EN, **Vanderziel AM**, **Loree AM**, **Vagnini KM**, **Joseph-Mofford GEM**, **Hecht LM**, and **Miller-Matero LR**. Psychological factors associated with binge eating among women with infertility. *Eat Behav* 2025; 57:101965. PMID: 40073751. Full Text

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Henry Ford Health, Center for Health Policy and Health Services Research, Detroit, MI, United States; Henry Ford Health, Behavioral Health, Detroit, MI, United States; Michigan State University, College of Human Medicine, East Lansing, MI.

Eating disorder pathology, including binge eating, is highly prevalent among women diagnosed with infertility. Binge eating has a range of consequences that may undermine fertility outcomes, yet population-specific risk and protective factors are unknown. Identifying factors associated with binge eating among this unique population may inform more sensitive and effective prevention and intervention efforts. In this cross-sectional observational study, women diagnosed with infertility completed validated self-report measures of psychiatric symptoms, eating disorder pathology, overvaluation of shape and weight (OSW), infertility distress, infertility acceptance, and trait mindfulness. Mann-Whitney U tests and two-part zero-inflated Poisson regression analyses were performed to identify associations between these factors and the presence and frequency of binge eating. In our sample (N = 188), 39.4 % endorsed recent binge eating (n = 74). These participants reported higher symptoms of anxiety ($p < .001$), depression ($p < .001$), OSW ($p < .001$), dietary restraint ($p < .001$), body mass index (<0.001), and lower mindfulness ($p = .003$) relative to those who denied binge eating. There were no group differences in infertility distress or acceptance. In a two-part zero-inflated Poisson regression model, higher OSW was the only factor significantly independently associated with higher odds of binge eating, whereas increased depression severity was significantly independently associated with greater binge eating frequency. Ultimately, OSW and depression may be particularly important treatment targets for women with infertility engaging in binge eating, above and beyond related psychological risk factors. Implications for future research and clinical practice are discussed.

Behavioral Health Services/Psychiatry/Neuropsychology

Henry A, Mo X, Finan C, Chaffin MD, Speed D, Issa H, Denaxas S, Ware JS, Zheng SL, Malarstig A, Gratton J, Bond I, Roselli C, Miller D, Chopade S, Schmidt AF, Abner E, Adams L, Andersson C, Aragam KG, Ärnlöv J, Asselin G, Raja AA, Backman JD, Bartz TM, Biddinger KJ, Biggs ML, Bloom HL, Boersma E, Brandimarto J, Brown MR, Brunak S, Bruun MT, Buckbinder L, Bundgaard H, Carey DJ, Chasman DI, Chen X, Cook JP, Czuba T, de Denus S, Dehghan A, Delgado GE, Doney AS, Dörr M, Dowsett J, Dudley SC, Engström G, Erikstrup C, Esko T, Farber-Eger EH, Felix SB, Finer S, Ford I, Ghanbari M, Ghasemi S, Ghouse J, Giedraitis V, Giulianini F, Gottdiener JS, Gross S, Guðbjartsson DF, **Gui H**, Gutmann R, Hägg S, Haggerty CM, Hedman Å K, Helgadottir A, Hemingway H, Hillege H, Hyde CL, Aagaard Jensen B, Jukema JW, Kardys I, Karra R, Kavousi M, Kizer JR, Kleber ME, Køber L, Koekemoer A, Kuchenbaecker K, Lai YP, **Lanfear D**, Langenberg C, Lin H, Lind L, Lindgren CM, Liu PP, London B, Lowery BD, Luan J, Lubitz SA, Magnusson P, Margulies KB, Marston NA, Martin H, März W, Melander O, Mordi IR, Morley MP, Morris AP, Morrison AC, Morton L, Nagle MW, Nelson CP, Niessner A, Niiranen T, Noordam R, Nowak C, O'Donoghue ML, Ostrowski SR, Owens AT, Palmer CNA, Paré G, Pedersen OB, Perola M, Pigeyre M, Psaty BM, Rice KM, Ridker PM, Romaine SPR, Rotter JI, Ruff CT, Sabatine MS, Sallah N, Salomaa V, Sattar N, Shalaby AA, Shekhar A, Smelser DT, Smith NL, Sørensen E, Srinivasan S, Stefansson K, Sveinbjörnsson G, Svensson P, Tammesoo ML, Tardif JC, Teder-Laving M, Teumer A, Thorgeirsson G, Thorsteinsdottir U, Torp-Pedersen C, Tragante V, Trompet S, Uitterlinden AG, Ullum H, van der Harst P, van Heel D, van Setten J, van Vugt M, Veluchamy A, Verschuuren M, Verweij N, Vissing CR, Völker U, Voors AA, Wallentin L, Wang Y, Weeke PE, Wiggins KL, **Williams LK**, Yang Y, Yu B, Zannad F, Zheng C, Asselbergs FW, Cappola TP, Dubé MP, Dunn ME, Lang CC, Samani NJ, Shah S, Vasan RS, Smith JG, Holm H, Shah S, Ellinor PT, Hingorani AD, Wells Q, and Lumbers RT. Genome-wide association study meta-analysis provides insights into the etiology of heart failure and its subtypes. *Nat Genet* 2025; Epub ahead of print. PMID: 40038546. Full Text

Heart failure (HF) is a major contributor to global morbidity and mortality. While distinct clinical subtypes, defined by etiology and left ventricular ejection fraction, are well recognized, their genetic determinants remain inadequately understood. In this study, we report a genome-wide association study of HF and its subtypes in a sample of 1.9 million individuals. A total of 153,174 individuals had HF, of whom 44,012 had a nonischemic etiology (ni-HF). A subset of patients with ni-HF were stratified based on left ventricular systolic function, where data were available, identifying 5,406 individuals with reduced ejection fraction and 3,841 with preserved ejection fraction. We identify 66 genetic loci associated with HF and its subtypes, 37 of which have not previously been reported. Using functionally informed gene prioritization methods, we predict effector genes for each identified locus, and map these to etiologic disease clusters through phenome-wide association analysis, network analysis and colocalization. Through heritability enrichment analysis, we highlight the role of extracardiac tissues in disease etiology. We then examine the differential associations of upstream risk factors with HF subtypes using Mendelian randomization. These findings extend our understanding of the mechanisms underlying HF etiology and may inform future approaches to prevention and treatment.

Behavioral Health Services/Psychiatry/Neuropsychology

Miller-Matero LR, **Vanderziel A**, **Haley EN**, Jackson KM, Moore RS, **Hamann A**, **Carlin AM**, **Genaw J**, and **Braciszewski JM**. Alcohol use after metabolic and bariatric surgery: a qualitative investigation of the relation with mood and food. *Health Psychol Behav Med* 2025; 13(1):2478029. PMID: 40098646. Full Text

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BACKGROUND: Individuals who undergo metabolic and bariatric surgery are at increased risk for an alcohol use disorder. Clarity on the relationships between mood, food, and alcohol use could inform interventions to reduce alcohol use and mitigate risk of alcohol use disorders after metabolic and bariatric surgery (MBS). METHODS: Twenty patients who underwent MBS at a single health care system and reported engaging in post-operative alcohol use were recruited. Participants were between 6 months and 3 years post-operative and reported consuming alcohol at least 2-3 times per month. Participants engaged in a 1-hour semi-structured interview about factors influencing post-operative mood, eating behaviors, and alcohol use. All interviews were recorded, transcribed, and coded by two independent raters. RESULTS: Statements by participants were deductively coded within different themes: (1) changes in mood, (2) changes in eating patterns, and (3) unintended alcohol use and eating. Participants reported positive changes in mood and eating behaviors following MBS, but also indicated potential for negative mood states and new eating patterns. They also suggested that mood was a driver of both eating and alcohol use, including unintended (i.e. unplanned) eating and unintended alcohol use. However, most did not consume food and alcohol at the same time. DISCUSSION: Food and alcohol may be used as a coping strategy for mood, though they are not often consumed together. There is currently a lack of post-operative interventions to reduce alcohol use and findings suggest that interventions could simultaneously target mood, unintended eating, and alcohol use.

Cardiology/Cardiovascular Research

Alaswad K, **O'Neill WO**, **Nakhle A**, **Koenig GC**, **Fuller BS**, and Wang DD. The Beck Procedure Revisited: Percutaneous Approach to Myocardial Perfusion Through the Coronary Sinus. *JACC Case Rep* 2025. PMID: Not assigned. Full Text

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Background: Many patients live with angina following treatment when all available therapies have failed. Providing retrograde arterial myocardial perfusion using the coronary venous system was performed. The

first previously reported percutaneous method might have limited application. Early Report Summary: We present a first-in-human successful, reproducible, and widely applicable percutaneous procedure using a noncovered coronary stent to connect the left circumflex (LCX) to the coronary sinus (CS) in a patient with previous placement of a CS Reducer. Discussion and Novelty: Unlike the previous report, our procedure shows for the first time that placement of a noncovered stent between the proximal LCX and the CS did not result in bleeding while effectively relieving the angina. Using a noncovered stent to create a bypass to the CS makes the procedure applicable to more patients with lifestyle-limiting angina. Take-Home Message: Using the noncovered stent from the LCX to the CS to provide myocardial perfusion might be feasible and safe.

Cardiology/Cardiovascular Research

Alexandrou M, Strepkos D, Carvalho PEP, Mutlu D, Ser OS, **Alaswad K**, **Basir MB**, Khelimskii D, Krestyaninov O, Khatri JJ, Young L, Goktekin O, Poommipanit P, Jaffer FA, Gorgulu S, Azzalini L, Ozdemir R, Uluganyan M, Raj LM, Mastrodemos O, Sara JS, Rangan BV, Jalli S, Voudris KV, Sandoval Y, Burke MN, and Brilakis ES. Vascular Access-Site Complications in Chronic Total Occlusion Percutaneous Coronary Intervention. *Catheter Cardiovasc Interv* 2025; Epub ahead of print. PMID: 40095762. Full Text

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BACKGROUND: Vascular access-site complications (VASC) can occur during chronic total occlusion (CTO) percutaneous coronary intervention (PCI). METHODS: We compared the baseline and procedural characteristics, and outcomes of patients with versus without VASC in a large multicenter CTO PCI registry. VASC was defined as any of the following: small hematoma (hematoma < 5 cm), large hematoma (hematoma ≥ 5 cm), arteriovenous fistula, pseudoaneurysm and acute arterial closure. RESULTS: VASC occurred in 158 of 16,810 CTO PCIs (0.9%). VASC patients were older (67 ± 11 vs. 64 ± 10 years, $p < 0.001$), more likely to be women (28.4% vs. 19.1%, $p = 0.004$) and less likely to be current smokers (18.9% vs. 27.2%, $p = 0.026$). They were more likely to have at least one femoral access (89.2% vs. 75.3%, $p < 0.001$) and less likely to have any radial access (38.0% vs. 52.3%, $p < 0.001$). Transfemoral access was more common in patients with VASC (60.1% vs. 45.7%, $p < 0.001$). VASC cases had higher J-CTO (2.57 vs. 2.38, $p = 0.05$) and PROGRESS-CTO major adverse cardiac events (MACE) scores (3.27 vs. 2.58, $p < 0.001$). They had similar technical (87.3% vs. 87.1%, $p > 0.9$) and procedural (82.3% vs. 85.9%, $p = 0.2$) success, but higher MACE (6.3% vs. 1.9%, $p < 0.001$) and bleeding (23.4% vs. 0.4%, $p < 0.001$). Female gender (odds ratio [OR] 1.95, 95% confidence intervals [CI] 1.24-3.00, $p = 0.003$), at least one femoral access (OR 2.02, 95% CI 1.09-4.04, $p = 0.034$) and sheath size (7-F: OR 2.16, 95% CI 1.12-4.60, $p = 0.031$; 8-F: OR 2.11, 95% CI 1.03-4.70,$p = 0.051$) were associated with VASC in multivariable analysis. CONCLUSION: Female sex, femoral access and larger sheaths ≥ 7 F were associated with VASC in patients undergoing CTO PCI.

Cardiology/Cardiovascular Research

Alhuneafat L, Al Ta'ani O, Arriola-Montenegro J, Al-Ajloun YA, Naser A, Chaponan-Lavalle A, Ordaya-Gonzales K, Pertuz GDR, Maaita A, **Jabri A**, Altibi A, Al-Abdouh A, Van't Hof J, and Gutierrez Bernal A. The burden of cardiovascular disease in Latin America and the Caribbean, 1990-2019: An analysis of the global burden of disease study. *Int J Cardiol* 2025; 428:133143. PMID: 40064205. Full Text

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INTRODUCTION: Cardiovascular disease (CVD) remains the leading cause of death globally, including the Latin America and the Caribbean (LAC) region. However, limited research has been conducted on the burden of CVD in this region. Our study aims to investigate the burden of CVD and related risk factors (RFs) in the LAC. METHODS: We used data from the Global Burden of Disease (GBD) 2019 to examine CVD prevalence in 33 LAC countries. Prevalence, mortality, and incidence were analyzed using Bayesian regression tools, demographic methods, and mortality-to-incidence ratios. Disability-adjusted life years (DALYs) were calculated, and RFs were evaluated under the GBD's comparative risk assessment framework. RESULTS: Between 1990 and 2019, CVD raw rates in the LAC increased by 116.7 %, while age-standardized prevalence decreased (-9.2 %). CVD raw mortality rose by 71.2 %, but age-standardized death rates fell by 69.8 %. Ischemic heart disease remained the most prevalent condition, with higher rates in men, while women had higher rates of stroke. Age-standardized DALYs decreased by 70.9 %. DALY rates varied across countries and were consistently higher in males. Leading RFs included HTN, high LDL, dietary risks, and elevated BMI. CONCLUSIONS: Despite progress in reducing the CVD burden in the LAC region, the impact on mortality and morbidity, particularly related to ischemic heart disease, remains substantial. Tailored interventions are necessary, considering country-specific variations in socio-economic factors, healthcare infrastructure, and political stability.

Cardiology/Cardiovascular Research
Alrayes H, **Chakfeh E**, **Lai LKL**, **Fram G**, **Zweig B**, **Lee JC**, **O'Neill B**, **Frisoli T**, **O'Neill W**, **Villablanca P**, and **Engel Gonzalez P**. Impromptu SVC Caval Implantation During Tricuspid Transcatheter Valve-in-Ring. *JACC Case Rep* 2025. PMID: Not assigned. Full Text

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An 84-year-old man with a history of tricuspid valve regurgitation after repair with an incomplete annuloplasty band presented with worsening tricuspid regurgitation. He underwent a transcatheter valve-in-ring procedure, which was complicated by proximal valve embolization. The procedure was salvaged by performing an ad hoc caval implantation, followed by an additional valve implantation within the tricuspid band, with an excellent result.

Cardiology/Cardiovascular Research
Aziz IN, **Jabri A**, Xu Y, Bilazarian S, Bentley D, Kaki A, Dupont A, **O'Neill W**, **Aronow HD**, Lemor A, Lichaa H, Truesdell AG, and **Basir MB**. Flow characteristics of reperfusion sheaths when utilizing large bore mechanical circulatory support devices. *Cardiovasc Revasc Med* 2025; Epub ahead of print. PMID: 40158891. Full Text

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BACKGROUND: Reperfusion sheaths are commonly utilized to prevent acute limb ischemia (ALI) when using large bore mechanical circulatory support devices, though little is known about flow characteristics of these sheaths. METHODS: The purpose of this assessment was to characterize the flow rates of various femoral to femoral (fem-fem) bypass circuits. We devised a test setup that maintains a preset input pressure for test devices to enable an accurate comparison of bypass techniques. RESULTS: Negligible flow rate increases were observed in active or passive ipsilateral and contralateral circuits when donor or receiver sheaths were sequentially increased in size. When using a contralateral fem-fem bypass circuit, the use of a Merit Prelude Pro 8F sheath paired with a 5F Arrow reperfusion sheath provided 167 ml/min of flow. If the reperfusion sheath was exchanged to a 6F sheath the flow rate was 169 ml/min, 175 ml/min with a 7F sheath and 179 ml/min with an 8F sheath, a total difference of 7 %. When maintaining a 6F reperfusion sheath as a constant, the use an ipsilateral fem-fem bypass circuit using an Abiomed 14F Low profile sheath provided 215 ml/min of flow, a 27 % higher flow than a contralateral 8F circuit. The use of an active pressure bypass system using an 18F ECMO cannula provided 356 ml/min, a 66 % higher flow than a 14F ipsilateral fem-fem bypass and 110 % higher flow than an 8F contralateral fem-fem bypass. CONCLUSION: Flow rate through a fem-fem bypass circuit is contingent upon the smallest diameter along the pathway which is typically the side port of the sheath. There are negligible changes in flow rate based on increasing donor or receiver sheath sizes. Novel, purpose-built reperfusion sheath taking these flow characteristics into account are needed to improve such systems.

Cardiology/Cardiovascular Research

Basala TR, Khalid MS, Ser OS, **Megaly M**, Glogoza M, Strepkos D, Rempakos A, Alexandrou M, Mutlu D, Carvalho P, Peng S, Mastrodemos O, Jalli S, Karacsonyi J, Sandoval Y, Wang Y, Sullivan P, Monyak DJ, Voudris K, Al-Ogaili A, Rangan BV, Burke MN, and Brilakis ES. Outcomes of Intracoronary Brachytherapy for In-Stent Restenosis. *Am J Cardiol* 2025; Epub ahead of print. PMID: 40157830. Full Text

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Because of limited alternative options, intracoronary brachytherapy (ICBT) continues to be used for treating in-stent restenosis (ISR). We examined the indications, characteristics, and outcomes of ICBT in consecutive patients who underwent ICBT for ISR between January 2014 and December 2023 at a tertiary care center. During the study period 343 patients underwent ICBT of 502 lesions. The median patient age was 67 [60, 74] years, 73.4% of the patients were men, 77.3% had prior myocardial infarction, and 49.4% had prior coronary artery bypass graft surgery. The most common target vessel was the right coronary artery (38.7%) and 7.37% of lesions were in bypass grafts (33 saphenous vein grafts, 4 arterial

grafts). A diffuse ISR pattern was found in 76.2% of lesions. Among the study lesions, 58.0% had 2 stent layers and 20.6% had 3 or more stent layers. Technical success was achieved in 96.1% of lesions. Follow-up was available for all patients with a mean follow-up of 701.5 days. The 3-year incidence of target lesion failure (TLF), target vessel myocardial infarction, and major adverse cardiac events were 36.4%, 17.2%, and 45.6%, respectively. In multivariable analysis, higher brachytherapy radiation dose was associated with a lower risk for TLF (aHR per 10 Gy: 0.73; 95% CI 0.54-0.93; p = 0.048). Repeat ICBT procedures had a higher incidence of TLF over 3 years compared with lesions treated with ICBT for the first time (log-rank test: p = 0.008). In conclusion, the 3-year incidence of TLF after ICBT is 36.4% and was lower with higher radiation dose and higher in lesions retreated with ICBT.

Cardiology/Cardiovascular Research
Belkin MN, **Cowger JA**, Fudim M, Tedford RJ, and Grinstein J. Reviving the Swan: Presenting the Chicago Hemodynamic Forum. *Circ Heart Fail* 2025; Epub ahead of print. PMID: 40116016. Full Text

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Cardiology/Cardiovascular Research
Brawner CA, and **Keteyian SJ**. Sedentary During the Week, but Active on the Weekend … Is the "Weekend Warrior" Pattern of Activity a Good Recommendation? *Mayo Clin Proc* 2025; 100(4):593-595. PMID: Not assigned. Full Text

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Cardiology/Cardiovascular Research
Cantey EP, Lopacinski A, Seth M, Hamilton DE, Dayoub EJ, Gandhi S, **Basir MB**, **Kaki A**, Madder RD, Sukul D, and Gurm HS. Managing Cardiogenic Shock Caused by Acute Myocardial Infarction: Invisible Challenges Revealed in a Statewide Registry. *J Am Coll Cardiol* 2025; Epub ahead of print. PMID: 40100173. Full Text

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Cardiology/Cardiovascular Research
Chou A, **Oye M**, **Modi K**, **Gupta K**, **Fram G**, **Dawdy J**, **Zweig B**, **Frisoli T**, **Gonzalez PE**, **Spinetto PV**, **O'Neill B**, **Szymanski T**, **Deporre A**, **Parikh S**, and **Lee J**. Safety of Transesophageal Echocardiography in Patients Referred for Tricuspid Valve Disease at a Center for Structural Heart Disease. *J Cardiothorac Vasc Anesth* 2025; Epub ahead of print. PMID: 40090789. Full Text

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OBJECTIVES: The aim of this study was to examine safety outcomes in patients referred for transesophageal echocardiograms (TEEs) for tricuspid valve disease. DESIGN: Retrospective observational study. SETTING: Single quaternary referral center specializing in structural heart disease. PARTICIPANTS: One hundred five patients referred for TEE for tricuspid valve disease between July 2022 and June 2023. INTERVENTIONS: This study was not interventional, but assessed the safety of TEE. METHODS AND MAIN RESULTS: The primary outcome was a composite of hypotension (mean arterial pressure [MAP] < 60 mmHg); use of epinephrine, norepinephrine, or calcium chloride; aborted studies due to documented clinical instability; emergent intubation; hospitalization or escalation of care post-TEE; oropharyngeal or gastrointestinal injury; or cardiac arrest. Secondary outcomes were 30-day cardiovascular mortality, all vasopressor use, and time spent per TEE. The primary outcome was noted in 32 patients (30.5%). The rate of cardiac arrest was 2.9% (3/105). Hypotension (MAP < 60 mmHg) was noted in 30 patients, with 7 patients needing hospitalization after TEE. No patients had oropharyngeal or gastrointestinal injury. There was a greater prevalence of moderate to severe right ventricular (RV) dilation (77% vs 53%; p = 0.022) and moderately to severely decreased RV function (48% vs 25%; p = 0.023) in patients who met the primary outcome. Both RV fractional area change (37.9% vs 29.8%; p = 0.003) and tricuspid annular plane systolic excursion (1.84 cm vs 1.45 cm; p = 0.002) were lower on baseline transthoracic echocardiogram. CONCLUSIONS: Patients with severe tricuspid regurgitation had a high prevalence of adverse events when undergoing TEE. Further studies are needed to compare these outcomes with other groups undergoing diagnostic TEE and delineate what risk factors may place these patients at greater risk.

Cardiology/Cardiovascular Research

Essa M, Decker SRR, Liang L, Song Y, Varghese MS, Figueroa JF, Sperling L, Fonarow GC, **Keteyian SJ**, Thompson MP, Beatty A, and Kazi DS. Use of Cardiac Rehabilitation in Older Patients with Myocardial Infarction Complicated by Cardiogenic Shock. *J Am Coll Cardiol* 2025; Epub ahead of print. PMID: 40099778. Full Text

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Cardiology/Cardiovascular Research

Fadel R, Elderkin J, **Alrayes H**, **Giustino G**, **Frisoli T**, **Basir MB**, **Apostolou D**, and **Villablanca P**. Left atrial veno-arterial extracorporeal membrane oxygenation as a bridge to surgical or percutaneous closure of post-myocardial infarction ventriculoseptal defects: a case series. *Eur Heart J Case Rep* 2025; 9(3):ytaf095. PMID: 40103800. Full Text

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BACKGROUND: Post-myocardial infarct (MI) ventricular septal defect (VSD) is a rare and severe complication of an acute MI with high mortality rate. The use of veno-arterial extracorporeal membrane oxygenation (VA-ECMO) as a bridge to surgical or percutaneous repair in cardiogenic shock secondary to post-MI-VSD has been published, but is limited to small case series primarily utilizing surgical ECMO, with the main drawback of potentially increasing afterload and left ventricle pressure, further worsening VSD shunting. Left-atrial VA-ECMO (LAVA-ECMO) can potentially absolve this concern given that it utilizes bi-atrial drainage through a trans-septal fenestrated cannula. CASE SUMMARY: Five patients were included in this series, all with VSD secondary to MI, and all managed with LAVA-ECMO as a bridge to repair. Average age was 62 ± 4.2 years, body mass index of 29.4 ± 4.5 kg/m(2), and left ventricular ejection fraction of 46.6 ± 13.8%. Haemodynamics monitoring pre- and post-LAVA-ECMO demonstrated improvement in right atrial, right ventricular, pulmonary, left atrial, and left ventricular pressures (Figure 1). Average time to repair was 7.4 ± 3.9 days. All five patients survived to repair, with four undergoing surgical and one undergoing percutaneous closure. Four out of five patients were decannulated successfully. DISCUSSION: This case series reports the successful use of LAVA-ECMO as a bridge to MI-VSD repair in patients with cardiogenic shock. Left-atrial VA-ECMO serves as a convenient approach to managing patients with MI-VSD related cardiogenic shock as it is implanted percutaneously, and can be done at the time of shock diagnosis, during right heart catheterization by trained interventionists.

Cardiology/Cardiovascular Research

Hanson ID, Palomo A, Tawney A, Dixon SR, Bentley D, Naidu SS, **Basir MB**, and **O'Neill WW**. Acute Myocardial Infarction and Stage E Shock: Insights From the RECOVER III Study. *J Soc Cardiovasc Angiogr Interv* 2025; 4(2):102462. PMID: 40109709. Full Text

Department of Cardiovascular Medicine, Corewell Health William Beaumont University Hospital, Royal Oak, Michigan.
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BACKGROUND: The present analysis reports characteristics and outcomes of Society of Cardiovascular Angiography & Interventions (SCAI) stage E shock patients with acute myocardial infarction with cardiogenic shock (AMICS) undergoing percutaneous coronary intervention (PCI) who improved to stage C or D within 24 hours of Impella support ("responders") vs those patients who remained in stage E ("nonresponders"). METHODS: The SCAI shock stage was assigned prior to initiation of Impella, and a second SCAI shock classification was performed within 24 hours of Impella support. SCAI shock stage was assigned independently by 2 reviewers; in cases where there was a discrepancy, a third reviewer adjudicated the stage assignment. Criteria such as a low pH (≤7.1), the need for multiple vasopressors/mechanical circulatory support devices, or the need for cardiopulmonary resuscitation were used to define stage E shock. RESULTS: Of the 415 RECOVER III patients, 298 presented in stage E shock; 152 (51.1%) were responders and 145 (48.8%) were nonresponders. Kaplan-Meier 30-day survival estimates were 56.9% and 28.6% in responders and nonresponders, respectively (P < .001). In multivariate analysis, fewer inotropic medications during Impella support (P < .0001), more lesions treated (P = .01), Impella support initiated pre-PCI (P = .03), and baseline white blood cell (P = .048) were all significant predictors for responsiveness to therapy. CONCLUSIONS: Stage E patients who improved to stage C/D within 24 hours of Impella support had significantly better survival than those who remained in stage E. Predictors of responsiveness to therapy were mostly related to shock treatment strategy, and not baseline characteristics. This suggests that whether stage E patients will improve with Impella support is difficult to determine at the time support is initiated, and the SCAI shock stage should be repeated within 24 hours to more accurately determine the prognosis.

Cardiology/Cardiovascular Research

Henry A, Mo X, Finan C, Chaffin MD, Speed D, Issa H, Denaxas S, Ware JS, Zheng SL, Malarstig A, Gratton J, Bond I, Roselli C, Miller D, Chopade S, Schmidt AF, Abner E, Adams L, Andersson C, Aragam KG, Ärnlöv J, Asselin G, Raja AA, Backman JD, Bartz TM, Biddinger KJ, Biggs ML, Bloom HL, Boersma E, Brandimarto J, Brown MR, Brunak S, Bruun MT, Buckbinder L, Bundgaard H, Carey DJ, Chasman DI, Chen X, Cook JP, Czuba T, de Denus S, Dehghan A, Delgado GE, Doney AS, Dörr M, Dowsett J, Dudley SC, Engström G, Erikstrup C, Esko T, Farber-Eger EH, Felix SB, Finer S, Ford I, Ghanbari M, Ghasemi S, Ghouse J, Giedraitis V, Giulianini F, Gottdiener JS, Gross S, Guðbjartsson DF, **Gui H**, Gutmann R, Hägg S, Haggerty CM, Hedman Å K, Helgadottir A, Hemingway H, Hillege H, Hyde CL, Aagaard Jensen B, Jukema JW, Kardys I, Karra R, Kavousi M, Kizer JR, Kleber ME, Køber L, Koekemoer A, Kuchenbaecker K, Lai YP, **Lanfear D**, Langenberg C, Lin H, Lind L, Lindgren CM, Liu PP, London B, Lowery BD, Luan J, Lubitz SA, Magnusson P, Margulies KB, Marston NA, Martin H, März W, Melander O, Mordi IR, Morley MP, Morris AP, Morrison AC, Morton L, Nagle MW, Nelson CP, Niessner A, Niiranen T, Noordam R, Nowak C, O'Donoghue ML, Ostrowski SR, Owens AT, Palmer CNA, Paré G, Pedersen OB, Perola M, Pigeyre M, Psaty BM, Rice KM, Ridker PM, Romaine SPR, Rotter JI, Ruff CT, Sabatine MS, Sallah N, Salomaa V, Sattar N, Shalaby AA, Shekhar A, Smelser DT, Smith NL, Sørensen E, Srinivasan S, Stefansson K, Sveinbjörnsson G, Svensson P, Tammesoo ML, Tardif JC, Teder-Laving M, Teumer A, Thorgeirsson G, Thorsteinsdottir U, Torp-Pedersen C, Tragante V, Trompet S, Uitterlinden AG, Ullum H, van der Harst P, van Heel D, van Setten J, van Vugt M, Veluchamy A, Verschuuren M, Verweij N, Vissing CR, Völker U, Voors AA, Wallentin L, Wang Y, Weeke PE, Wiggins KL, **Williams LK**, Yang Y, Yu B, Zannad F, Zheng C, Asselbergs FW, Cappola TP, Dubé MP, Dunn ME, Lang CC, Samani NJ, Shah S, Vasan RS, Smith JG, Holm H, Shah S, Ellinor PT, Hingorani AD, Wells Q, and Lumbers RT. Genome-wide association study meta-analysis provides insights into the etiology of heart failure and its subtypes. *Nat Genet* 2025; Epub ahead of print. PMID: 40038546. Full Text

Heart failure (HF) is a major contributor to global morbidity and mortality. While distinct clinical subtypes, defined by etiology and left ventricular ejection fraction, are well recognized, their genetic determinants remain inadequately understood. In this study, we report a genome-wide association study of HF and its subtypes in a sample of 1.9 million individuals. A total of 153,174 individuals had HF, of whom 44,012 had a nonischemic etiology (ni-HF). A subset of patients with ni-HF were stratified based on left ventricular systolic function, where data were available, identifying 5,406 individuals with reduced ejection fraction and 3,841 with preserved ejection fraction. We identify 66 genetic loci associated with HF and its subtypes, 37 of which have not previously been reported. Using functionally informed gene prioritization methods, we predict effector genes for each identified locus, and map these to etiologic disease clusters through phenome-wide association analysis, network analysis and colocalization. Through heritability enrichment analysis, we highlight the role of extracardiac tissues in disease etiology. We then examine the differential associations of upstream risk factors with HF subtypes using Mendelian randomization. These findings extend our understanding of the mechanisms underlying HF etiology and may inform future approaches to prevention and treatment.

Cardiology/Cardiovascular Research

Jain R, Kransdorf EP, **Cowger J**, Jeevanandam V, and Kobashigawa JA. Donor Selection for Heart Transplantation in 2025. *JACC Heart Fail* 2025; 13(3):389-401. PMID: 39570235. Full Text

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The number of candidates on the waiting list for heart transplantation (HT) continues to far outweigh the number of available organs, and the donor heart nonuse rate in the United States remains significantly higher than that of other regions such as Europe. Although predicting outcomes in HT remains challenging, our overall understanding of the factors that play a role in post-HT outcomes continues to grow. We observe that many donor risk factors that are deemed "high-risk" do not necessarily always adversely affect post-HT outcomes, but are in fact nuanced and interact with other donor and recipient

risk factors. The field of HT continues to evolve, with ongoing development of technologies for organ preservation during transport, expansion of the practice of donation after circulatory death, and proposed changes to organ allocation policy. As such, the field must continue to refine its processes for donor selection and risk prediction in HT.

Cardiology/Cardiovascular Research

Khalique OK, Zaid S, Tang GHL, Abdel-Wahab M, Akodad M, Bapat VN, Bax JJ, Blackman DJ, Blanke P, Bleiziffer S, Capodanno D, Cavalcante JL, Dasi LP, De Backer O, De Beuel M, Duncan A, Dweck MR, Fukui M, Gupta A, Hayashida K, Herrmann HC, Kaneko T, Karam N, Khan JM, Kovac J, Landes U, Leipsic JA, Leon MB, Mack MJ, Madhavan MV, Makar MM, Makkar RR, Al Mallah M, Meier D, Modine T, Okada A, Parikh RK, Parma R, Patel D, Pibarot P, Prendergast B, Quader N, Reardon MJ, Rogers T, Safi LM, Sellers SL, Skaf S, Tarantini G, Tchetche D, van Mieghem N, **Wang DD**, Webb JG, Windecker S, Yakubov SJ, Delgado V, Hahn RT, and Jilaihawi H. Best Practices for Imaging of Transcatheter Valve Failure: An Update From the Heart Valve Collaboratory. *J Am Coll Cardiol* 2025; 85(10):1042-1055. PMID: 40074470. Full Text

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This updated Heart Valve Collaboratory framework addresses the growing concern for transcatheter valve failure (TVF) following transcatheter aortic valve replacement (TAVR). With the increasing volume of redo-TAV and surgical TAV explantation, there is a critical need for standardized pathways and protocols for evaluating TVF using echocardiography and cardiac computed tomography (CT) angiography. This document clarifies prior definitions of bioprosthetic valve deterioration and bioprosthetic valve failure in a practical, imaging directed context for TAVR. It discusses various imaging modalities for diagnosing TVF, including echocardiography, cardiac CT angiography, cardiac magnetic resonance, and positron emission tomography/CT. Recommendations are provided on the systematic imaging for: 1) follow-up post-TAVR; 2) procedural planning for redo-TAV; and 3) post-redo-TAV, emphasizing the importance of regular monitoring and the need for comprehensive imaging data to optimize patient outcomes in the lifetime management of aortic valve disease.

Cardiology/Cardiovascular Research

Lindman BR, Pibarot P, Schwartz A, Oldemeyer JB, Su YR, Goel K, Cohen DJ, Fearon WF, Babaliaros V, Daniels D, Chhatriwalla A, Suradi HS, Shah P, Szerlip M, Mack MJ, Dahle T, **O'Neill WW**, Davidson CJ, Makkar R, Sheth T, Depta J, DeVries JT, Southard J, Pop A, Sorajja P, Hahn RT, Zhao Y, Leon MB, and Généreux P. Cardiac Biomarkers in Patients with Asymptomatic Severe Aortic Stenosis: Analysis from the EARLY TAVR Trial. *Circulation* 2025; Epub ahead of print. PMID: 40163596. Full Text

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BACKGROUND: The EARLY TAVR trial demonstrated that early transcatheter aortic valve replacement (TAVR) intervention was superior to clinical surveillance (CS) with delayed TAVR in patients with asymptomatic, severe aortic stenosis (AS). Cardiac biomarkers are associated with maladaptive remodeling, symptom onset, and worse outcomes after TAVR. Whether elevated biomarkers identify asymptomatic patients more likely to benefit from early intervention is unknown. METHODS: A core laboratory measured N-terminal pro-B-type natriuretic peptide (NT-proBNP) and high sensitivity cardiac troponin T (hs-cTnT). Associations between biomarker levels and risk of the trial primary endpoint (death, stroke, or unplanned cardiovascular hospitalization) and other secondary endpoints were examined with Kaplan-Meier curves and Cox proportional hazard models. Interaction tests were performed to assess whether the treatment effect of early TAVR, compared with CS, differed according to biomarker levels. RESULTS: Among 901 patients randomized in EARLY TAVR, 798 (89%) had biospecimens measured (median NT-proBNP 287 [145, 601]; median hs-cTnT 14.6 [10.5, 21.0]). Higher levels of NT-proBNP and hs-cTnT were broadly associated with higher event rates for multiple endpoints. In general, there was no significant interaction between baseline biomarkers and treatment group with respect to any composite or individual endpoint examined, although trends broadly demonstrated a greater relative benefit of early TAVR at lower biomarker levels. There was a significant interaction between hs-cTnT and treatment group with respect to death or heart failure hospitalization (HFH) (interaction p=0.04) and HFH alone (interaction p=0.03) such that the relative benefit of early TAVR was greater for patients with normal, rather than elevated, levels of hs-cTnT at baseline. For some endpoints, higher baseline NT-proBNP was associated with numerically greater absolute risk reduction with early TAVR than lower NT-proBNP levels. CONCLUSIONS: In patients with asymptomatic severe high gradient AS, higher NT-proBNP and hs-cTnT levels were broadly associated with higher event rates as expected. However, the relative benefit of an early TAVR strategy was consistent regardless of baseline biomarker levels and, contrary to our hypothesis, tended to be more pronounced in those with the lowest biomarker levels. These findings suggest limited value for single measurements of these biomarkers to guide the timing of TAVR in asymptomatic patients.

Cardiology/Cardiovascular Research

Mutlu D, Strepkos D, Ser OS, Carvalho PEP, Alexandrou M, Jalli S, Azzalini L, Ybarra L, **Alaswad K**, Jaffer FA, Davies R, Rangan BV, Sandoval Y, Nicholas Burke M, Gorgulu S, and Brilakis ES. Traditional Versus Dual Lumen Microcatheter-Assisted Parallel Wiring in Chronic Total Occlusion Percutaneous Coronary Intervention: Insights From the PROGRESS-CTO Registry. *Catheter Cardiovasc Interv* 2025; Epub ahead of print. PMID: 40065565. Full Text

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BACKGROUND: The effectiveness and safety of traditional versus dual lumen microcatheter (DLMC)-assisted parallel wiring in chronic total occlusion (CTO) percutaneous coronary intervention (PCI) has received limited study. AIMS: To compare traditional versus dual lumen microcatheter (DLMC)-assisted parallel wiring. METHODS: We compared the clinical and angiographic characteristics and outcomes of traditional versus DLMC-assisted parallel wiring after failed antegrade wiring (AW) in a large, multicenter CTO PCI registry. RESULTS: Among 1353 CTO PCIs with failed AW with a single wire, traditional parallel wiring (n = 1081) or DLMC-assisted parallel wiring (n = 272) were utilized at the operator's discretion. The baseline characteristics of patients were similar in both groups except for higher prevalence of diabetes mellitus, and lower prevalence of hypertension, prior heart failure, prior MI and cerebrovascular disease in

DLMC patients. Lesions in the DLMC group were more likely to have proximal cap ambiguity, side branch at the proximal cap, blunt/no stump, moderate/severe calcification, and had higher J-CTO score (2.6 ± 1.0 vs. 2.1 ± 1.3, p < 0.001). Technical (87.1% vs. 74.3%, p < 0.001) and procedural (83.8% vs. 75.5%, p = 0.001) success and the incidence of in-hospital major cardiac adverse events (MACE) (4.8% vs. 2.0%, p = 0.020) were higher in the DLMC group. In propensity score matching analysis, DLMC-assisted wiring was associated with higher technical success (odds ratio [OR] 2.17, 95% confidence interval [CI] 1.33-3.54, p = 0.002) and no significant difference in MACE (OR 2.00, 95% CI 0.89-4.50, p = 0.093). CONCLUSIONS: In lesions that could not be crossed with AW, DLMC-assisted parallel wiring was associated with a higher likelihood of technical success, without an increased risk of MACE, compared with traditional parallel wiring.

Cardiology/Cardiovascular Research

Pagani FD, **Cowger JA**, Jorde UP, Salerno C, Naka Y, Bhat G, Milano C, Druker V, and Long JW. Design and rationale for the clinical investigation of a novel, magnetically levitated left ventricular assist device for the treatment of refractory heart failure. *J Heart Lung Transplant* 2025; Epub ahead of print. PMID: 40064407. Full Text

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BACKGROUND: Contemporary durable left ventricular assist devices (LVAD) have established current benchmarks for patient outcomes, but introduction of more novel technology is lacking. The BrioVAD System (BrioHealth Solutions, Burlington, MA) is an innovative, fully magnetically levitated pump intended to provide short-term (ST) and long-term (LT) mechanical circulatory support. METHODS: The Investigation of a Novel, MagNetically Levitated VAD for the Treatment of RefractOry Left Ventricular HeArT FailurE Clinical Trial (INNOVATE) is designed to evaluate safety and efficacy of the BrioVAD by demonstrating non-inferiority to the HeartMate 3 (HM3; Abbott Labs, Chicago, IL). INNOVATE is a multi-center, prospective, non-blinded, randomized (2 BrioVAD: 1 HM3), controlled, non-inferiority study designed as a staged pivotal study with a pre-defined safety phase. Exclusion criteria are designed to enroll a patient population that aligns with contemporary clinical practice. Primary endpoints include a composite of survival to transplant, cardiac recovery, or 6 months (ST) or 24 months (LT) of LVAD support free from debilitating stroke (modified Rankin Scale > 3), or reoperation to replace the pump. A powered secondary outcome evaluates days spent in hospital, skilled nursing facility, or inpatient rehabilitation. RESULTS: INNOVATE study screening and enrollment began in 2024. Completed enrollment of the safety cohort (n = 45) is projected in early 2025. Completion of the ST cohort (n = 237) and LT cohort (n = 402) is projected for 2026 and 2027, respectively. CONCLUSIONS: INNOVATE represents a contemporary clinical trial design evaluating unique design features of the BrioVAD System with the expectation to improve patient outcomes.

Cardiology/Cardiovascular Research

Rao SV, Brooks MM, D'Agostino HEA, Steg PG, Simon T, **Aronow HD**, Goldsweig AM, Malik S, Alsweiler C, Ho KK, Dehghani P, Caixeta A, Quraishi AR, Robinson S, Traverse JH, Siddiqi O, Fergusson DA, Potter BJ, Schulman-Marcus J, Keating FK, and Carson JL. Effect of Red Blood Cell Transfusion Strategy on Clinical Outcomes Among Patients with Acute Myocardial Infarction Undergoing Revascularization: A Prespecified Analysis of the MINT Trial. *Circ Cardiovasc Interv* 2025; Epub ahead of print. PMID: 40159118. Full Text

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Albany Medical College, Albany, NY.
University of Vermont, Burlington, VT.
Rutgers Robert Wood Johnson Medical School, New Brunswick, NJ.

Background: The Myocardial Ischemia and Transfusion (MINT) Trial (N=3504) randomized patients with acute MI and a hemoglobin ≤ 10 g/dL to liberal (maintain Hgb ≥ 10 g/dL) or restrictive (maintain Hgb ≥ 8 g/dL) red blood cell transfusion. The results suggested a benefit on 30-day death or MI with a liberal transfusion strategy. The effect of transfusion in acute MI patients undergoing revascularization is unclear. Methods: In this pre-specified analysis of the MINT trial, patients who underwent revascularization (N=1002) before randomization but during index hospitalization were compared with those who did not (N=2442). The primary outcome was 30-day death or MI; secondary outcomes included 30-day death, recurrent MI, the composite of death, recurrent MI, ischemia driven unscheduled revascularization, or readmission for ischemic cardiac diagnosis, heart failure, and cardiac death. Multivariable log binomial regression was used to determine the relative risks of the primary and secondary outcomes by transfusion strategy for revascularized and non-revascularized patients with interaction terms. Results: Patients undergoing revascularization were younger, more often female, and had fewer comorbidities than those who did not. There was no significant interaction between revascularization and assigned transfusion strategy for any outcome except cardiac death. Compared with liberal transfusion, restrictive transfusion increased the risk of 30-day cardiac death among non-revascularized patients [RR 2.45 (1.58, 3.81)] but not among revascularized patients [(RR 0.97 (0.59, 1.60), interaction p 0.006]. Conclusions: In this analysis of the MINT trial, revascularization did not alter the effect of randomized transfusion strategy on 30-day death or MI. The hypothesis-generating finding that a restrictive transfusion strategy was associated with an increased risk of cardiac death among anemic patients with acute MI who do not undergo revascularization requires confirmation.

Cardiology/Cardiovascular Research

Stehlik J, Farr MA, Mehra MR, Schroder JN, D'Alessandro DA, Pal JD, Villavicencio MA, Gruber PJ, Couper GS, Shudo Y, Patel PC, Daneshmand MA, Klein L, Shah AS, Skipper ER, Esmailian F, Goldstein D, Ohira S, Lozonschi L, Kaczorowski DJ, Takeda K, Malyala RSR, Haft JW, Meyer DM, Sun BC, Pretorius V, Kilic A, Anyanwu AC, **Williams CT**, Pham DT, Kai M, Sulemanjee NZ, Itoh A, Funamoto M, Salerno CT, Ikonomidis JS, Durham LA, Shaffer A, Zhou X, Zafar F, Pinney SP, and Milano CA. Clinical Outcomes With Normothermic Pulsatile Organ Perfusion in Heart Transplantation: A Report From the OCS Heart Perfusion Registry. *Circulation* 2025; 151(13):896-909. PMID: 40052272. Full Text

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BACKGROUND: A preservation system, the Organ Care System (OCS; TransMedics) uses normothermic pulsatile perfusion during organ transport for heart transplantation. This system has demonstrated favorable outcomes in hearts recovered from extended-criteria donors after brain death (DBD) and donors after circulatory death (DCD). METHODS: The OCS Heart Perfusion Registry collects data on US heart transplantations using the OCS, static cold storage (SCS), or thoracoabdominal normothermic regional perfusion (NRP) and donor hearts recovered from DBD or DCD donors. We analyzed donor and recipient characteristics and posttransplantation outcomes in patients transplanted with OCS donor hearts (either DBD or DCD) compared with SCS hearts, and with OCS hearts from DCD donors compared with those recovered with NRP followed by SCS. Propensity score matching was used in survival analyses to adjust for differences among recipient characteristics. RESULTS: Between 2021 and 2023, 3225 consecutive heart transplantations enrolled from 56 centers were analyzed in the Heart Perfusion Registry. The OCS was used in 854 of 3225 heart transplantations (26.4%), among which 340 (39.8%) were DBD and 514 (60.2%) were DCD donors, whereas 2174 DBD donors were recovered with SCS and another 197 DCD donors with NRP techniques. The OCS-DBD group experienced a greater number of organ offer refusals before final acceptance (13 versus 6; Wilcoxon rank sum, P<0.001) and a longer transport distance (667 miles versus 232 miles; Wilcoxon rank sum, P<0.001) compared with SCS-DBD. Survival at 12 months was similar between the 2 groups (89.9% for OCS-DBD versus 90.6% for SCS-DBD; marginal Cox model, P=0.54). Among the OCS-DCD and SCS-DBD groups, survival at 12 months was also similar (91.0% versus 92.5%, respectively; marginal Cox model, P=0.32). The OCS-DCD and NRP-DCD groups demonstrated similar survival (91.0% versus 91.7%, respectively; log rank, P=0.63), although the transport distance was longer in OCS-DCD compared with DCD with NRP followed by SCS (400 miles versus 223 miles; Wilcoxon rank sum, P<0.001). By 2023, 90% of all OCS donor management and recovery was performed with dedicated organ recovery teams. CONCLUSIONS: We

demonstrate that real-world implementation of the OCS for DBD donors (using predominantly a dedicated recovery team) is associated with expanded donor criteria, longer transport distance, and excellent posttransplantation outcomes. In OCS-DCD donors, outcomes parallel those of donors recovered with NRP-DCD and compare favorably with DBD donor organs.

Cardiology/Cardiovascular Research
Vedantam K, Torres CA, Elmariah S, **Villablanca P**, Goessl M, Zajarias A, Leon MB, and Beohar N. Racial Disparities Among Patients Undergoing Balloon-Expandable Transcatheter Aortic Valve Replacement. *J Soc Cardiovasc Angiogr Interv* 2025; 4(2):102495. PMID: 40109708. Full Text

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BACKGROUND: Aortic stenosis is the most frequently acquired native valve disease. Transcatheter aortic valve replacement (TAVR) has emerged as a transformative intervention for patients with severe aortic stenosis. Despite its success, studies have shed light on racial and ethnic disparities in utilization and outcomes of TAVR. METHODS: Using the Transcatheter Valve Therapy Registry between November 2011 through June 2023, we evaluated volume trends of SAPIEN balloon-expandable TAVR performed by race/ethnicity, and its association with in-hospital and 1-year outcomes after the procedure. RESULTS: In the 12-year period, 395,618 patients were identified; 357,729 (90.42%) were White, 18,810 (4.75%) Hispanic, 15,100 (3.82%) Black, and 3979 (1.01%) Asian. There was an overall rising trend in proportional usage of TAVR among Hispanics (from 3.3% in 2011/2012 to 5.2% in 2023, P < .01) and Asian patients (from 1.1% in 2011/2012 to 1.3% in 2023, P < .01). Adjusted 1-year major adverse cardiac events (all-cause mortality, stroke, or rehospitalization) were comparable among Black patients (hazard ratio [HR], 1.00; 95% CI, 0.97-1.03; P = .82) and lower among Asian (HR, 0.91; 95% CI, 0.86-0.97; P < .01) and Hispanic patients (HR, 0.89; 95% CI, 0.86-0.91; P < .01) compared with White patients. CONCLUSIONS: Evidence supports favorable outcomes across different ethnic groups, despite the presence of higher levels of comorbidities and lower TAVR utilization. Modest improvements in TAVR utilization disparities among Asian and Hispanic patients have occurred since its introduction; however, utilization in Black patients remains low despite favorable outcomes. Further efforts are needed to understand the reasons and mitigate disparities in minority patients.

Cardiology/Cardiovascular Research
Venkateswaran VR, **She R**, Gardell SJ, **Luzum JA**, **Gupta R**, **Zhang K**, **Williams LK**, **Sabbah HN**, and **Lanfear DE**. Association of plasma metabolites and cardiac mitochondrial function with heart failure progression. *ESC Heart Fail* 2025; Epub ahead of print. PMID: 40064034. Full Text

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AIMS: Plasma metabolites are prognostic in heart failure with reduced ejection fraction (HFrEF), with citric acid cycle metabolites linked to ejection fraction (EF) changes. We investigated these mechanisms in a canine chronic HFrEF model. We tested associations between changes in plasma metabolites, left ventricular (LV) end-diastolic volume and cardiomyocyte mitochondrial function. METHODS: Eighteen dogs underwent microembolization to induce moderate HFrEF (target LVEF 35%-40%). Plasma metabolites, LV size and mitochondrial function were assessed over 12 months. RESULTS: Plasma

metabolite heatmap showed acylcarnitine changes, with early alterations in organic acids and amino acids predicting later adverse LV remodelling. Using either baseline or change over time, 13 metabolites correlated with 12 month LV enlargement. This is mostly often at 3 months (11 of 13), notably C18:2 (r = -0.58, P = 0.003) and cardiac anaplerotic substrates like glutamine (r = -0.52, P = 0.009) and 3-HBA (r = -0.43, P = 0.035). Impaired cardiomyocyte mitochondrial function correlated with LV enlargement (max ATP synthesis 12.7 vs. 19.9 nmol/min/mg, P = 0.0036; ADP-stimulated respiration 224 vs. 308 nAtom O/min/mg protein; P = 0.0064). Plasma metabolites correlated with mitochondrial parameters at 12 month, particularly with MAX ATP: malate (r = -0.75, P < 0.001), fumarate (r = -0.6, P = 0.008) and glutamine (r = 0.51, P = 0.031). CONCLUSIONS: In canine HFrEF, plasma acylcarnitines, citric acid cycle or anaplerotic metabolites predicted adverse LV remodelling. LV enlargement correlated with reduced cardiomyocyte mitochondrial function, which in turn was also associated with increased citric acid cycle metabolites. Together, these data suggest impaired cardiac energetic function drives plasma metabolite associations in HFrEF progression.

Cardiology/Cardiovascular Research

Zughaib MT, **Patel H**, **Assaf AD**, **Saba S**, and **Alexander P**. Managing Commissural Mitral Valve Regurgitation Following Transcatheter Mitral Valve Repair Using the Amplatzer Occluder Device. *Cureus* 2025; 17(2):e78507. PMID: 40062032. Full Text

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Mitral regurgitation (MR) is a common valvular abnormality in patients in the Western world. Treatment options include surgery and edge-to-edge repair of the mitral valve leaflets using the MitraClip device. However, MR may recur, and MitraClip can be unsuccessful, posing a challenging management dilemma. We present a case involving a 74-year-old male patient who originally presented due to severe symptomatic MR. The patient originally underwent successful intervention with a MitraClip. However, the patient reported recurrent dyspnea with little effort approximately six months after the index procedure. A repeat 3D transesophageal echocardiogram revealed severe recurrent MR at the medial commissure with an eccentric jet, similar to findings from prior studies. Due to the medial location of the defect, limited space to steer an additional clip, and high surgical risk, the patient was not a suitable candidate for surgical intervention or repeat MitraClip (Abbott Vascular, Santa Clara, CA) placement. The severe recurrent commissural MR was successfully managed using an Amplatzer Patent Foramen Ovale Occluder device (St. Jude Medical, Minneapolis, MN) in an off-label fashion.

Center for Health Policy and Health Services Research

Haley EN, **Vanderziel AM**, **Loree AM**, **Vagnini KM**, **Joseph-Mofford GEM**, **Hecht LM**, and **Miller-Matero LR**. Psychological factors associated with binge eating among women with infertility. *Eat Behav* 2025; 57:101965. PMID: 40073751. Full Text

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Eating disorder pathology, including binge eating, is highly prevalent among women diagnosed with infertility. Binge eating has a range of consequences that may undermine fertility outcomes, yet population-specific risk and protective factors are unknown. Identifying factors associated with binge eating among this unique population may inform more sensitive and effective prevention and intervention

efforts. In this cross-sectional observational study, women diagnosed with infertility completed validated self-report measures of psychiatric symptoms, eating disorder pathology, overvaluation of shape and weight (OSW), infertility distress, infertility acceptance, and trait mindfulness. Mann-Whitney U tests and two-part zero-inflated Poisson regression analyses were performed to identify associations between these factors and the presence and frequency of binge eating. In our sample (N = 188), 39.4 % endorsed recent binge eating (n = 74). These participants reported higher symptoms of anxiety ($p < .001$), depression ($p < .001$), OSW ($p < .001$), dietary restraint ($p < .001$), body mass index (<0.001), and lower mindfulness ($p = .003$) relative to those who denied binge eating. There were no group differences in infertility distress or acceptance. In a two-part zero-inflated Poisson regression model, higher OSW was the only factor significantly independently associated with higher odds of binge eating, whereas increased depression severity was significantly independently associated with greater binge eating frequency. Ultimately, OSW and depression may be particularly important treatment targets for women with infertility engaging in binge eating, above and beyond related psychological risk factors. Implications for future research and clinical practice are discussed.

Center for Health Policy and Health Services Research
Miller-Matero LR, **Vanderziel A**, **Haley EN**, Jackson KM, Moore RS, **Hamann A**, **Carlin AM**, **Genaw J**, and **Braciszewski JM**. Alcohol use after metabolic and bariatric surgery: a qualitative investigation of the relation with mood and food. *Health Psychol Behav Med* 2025; 13(1):2478029. PMID: 40098646. Full Text

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BACKGROUND: Individuals who undergo metabolic and bariatric surgery are at increased risk for an alcohol use disorder. Clarity on the relationships between mood, food, and alcohol use could inform interventions to reduce alcohol use and mitigate risk of alcohol use disorders after metabolic and bariatric surgery (MBS). METHODS: Twenty patients who underwent MBS at a single health care system and reported engaging in post-operative alcohol use were recruited. Participants were between 6 months and 3 years post-operative and reported consuming alcohol at least 2-3 times per month. Participants engaged in a 1-hour semi-structured interview about factors influencing post-operative mood, eating behaviors, and alcohol use. All interviews were recorded, transcribed, and coded by two independent raters. RESULTS: Statements by participants were deductively coded within different themes: (1) changes in mood, (2) changes in eating patterns, and (3) unintended alcohol use and eating. Participants reported positive changes in mood and eating behaviors following MBS, but also indicated potential for negative mood states and new eating patterns. They also suggested that mood was a driver of both eating and alcohol use, including unintended (i.e. unplanned) eating and unintended alcohol use. However, most did not consume food and alcohol at the same time. DISCUSSION: Food and alcohol may be used as a coping strategy for mood, though they are not often consumed together. There is currently a lack of post-operative interventions to reduce alcohol use and findings suggest that interventions could simultaneously target mood, unintended eating, and alcohol use.

Center for Health Policy and Health Services Research
Neale J, Kelly BC, **Braciszewski JM**, Kesten J, Lankenau S, Mayock P, and Merrill J. Over a decade later and Addiction journal is still committed to publishing qualitative research. *Addiction* 2025; Epub ahead of print. PMID: 40084416. Full Text

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Center for Health Policy and Health Services Research

Pladevall-Vila M, Ziemiecki R, Johannes CB, Khan AM, **Mines D**, Ebert N, Kovesdy CP, Thomsen RW, Baak BN, García-Sempere A, Kanegae H, Coleman CI, Walsh M, Andersen IT, Bernal CR, Cabaniñas CR, Christiansen CF, Farjat AE, Gay A, Gee P, Herings RMC, Hurtado I, Kashihara N, Kristensen FPB, Liu F, Okami S, Overbeek JA, Beest F, Yamashita S, Yano Y, Layton JB, Vizcaya D, and Oberprieler NG.
Clinical Profile and Treatment Patterns in Individuals with Type 2 Diabetes and Chronic Kidney Disease Who Initiate a GLP-1 Receptor Agonist: A Multinational Cohort Study. *Diabetes Ther* 2025; Epub ahead of print. PMID: 40106222. Full Text

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INTRODUCTION: Novel therapies are emerging for the prevention of chronic kidney disease (CKD) progression in patients with type 2 diabetes (T2D). Within the FOUNTAIN platform (NCT05526157; EUPAS48148), this real-world study aimed to characterize cohorts of adults with CKD and T2D starting therapy with a glucagon-like peptide-1 receptor agonist (GLP-1 RA) in Europe, Japan, and the United States (US) during 2012-2021. METHODS: This multinational, multicohort study was conducted in five data sources: the Danish National Health Registers (DNHR) (Denmark), PHARMO Data Network (PHARMO) (The Netherlands), Valencia Health System Integrated Database (VID) (Spain), Japan Chronic Kidney Disease Database Extension (J-CKD-DB-Ex) (Japan), and Optum's de-identified Clinformatics® Data Mart Database (CDM) (US). Eligible patients had T2D (defined by data source-specific algorithms) and CKD (based on diagnosis codes, estimated glomerular filtration rate values, and/or urine albumin-to-creatinine ratio) and initiated an GLP-1 RA during 2012-2021. Baseline demographic, lifestyle, and clinical characteristics were analyzed, and treatment patterns were described. RESULTS: Study cohorts included 18,929 GLP-1 RA initiators in DNHR; 476 in PHARMO; 11,798 in VID; 329 in J-CKD-DB-Ex; and 70,158 in CDM. Across cohorts, mean age ranged from 66.1 years in J-CKD-DB-Ex to 67.9 years in CDM, and between 46.6% (PHARMO) and 59.6% (J-CKD-DB-Ex) of patients were men. There was a steady increase in GLP-1 RA initiators from 2012 (when 1.6-4.8% of GLP-1 RA initiators started therapy) to 2019 (when 19.8-31.5% started therapy). The median duration of initial treatment with a GLP-1 RA ranged from 2.3 months (PHARMO) to 12.4 months (VID). At 1-year follow-up, between 52% (CDM) and 78% (DNHR) of patients were receiving treatment. Findings suggested that GLP-1 RA use was independent of CKD severity. CONCLUSIONS: During 2012-2021, GLP-1 RA use

steadily increased across multinational cohorts of patients with T2D and CKD, and persistence with treatment was high. GLP-1 use was independent of CKD severity.

Center for Health Policy and Health Services Research
Vance AJ, Henderson J, Yin Z, Costa DK, and Meghea C. Healthcare Utilization and Costs Among Commercially Insured Infants With and Without Medically Complex Conditions. *Adv Neonatal Care* 2025; 25(2):138-148. PMID: 40085949. Full Text

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BACKGROUND: Little is known about healthcare use and costs for commercially insured infants in the first year of life following a Neonatal Intensive Care Unit (NICU) hospitalization. PURPOSE: To evaluate healthcare utilization and costs in the 12-months after a neonatal hospitalization among commercially insured infants, comparing infants with and without medically complex conditions. METHODS: This retrospective, cross-sectional, cohort study uses data from the IBM MarketScan Commercial database (2015-2019). The cohort included infants with and without medically complex conditions, hospitalized at birth in the NICU, discharged alive, and had 12-months continuous coverage. The primary outcomes are healthcare utilization (i.e., hospital readmissions, emergency department (ED) visits, and primary care and specialty outpatient visits) and out-of-pocket (OOP) costs. RESULTS: The analysis included 23,940 infants, of which 84% resided in urban areas, 48% were born term (>37 weeks) and 43% had a medically complex diagnosis. Medically complex infants exhibited higher rates of readmissions, ED visits, specialist utilization, and specialty services. Average OOP costs for medically complex infants was $1893, compared to $873 for noncomplex infants. Almost half (48%) of the cohort had costs that exceeded $500 in the first year of life. IMPLICATIONS FOR PRACTICE AND RESEARCH: This study provides insights into the financial implications of post-NICU care for infants. Findings underscore the importance of considering medical complexity over gestational age when understanding healthcare use and spending patterns. Policymakers, healthcare providers, and families can use these insights to address the financial challenges associated with caring for infants with complex medical conditions beyond the NICU.

Center for Health Policy and Health Services Research
Young-Wolff KC, Chi FW, Campbell CI, Alexeeff SE, Ansley D, **Vanderziel A**, and Lapham GT. Frequency of Preconception and Prenatal Cannabis Use and Nausea and Vomiting in Pregnancy. *Obstet Gynecol* 2025; Epub ahead of print. PMID: 40080822. Full Text

Division of Research, Kaiser Permanente Northern California, Pleasanton, the Department of Psychiatry and Behavioral Sciences, University of California, San Francisco, San Francisco, and Regional Offices, Kaiser Permanente Northern California, Pleasanton, California; the Center for Health Policy and Health Services Research, Henry Ford Health, Detroit, Michigan; and the Health Research Institute, Kaiser Permanente Washington, and the Department of Health Systems and Population Health, University of Washington, Seattle, Washington.

This cross-sectional study analyzed associations between preconception and prenatal cannabis use and first-trimester nausea and vomiting in pregnancy (NVP) using data from 356,343 pregnancies in a large health care system (2011-2022). Prevalence of preconception and prenatal cannabis use was 11.3% (2.7% daily, 2.4% weekly, 6.3% monthly or less) and 6.5% (0.7% daily, 0.7% weekly, 1.4% monthly or less, 3.7% positive toxicology with no self-reported use), respectively. Based on International Classification of Diseases diagnostic codes, 3.6% of patients were diagnosed with severe NVP and 16.0% with mild NVP. Self-reported preconception daily cannabis use was associated with greater odds of mild (adjusted odds ratio [aOR] 1.68, 95% CI, 1.59-1.77) and severe (aOR 2.61, 95% CI, 2.40-2.84) NVP when compared with individuals without preconception use. Self-reported weekly cannabis use was

associated with greater odds of mild (aOR 1.26, 95% CI, 1.19-1.34) and severe (aOR 1.73, 95% CI, 1.57-1.90) NVP compared with no preconception use. Similarly, self-reported prenatal daily cannabis use was associated with greater odds of mild (aOR 1.97, 95% CI, 1.79-2.17) and severe (aOR 3.80, 95% CI, 3.28-4.39) NVP compared with no prenatal use. Self-reported weekly cannabis use was associated with greater odds of mild (aOR 1.85, 95% CI, 1.68-2.03) and severe (aOR 2.87, 95% CI, 2.47-3.34) NVP compared with individuals without prenatal use. This study found that preconception and prenatal cannabis use were associated with increased odds of both mild and severe NVP during the first trimester, with the highest odds observed among individuals using cannabis daily before or during early pregnancy. Findings underscore the need for patient education and medically appropriate therapies for NVP management.

Center for Individualized and Genomic Medicine Research

Chadwick J, Hinterberg MA, Asselbergs FW, Biegel H, Boersma E, Cappola TP, Chirinos JA, Coresh J, Ganz P, Gordon DA, Kureshi N, Loupey KM, Orlenko A, Ostroff R, Sampson L, Shrestha S, Sweitzer NK, Williams SA, Zhao L, Kardys I, and **Lanfear DE**. Harnessing the Plasma Proteome to Predict Mortality in Heart Failure Subpopulations. *Circ Heart Fail* 2025; Epub ahead of print. PMID: 40052265. Full Text

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Department of Computational Biomedicine, Cedars-Sinai Medical Center, Los Angeles, CA (A.O.).
Sarver Heart Center, University of Arizona, Tucson (N.K.S.).
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BACKGROUND: We derived and validated proteomic risk scores (PRSs) for heart failure (HF) prognosis that provide absolute risk estimates for all-cause mortality within 1 year. METHODS: Plasma samples from individuals with HF with reduced ejection fraction (HFrEF; ejection fraction <40%; training/validation n=1247/762) and preserved ejection fraction (HFpEF; ejection fraction ≥50%; training/validation n=725/785) from 3 independent studies were run on the SomaScan Assay measuring ≈5000 proteins. Machine learning techniques resulted in unique 17- and 14-protein models for HFrEF and HFpEF that predict 1-year mortality. Discrimination was assessed via C-index and 1-year area under the curve (AUC), and survival curves were visualized. PRSs were also compared with Meta-Analysis Global Group in Chronic HF (MAGGIC) score and NT-proBNP (N-terminal pro-B-type natriuretic peptide) measurements and further assessed for sensitivity to disease progression in longitudinal samples (HFrEF: n=396; 1107 samples; HFpEF: n=175; 350 samples). RESULTS: In validation, the HFpEF PRS performed significantly better (P≤0.1) for mortality prediction (C-index, 0.79; AUC, 0.82) than MAGGIC (C-index, 0.71; AUC, 0.74) and NT-proBNP (PRS C-index, 0.76 and AUC, 0.81 versus NT-proBNP C-index, 0.72 and AUC, 0.76). The HFrEF PRS performed comparably to MAGGIC (PRS C-index, 0.76 and AUC, 0.83 versus MAGGIC C-index, 0.75 and AUC, 0.84) but had a significantly better C-Index (P=0.026) than NT-proBNP (PRS C-index, 0.75 and AUC, 0.78 versus NT-proBNP C-index, 0.73 and AUC, 0.77). PRS included known HF pathophysiology biomarkers (93%) and novel proteins (7%). Longitudinal assessment revealed that HFrEF and HFpEF PRSs were higher and increased more over time in individuals who experienced a fatal event during follow-up. CONCLUSIONS: PRSs can provide valid, accurate, and dynamic prognostic estimates for patients with HF. This approach has the potential to improve longitudinal monitoring of patients and facilitate personalized care.

Center for Individualized and Genomic Medicine Research

Henry A, Mo X, Finan C, Chaffin MD, Speed D, Issa H, Denaxas S, Ware JS, Zheng SL, Malarstig A, Gratton J, Bond I, Roselli C, Miller D, Chopade S, Schmidt AF, Abner E, Adams L, Andersson C, Aragam KG, Ärnlöv J, Asselin G, Raja AA, Backman JD, Bartz TM, Biddinger KJ, Biggs ML, Bloom HL, Boersma E, Brandimarto J, Brown MR, Brunak S, Bruun MT, Buckbinder L, Bundgaard H, Carey DJ, Chasman DI, Chen X, Cook JP, Czuba T, de Denus S, Dehghan A, Delgado GE, Doney AS, Dörr M, Dowsett J, Dudley SC, Engström G, Erikstrup C, Esko T, Farber-Eger EH, Felix SB, Finer S, Ford I, Ghanbari M, Ghasemi S, Ghouse J, Giedraitis V, Giulianini F, Gottdiener JS, Gross S, Guðbjartsson DF, **Gui H**, Gutmann R, Hägg S, Haggerty CM, Hedman Å K, Helgadottir A, Hemingway H, Hillege H, Hyde CL, Aagaard Jensen B, Jukema JW, Kardys I, Karra R, Kavousi M, Kizer JR, Kleber ME, Køber L, Koekemoer A, Kuchenbaecker K, Lai YP, **Lanfear D**, Langenberg C, Lin H, Lind L, Lindgren CM, Liu PP, London B, Lowery BD, Luan J, Lubitz SA, Magnusson P, Margulies KB, Marston NA, Martin H, März W, Melander O, Mordi IR, Morley MP, Morris AP, Morrison AC, Morton L, Nagle MW, Nelson CP, Niessner A, Niiranen T, Noordam R, Nowak C, O'Donoghue ML, Ostrowski SR, Owens AT, Palmer CNA, Paré G, Pedersen OB, Perola M, Pigeyre M, Psaty BM, Rice KM, Ridker PM, Romaine SPR, Rotter JI, Ruff CT, Sabatine MS, Sallah N, Salomaa V, Sattar N, Shalaby AA, Shekhar A, Smelser DT, Smith NL, Sørensen E, Srinivasan S, Stefansson K, Sveinbjörnsson G, Svensson P, Tammesoo ML, Tardif JC, Teder-Laving M, Teumer A, Thorgeirsson G, Thorsteinsdottir U, Torp-Pedersen C, Tragante V, Trompet S, Uitterlinden AG, Ullum H, van der Harst P, van Heel D, van Setten J, van Vugt M, Veluchamy A, Verschuuren M, Verweij N, Vissing CR, Völker U, Voors AA, Wallentin L, Wang Y, Weeke PE, Wiggins KL, **Williams LK**, Yang Y, Yu B, Zannad F, Zheng C, Asselbergs FW, Cappola TP, Dubé MP, Dunn ME, Lang CC, Samani NJ, Shah S, Vasan RS, Smith JG, Holm H, Shah S, Ellinor PT, Hingorani AD, Wells Q, and Lumbers RT. Genome-wide association study meta-analysis provides insights into the etiology of heart failure and its subtypes. *Nat Genet* 2025; Epub ahead of print. PMID: 40038546. Full Text

Heart failure (HF) is a major contributor to global morbidity and mortality. While distinct clinical subtypes, defined by etiology and left ventricular ejection fraction, are well recognized, their genetic determinants remain inadequately understood. In this study, we report a genome-wide association study of HF and its subtypes in a sample of 1.9 million individuals. A total of 153,174 individuals had HF, of whom 44,012 had a nonischemic etiology (ni-HF). A subset of patients with ni-HF were stratified based on left ventricular systolic function, where data were available, identifying 5,406 individuals with reduced ejection fraction and 3,841 with preserved ejection fraction. We identify 66 genetic loci associated with HF and its subtypes, 37 of which have not previously been reported. Using functionally informed gene prioritization methods, we predict effector genes for each identified locus, and map these to etiologic disease clusters through phenome-wide association analysis, network analysis and colocalization. Through heritability enrichment analysis, we highlight the role of extracardiac tissues in disease etiology. We then examine the differential associations of upstream risk factors with HF subtypes using Mendelian randomization. These findings extend our understanding of the mechanisms underlying HF etiology and may inform future approaches to prevention and treatment.

Center for Individualized and Genomic Medicine Research

Venkateswaran VR, **She R**, Gardell SJ, **Luzum JA**, **Gupta R**, **Zhang K**, **Williams LK**, **Sabbah HN**, and **Lanfear DE**. Association of plasma metabolites and cardiac mitochondrial function with heart failure progression. *ESC Heart Fail* 2025; Epub ahead of print. PMID: 40064034. Full Text

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AIMS: Plasma metabolites are prognostic in heart failure with reduced ejection fraction (HFrEF), with citric acid cycle metabolites linked to ejection fraction (EF) changes. We investigated these mechanisms in a canine chronic HFrEF model. We tested associations between changes in plasma metabolites, left ventricular (LV) end-diastolic volume and cardiomyocyte mitochondrial function. METHODS: Eighteen dogs underwent microembolization to induce moderate HFrEF (target LVEF 35%-40%). Plasma metabolites, LV size and mitochondrial function were assessed over 12 months. RESULTS: Plasma metabolite heatmap showed acylcarnitine changes, with early alterations in organic acids and amino acids predicting later adverse LV remodelling. Using either baseline or change over time, 13 metabolites correlated with 12 month LV enlargement. This is mostly often at 3 months (11 of 13), notably C18:2 (r = -0.58, P = 0.003) and cardiac anaplerotic substrates like glutamine (r = -0.52, P = 0.009) and 3-HBA (r = -0.43, P = 0.035). Impaired cardiomyocyte mitochondrial function correlated with LV enlargement (max ATP synthesis 12.7 vs. 19.9 nmol/min/mg, P = 0.0036; ADP-stimulated respiration 224 vs. 308 nAtom O/min/mg protein; P = 0.0064). Plasma metabolites correlated with mitochondrial parameters at 12 month, particularly with MAX ATP: malate (r = -0.75, P < 0.001), fumarate (r = -0.6, P = 0.008) and glutamine (r = 0.51, P = 0.031). CONCLUSIONS: In canine HFrEF, plasma acylcarnitines, citric acid cycle or anaplerotic metabolites predicted adverse LV remodelling. LV enlargement correlated with reduced cardiomyocyte mitochondrial function, which in turn was also associated with increased citric acid cycle metabolites. Together, these data suggest impaired cardiac energetic function drives plasma metabolite associations in HFrEF progression.

Dermatology

Armstrong AW, Kircik L, **Stein Gold L**, Strober B, De Oliveira C, Vaile J, Jou YM, Daamen C, Scharnitz T, and Lebwohl M. Deucravacitinib: Laboratory Parameters Across Phase 3 Plaque Psoriasis Trials. *Dermatol Ther (Heidelb)* 2025; Epub ahead of print. PMID: 40113724. Full Text

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INTRODUCTION: Deucravacitinib, an oral, selective, allosteric tyrosine kinase 2 inhibitor, is approved in the USA and other countries for treatment of adults with moderate to severe plaque psoriasis who are candidates for systemic therapy. In POETYK PSO-1 and PSO-2, deucravacitinib was superior to placebo and apremilast and well tolerated in patients with plaque psoriasis. Patients who completed PSO-1/PSO-2 could enroll in the POETYK long-term extension (LTE) trial. This analysis evaluates the effects of deucravacitinib on laboratory parameters. METHODS: POETYK PSO-1 and PSO-2 were 52-week, phase 3, double-blinded trials that randomized patients 1:2:1 to placebo, deucravacitinib 6 mg once daily, or apremilast 30 mg twice daily. At week 52, eligible patients enrolled in POETYK LTE and received open-label deucravacitinib. Mean changes from baseline in laboratory parameters, laboratory adverse events (AEs), and laboratory AEs resulting in discontinuation were evaluated over 3 years. RESULTS: A total of 1519 patients received one or more doses of deucravacitinib across trials. Total exposure over 3 years was 3294.3 person-years. No clinically relevant mean changes were observed in laboratory parameters. Grade ≥ 3 laboratory AEs were infrequent during the 1-year period, with incidence rates remaining stable in patients treated with deucravacitinib through 3 years. Most laboratory AEs remained at the same grade; shifts to higher grades were infrequent, with most increases being to grade ≤ 2. Discontinuations due to laboratory AEs were rare. CONCLUSIONS: Deucravacitinib did not result in clinically meaningful changes in laboratory parameters over 3 years, including changes seen with Janus kinase (JAK) 1,2,3 inhibitors. Grade ≥ 3 laboratory AEs and discontinuations were rare. TRIAL REGISTRATION: ClinicalTrials.gov identifier, POETYK PSO-1 (NCT03624127), POETYK PSO-2 (NCT03611751), POETYK LTE (NCT04036435).

Dermatology

Benner J, Adair N, Hitt B, Nguyen VL, **Hamzavi IH**, and Sussman M. Autologous skin cell suspension plus phototherapy in stable vitiligo: findings from a US economic model. *J Med Econ* 2025; 28(1):425-435. PMID: 40042162. Full Text

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INTRODUCTION: A cell harvesting device for preparing non-cultured autologous skin cell suspension (ASCS) at the point-of-care is FDA-approved for repigmentation of stable depigmented vitiligo lesions in patients 18 years and older. The pivotal RSVP trial showed ≥80% repigmentation at Week-24 in 36% of lesions treated with laser ablation, ASCS, and narrowband ultraviolet B phototherapy compared to 0% with phototherapy alone ($p = 0.012$). The objective of this analysis was to evaluate the potential economic impact of laser ablation plus ASCS with phototherapy versus phototherapy alone for repigmentation of stable vitiligo lesions from a US payer perspective. METHODS: A 5-year decision-tree model was developed reflecting clinical pathways of adults with stable vitiligo lesions who had an inadequate response to prior topicals and phototherapy. Patients entering the model were treated with ASCS plus phototherapy or phototherapy alone and assessed for treatment response at Weeks-24 and 52 based on the RSVP trial's effectiveness endpoints. Durable response for Year-2 onwards was proxied by melanocyte-keratinocyte transplantation data. Model outcomes included per-patient total and incremental healthcare costs, treatment costs and total costs, cost per-patient per-month (PPPM), and cost per-patient per-year (PPPY). One-way sensitivity analyses assessed model result robustness. RESULTS: The cumulative total per-patient cost for ASCS plus phototherapy increased from $28,177 to $92,779 between Year-1 and Year-5. Phototherapy alone increased from $21,146 to $101,518 over the same period. Compared to phototherapy alone, ASCS plus phototherapy incurred $7,030 more total per-patient cumulative costs in Year-1 and $8,738 less by Year-5 (-$146 PMPM; -$1,748 PPPY). Breakeven occurred between Years 2-3. Results were most sensitive to changes in ASCS response at Weeks-24 and 52 and healthcare costs. CONCLUSION: Among adults with stable vitiligo with prior inadequate response to topicals or phototherapy, ASCS treatment may lead to lower all-cause direct medical costs over 5 years compared to phototherapy alone.

Dermatology

Bhatia N, Del Rosso J, **Stein Gold L**, Lain E, Draelos ZD, and Sidgiddi S. Efficacy, Safety, and Tolerability of Oral DFD-29, a Low-Dose Formulation of Minocycline, in Rosacea: Two Phase 3 Randomized Clinical Trials. *JAMA Dermatol* 2025; Epub ahead of print. PMID: 40042869. Full Text

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INTRODUCTION: A low-dose modified formulation of minocycline hydrochloride, DFD-29, is under evaluation for treating papulopustular rosacea (PPR). OBJECTIVE: To determine the efficacy and safety of DFD-29, 40 mg, compared with doxycycline, 40 mg, and placebo for treating PPR. DESIGN, SETTING, AND PARTICIPANTS: This study included data from 2 double-blind, placebo-controlled, phase 3 randomized clinical trials (MVOR-1 and MVOR-2) conducted between March 2022 and May 2023 at 61 centers in the US and Germany. Healthy adults 18 years and older with moderate to severe PPR were included. INTERVENTIONS: Participants were randomized 3:3:2 to oral DFD-29 (minocycline hydrochloride capsules), 40 mg; doxycycline, 40 mg; or placebo once daily for 16 weeks. MAIN OUTCOMES AND MEASURES: The coprimary efficacy outcomes were (1) proportion of participants with Investigator's Global Assessment (IGA) treatment success with DFD-29 vs placebo and (2) total inflammatory lesion count reductions with DFD-29 vs placebo. Secondary outcomes included comparisons between DFD-29 and doxycycline in coprimary outcomes and between DFD-29 and placebo

in erythema reduction. RESULTS: Of 653 participants enrolled, 323 were randomized in MVOR-1 (247 [76.5%] women; mean [SD] age, 47.2 [13.7] years) and 330 were randomized in MVOR-2 (249 [75.5%] women; mean [SD] age, 51.6 [14.0] years). DFD-29 demonstrated superior efficacy in IGA success rates compared with placebo (MVOR-1: treatment difference [TD], 32.9%; 95% CI, 19.6-46.2; P < .001; MVOR-2: TD, 34.1%; 95% CI, 21.3-46.8; P < .001) and compared with doxycycline (MVOR-1: TD, 18.0%; 95% CI, 5.0-31.1; P = .01; MVOR-2: TD, 28.3%; 95% CI, 17.4-39.3; P < .001). DFD-29 also showed superior efficacy in least-squares mean reductions in total inflammatory lesions vs placebo (MVOR-1: TD, -9.2; 95% CI, -11.5 to -6.9; P < .001; MVOR-2: TD, -6.8; 95% CI, -8.9 to -4.8; P < .001) and doxycycline (MVOR-1: TD, -4.7; 95% CI, -6.7 to -2.8; P < .001; MVOR-2: TD, -3.5; 95% CI, -5.4 to -1.6; P < .001). Adverse events with DFD-29, doxycycline, and placebo were reported in 32 of 121 (26.4%), 25 of 116 (21.6%), and 27 of 76 (35.5%), respectively, in MVOR-1 and 51 of 122 (41.8%), 40 of 121 (33.1%), and 30 of 82 (36.6%), respectively, in MVOR-2. The most common adverse events with DFD-29, doxycycline, and placebo were nasopharyngitis, reported in 4 of 121 (3.3%), 2 of 116 (1.7%), and 3 of 76 (3.9%), respectively, in MVOR-1 and 13 of 122 (10.7%), 10 of 121 (8.3%), and 13 of 82 (15.9%), respectively, in MVOR-2, and COVID-19, reported in 4 of 121 (3.3%), 3 of 116 (2.6%), and 4 of 76 (5.3%) in MVOR-1 and 7 of 122 (5.7%), 8 of 121 (6.6%), and 5 of 82 (6.1%) in MVOR-2. CONCLUSIONS AND RELEVANCE: In this study, DFD-29 was superior in efficacy to both doxycycline and placebo and demonstrated a favorable risk-benefit profile in the treatment of PPR. TRIAL REGISTRATION: ClinicalTrials.gov Identifiers: NCT05296629 and NCT05343455.

Dermatology

Callender VD, Baldwin H, **Gold LS**, Cook-Bolden FE, Guenin E, and Alexis AF. Efficacy and safety of fixed-dose clindamycin phosphate 1.2%/adapalene 0.15%/benzoyl peroxide 3.1% gel in Hispanic participants with moderate-to-severe acne: a pooled analysis. *J Dermatolog Treat* 2025; 36(1):2480232. PMID: 40122140. Full Text

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INTRODUCTION: Clindamycin phosphate 1.2%/adapalene 0.15%/benzoyl peroxide 3.1% (CAB) gel is the only fixed-dose, triple-combination approved for acne. In phase 2 and 3 studies, CAB demonstrated superior efficacy to vehicle and component dyads. This post hoc analysis examined efficacy/tolerability of CAB in 147 self-identified Hispanic/Latino participants (referred to as Hispanic). METHODS: Data were pooled from one phase 2 (NCT03170388) and two phase 3 (NCT04214652, NCT04214639) double-blind, 12-week studies. Eligible participants aged ≥9 years with moderate to severe acne were randomized to once-daily CAB or vehicle. Endpoints included ≥2-grade reduction from baseline in Evaluator's Global Severity Score with clear/almost clear skin (treatment success) and inflammatory/noninflammatory lesion counts. Treatment-emergent adverse events (TEAEs) were assessed. RESULTS: At week 12, 56.2% of CAB-treated participants achieved treatment success vs 18.4% with vehicle ($p < 0.001$). Reductions in inflammatory/noninflammatory lesions were 77.1%/76.2% with CAB vs 56.4%/45.0% with vehicle, respectively ($p < 0.001$, all). CAB TEAE rates were similar to overall study populations (27.0% vs 24.6%-36.2%). Baseline hyperpigmentation scores decreased from 0.6 to 0.3 (1 = mild) at week 12 with CAB. CAB gel was efficacious, safe, and well tolerated in Hispanic participants. Limitations include lack of Fitzpatrick skin phototype and short study duration. CONCLUSIONS: This study provides support for acne treatment with CAB in ethnically diverse populations.

Dermatology
Cork MJ, Deleuran M, Geng B, Silverberg JI, Simpson EL, **Stein Gold LF**, Irvine AD, Romero W, Valdez H, Fan H, and Alderfer J. Long-Term Safety of Abrocitinib in Moderate-to-Severe Atopic Dermatitis: Integrated Analysis by Age. *J Allergy Clin Immunol Pract* 2025; Epub ahead of print. PMID: 40081761. Full Text

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BACKGROUND: Abrocitinib has a manageable long-term safety profile for patients with moderate-to-severe atopic dermatitis. Identifying populations at higher risk of adverse events (AEs) will help optimize dose selection. OBJECTIVE: To evaluate abrocitinib long-term safety by age. METHODS: Data (September 25, 2021 cutoff) from JADE clinical trials were pooled in a consistent-dose cohort (patients who received the same abrocitinib dose throughout exposure) or a variable-dose cohort (patients who received abrocitinib 200 mg [12 weeks], were randomly assigned later to receive abrocitinib 200 mg, 100 mg, or placebo [up to 40 weeks], and assigned to receive abrocitinib 200 mg or 100 mg in the long-term study). Data were stratified post hoc by age at baseline (12 to <18 years, 18 to <40 years, 40 to <65 years, and ≥65 years). Incidence rates (IRs) of treatment-emergent AEs (TEAEs) of special interest were assessed. RESULTS: Analysis included 3802 patients (exposure: 5214 patient-years). IRs for serious AEs, TEAEs leading to study discontinuation, serious infections, herpes zoster, thrombocytopenia, lymphopenia, nonmelanoma skin cancer (NMSC), malignancies (excluding NMSC), major cardiovascular events, and venous thromboembolism were numerically higher in patients aged ≥65 years than in younger patients. Overall, adolescents had the lowest rates for TEAEs of special interest. CONCLUSIONS: Abrocitinib has a manageable long-term safety profile. TEAEs of special interest were lower in adolescents and higher in the ≥65-year age group. Risk of specific TEAEs was numerically higher in patients aged ≥65 years treated with abrocitinib 200 mg and underscores the importance of dose selection in older patients.

Dermatology
Gao DX, and **Lim HW**. The Changing Landscape of Photodermatology. *J Invest Dermatol* 2025; Epub ahead of print. PMID: 40072402. Full Text

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Dermatology
Pandya AG, Mahmoud BH, **Huggins RH**, Ganesan AK, Silverberg NB, Munavalli G, Weiss E, Zubair R, Lal K, Jensen JD, Skelsey MK, Ezra N, Siperstein R, Noell C, **Grekin SK**, and **Hamzavi IH**. Autologous Cell Harvesting Device Provides Repigmentation and Improves Quality-of-Life for Patients with Stable Vitiligo Lesions in a Large and Diverse Patient Population: A pre-post study. *J Am Acad Dermatol* 2025; Epub ahead of print. PMID: 40158537. Full Text

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INTRODUCTION: The mental health burden associated with vitiligo can significantly impact patients' quality-of-life. Although successful for repigmentation of stable vitiligo, adoption of surgical melanocyte transplantation remains limited due to time and skilled-expertise requirements. A cell harvesting device prepares autologous skin cell suspension (ASCS) at point-of-care, simplifying the process. OBJECTIVE: To confirm early and favorable repigmentation response and evaluate health-related quality-of-life changes following ASCS treatment of stable vitiligo. METHODS: In this large (N=107), prospective, multicenter study, vitiligo lesions were laser-ablated and received ASCS treatment followed by at-home phototherapy. RESULTS: All Fitzpatrick skin types and major vitiligo sub-types were represented. Excellent repigmentation response (≥80%) was observed by Week 4. By Week-24, all lesions demonstrated improvement; 67% achieved >50% repigmentation, 42% achieved ≥80% repigmentation, and 8% achieved complete repigmentation. Vitiligo Noticeability Scale response was attained by 27.7% of lesions; 72.3% of patients reported treatment satisfaction. Significant improvement from baseline in Vitiligo Quality-of-Life Instrument ($p<0.05$) was observed at Week-24. LIMITATIONS: No control. CONCLUSIONS: The cell harvesting device provides a simplified, more accessible technique for melanocyte transplantation. ASCS is highly effective for repigmentation of stable vitiligo lesions, with positive patient-reported outcomes and improvement in quality-of-life, as demonstrated in this large, diverse population.

Dermatology

Passeron T, **Lim H**, Krutmann J, Dreno B, Abdulla S, Ting P, Li M, Chemani N, Kerob D, Le Floch C, and Dayeh NR. Here Comes the Sun! A Study on Sun Exposure and Associated Risks in the Canadian Population. *J Cutan Med Surg* 2025; 29(2_suppl):3s-12s. PMID: 40026168. Full Text

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OBJECTIVE: To evaluate the awareness of and attitudes toward various aspects of sun-exposure risks and protection methods among Canadians. METHODS: An online survey conducted from September 28 to October 18, 2021, included 17,001 participants aged 18 years and above from 17 countries across 5 continents; the data presented are those of the Canadian population (n = 1,000). The survey focused on demographics, sun-exposure habits, comprehension of risks, and knowledge of photoprotection. The results were analyzed using descriptive statistics to identify prevalent trends and discrepancies in sun-protective behaviours among Canadians. RESULTS: The majority of Canadian respondents (93%) acknowledged the health risks associated with sun exposure. While 81% of Canadians reported using some form of sun protection, only 10% systematically implemented all recommended protective measures, highlighting a gap in knowledge translation. Misconceptions regarding the safety of tanned skin and the effectiveness of sunscreens were widespread, particularly in younger demographics and in individuals with darker skin. Knowledge and preventive behaviours were markedly better among individuals who regularly consult dermatologists. CONCLUSIONS: This study highlights general awareness of sun-protective behaviours but a lack of universal and comprehensive implementation among Canadians. Given the knowledge gaps in younger demographics and darker skin phototypes, targeted educational initiatives are essential to correct prevalent misconceptions about sun exposure and tanned skin. Dermatologists and other health care professionals can play a pivotal role in education and primary prevention strategies for skin cancer and other sun-related comorbidities.

Diagnostic Radiology

Bui J, **Chalom T**, **Nathanson SD**, **Schwartz TL**, **Hunt K**, **Alkhoory W**, and **Xu Z**. Invasive ductal carcinoma at the site of a cosmetic nipple piercing. *J Surg Case Rep* 2025; 2025(3):rjaf132. PMID: 40079036. Full Text

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We report a young female patient diagnosed with an invasive ductal carcinoma at the site of a prior cosmetic nipple piercing. She had no significant familial, genetic, or other carcinogenic risk factors to account for her presentation. A review of the literature confirms that trauma can occasionally be associated with invasive breast cancer, but such a connection has not previously been related to nipple piercing procedures.

Diagnostic Radiology

Fallahi A, Nazem-Zadeh MR, Hosseini-Tabatabaei N, Habibabadi JM, Hashemi-Fesharaki SS, and **Soltanian-Zadeh H**. Language and Memory Network Alterations in Temporal Lobe Epilepsy: A Functional and Structural Connectivity Study. *AJNR Am J Neuroradiol* 2025; Epub ahead of print. PMID: 40081848. Full Text

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BACKGROUND AND PURPOSE: This study evaluated preoperative alterations and postoperative reorganization of the joint language-memory network (LMN) from the perspective of resting-state functional and structural connectivity in Temporal lobe epilepsy (TLE). Graph theory and machine learning approaches were employed to explore automatic lateralization. MATERIALS AND METHODS: Resting-state fMRI and DTI data were obtained from 20 healthy subjects and 35 patients with TLE. Functional and structural connectivity were calculated within the LMN before and after temporal lobectomy. ANOVA was performed to identify significant connectivity differences between groups. Four local graph measures were extracted from functional and structural connectivity matrices. Standard feature selection techniques and genetic algorithm (GA) methods were applied to select the optimal features. Subsequently, the K-nearest neighbor, support vector machine (SVM), Naive Bayes, and logistic regression classification methods were used to classify healthy controls (HCs) and pre-surgical TLE groups, as well as pre-surgical left TLE (LTLE) and right TLE (RTLE) groups. Also, relationships between psychological scores and the selected features were evaluated using a linear regression method. RESULTS: The results demonstrated increased functional and decreased structural connectivity in TLE patients before surgery. After surgery, significant connections revealed reduced functional connectivity and increased structural connectivity in TLE patients. Functional analysis identified the left parahippocampal region in LTLE and the right temporal regions in RTLE as key areas. Structural connectivity analysis showed that memory-related areas in the bilateral occipital region and the left language-related area were the origins of alterations. The GA method achieved the highest classification performance using SVM for fMRI and DTI graph measures, with accuracy rates of 97% and 88% for distinguishing LTLE from RTLE, and 93% and 87% for distinguishing TLE from HC, respectively. Moreover, a significant relationship was observed between the best-selected features and memory-assisted cognitive tests. CONCLUSIONS: Pre-surgical functional hyperconnectivity and post-surgical hypoconnectivity and also newly observed bilateral postsurgical structural connectivity, highlighting functional and structural alterations in the LMN network. Additionally, the study underscores the potential of machine learning for TLE diagnosis and lateralization. A limited sample size, particularly in the postsurgical group was one of the constraints of this study. ABBREVIATIONS: TLE=Temporal lobe epilepsy; LMN=Language-memory network; GA=Genetic algorithm; HC=Healthy controls; LTLE=Left TLE; RTLE=Right TLE; AUC=Area under the curve.

Diagnostic Radiology

Zhang J, Brunnquell CL, Andrews TJ, Behrman RH, Brown KL, Greenspan BS, Hou P, Kanal KM, Khosravi HR, Liang Y, Lipford ME, **Musall BC**, Mustafa AA, **Rubinstein AE**, Russell BJ, Sanchez AA, Tipnis S, and Sensakovic WF. Updating the American Association of Physicists in Medicine (AAPM) Diagnostic Radiology Resident Physics Curriculum: Strategies, Content, and Dissemination. *Acad Radiol* 2025; Epub ahead of print. PMID: 40055055. Full Text

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RATIONALE AND OBJECTIVES: The Diagnostic Radiology Resident Physics Curriculum (DRRPC), initiated in 2007 by the American Association of Physicists in Medicine (AAPM) and last updated in 2018, is an essential educational resource for those teaching physics to radiology residents. Regular updates are crucial to ensure the curriculum aligns with evolving technologies and clinical practices, maintaining its relevance and effectiveness in educating the next generation of radiologists. The paper aims to describe the update strategies of the DRRPC, focusing on the current iteration, its structure, and the newest updates. MATERIALS AND METHODS: The update process, led by the Diagnostic Radiology Resident Physics Curriculum Working Group, commenced with a comprehensive survey targeting AAPM members who contribute to radiology physics teaching. The survey was conducted to assess the curriculum's current applicability and gather feedback for improvements. Subsequent updates were based on extensive stakeholder consultations and detailed analysis of survey data. RESULTS: The revision process has led to significant enhancements in the curriculum, emphasizing practical clinical applications and the integration of cutting-edge technology. New modules on advanced image processing, artificial intelligence, informatics, and radiopharmaceutical therapy were developed, responding to the evolving needs of radiological education and practice. CONCLUSION: The updated DRRPC supports educators in providing a dynamic and relevant training experience.

Emergency Medicine

Husain A, Chalek A, Husain K, Reece RJ, and Dunne RB. Validation of the Termination of Resuscitation Rules in Detroit. *Cureus* 2025; 17(2):e79846. PMID: 40161053. Full Text

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Background and objective The termination of resuscitation (TOR) criteria - which recommends termination when a non-traumatic arrest in an adult is unwitnessed by emergency medical services (EMS), no shocks are administered, and no return of spontaneous circulation (ROSC) occurs - guide physicians in determining the viability of continuing cardiopulmonary resuscitation (CPR) and transporting patients to the hospital. We examined the level of compliance with the current basic life support (BLS) TOR rule and assessed alternative sets of rules to retrospectively derive improved TOR guidelines for out-of-hospital cardiac arrests (OHCA) in Detroit. Methods This was a retrospective study involving non-traumatic OHCA cases in Detroit from January 1, 2017, to December 31, 2019, which spans the time frame before and after the BLS TOR rule was officially implemented (June 1, 2018). Data were extracted from the Detroit Cardiac Arrest Registry (DCAR). Patients younger than 18 years of age, those with arrests of traumatic origin, or those with no resuscitation attempted were excluded. Results A total of 1,306 individuals were included in our analysis: 656 OHCA cases before the implementation of the BLS TOR rule in Detroit and 650 OHCA after the implementation. BLS TOR criteria were applied to the pre-TOR implementation data with a resulting specificity of 79% (95% CI: 50.7-80.8) and positive predictive value (PPV) of 97.3% (95% CI: 95.5-98.6). Survival to hospital discharge when termination was recommended was projected at 2.9% (13/444). The overall transportation rate was 85% (559/656). Post-TOR implementation, specificity was 88.9% (95% CI: 78.6-99.1) and PPV was 99.1% (95% CI: 98.3-99.9). Survival to hospital discharge was 0.88% (4/453) with a 69% (451/650) overall transportation rate. Post-hoc addition of age or EMS time to the patient side increased transportation rates to 81% (529/650) and 88% (571/650), respectively, and decreased false positive terminations to 0.84% (2/237) and 0% (0/148), respectively. Conclusions Overall survival and futile transportation rates decreased when TOR was applied since the implementation of the BLS TOR rule in Detroit. The addition of EMS time to the patient side or patient age to current TOR guidelines suggested improved performance. Although the additional criteria resulted in higher transportation rates, these factors may be useful for physicians to consider when deciding to transport patients. However, further derivation and validation are needed to create optimal TOR guidelines.

Endocrinology and Metabolism

Bhadada SK, Das L, Pal R, and **Rao DS**. Preface. *Best Pract Res Clin Endocrinol Metab* 2025; 39(2):101987. PMID: 40069037. Full Text

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Endocrinology and Metabolism

Kudva YC, Raghinaru D, Lum JW, Graham TE, Liljenquist D, Spanakis EK, Pasquel FJ, Ahmann A, Ahn DT, Aleppo G, Blevins T, **Kruger D**, Brown SA, Levy CJ, Weinstock RS, Steenkamp DW, Spaic T, Hirsch IB, Broyles F, Rickels MR, Tsoukas MA, Raskin P, Hatipoglu B, Desjardins D, Terry AN, Singh LG, Davis GM, Schmid C, Kravarusic J, Coyne K, Casaubon L, Espinosa V, **Jones JK**, **Estrada K**, Afreen S, Levister C, O'Malley G, Liu SL, Marks S, Peleckis AJ, Pasqua MR, Tardio V, Kurek C, Luker RD, Churchill J, Tajrishi FZ, Dean A, Dennis B, Fronczyk E, Perez J, **Mukhashen S**, Dhillon J, Ipek A, Bzdick S, Atakov Castillo A, Driscoll M, Averkiou X, Dalton-Bakes CV, Moore A, Jordan LF, Lesniak A, Pinsker JE, Sasson-Katchalski R, Campos T, Spanbauer C, Kanapka L, Kollman C, and Beck RW. A Randomized Trial of Automated Insulin Delivery in Type 2 Diabetes. *N Engl J Med* 2025; Epub ahead of print. PMID: 40105270. Full Text

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BACKGROUND: Automated insulin delivery (AID) systems have been shown to be beneficial for patients with type 1 diabetes, but data are needed from randomized, controlled trials regarding their role in the management of insulin-treated type 2 diabetes. METHODS: In this 13-week, multicenter trial, adults with insulin-treated type 2 diabetes were randomly assigned in a 2:1 ratio to receive AID or to continue their pretrial insulin-delivery method (control group); both groups received continuous glucose monitoring (CGM). The primary outcome was the glycated hemoglobin level at 13 weeks. RESULTS: A total of 319 patients underwent randomization. Glycated hemoglobin levels decreased by 0.9 percentage points (from 8.2±1.4% at baseline to 7.3±0.9% at week 13) in the AID group and by 0.3 percentage points (from 8.1±1.2% to 7.7±1.1%) in the control group (mean adjusted difference, -0.6 percentage points; 95% confidence interval [CI], -0.8 to -0.4; P<0.001). The mean percentage of time that patients were in the

target glucose range of 70 to 180 mg per deciliter increased from 48±24% to 64±16% in the AID group and from 51±21% to 52±21% in the control group (mean difference, 14 percentage points; 95% CI, 11 to 17; P<0.001). All other multiplicity-controlled CGM outcomes reflective of hyperglycemia that were measured were significantly better in the AID group than in the control group. The frequency of CGM-measured hypoglycemia was low in both groups. A severe hypoglycemia event occurred in one patient in the AID group. CONCLUSIONS: In this 13-week, randomized, controlled trial involving adults with insulin-treated type 2 diabetes, AID was associated with a greater reduction in glycated hemoglobin levels than CGM alone. (Funded by Tandem Diabetes Care; 2IQP ClinicalTrials.gov number, NCT05785832.).

Endocrinology and Metabolism

Kumari P, Garg S, Arya AK, Kaur J, Sachdeva NK, Saikia UN, Dahiya D, Bhadada SK, and **Rao SD**. Enhancer of zeste homolog 2 (EZH2) in endocrine tumors: current knowledge and future directions. *Expert Opin Ther Targets* 2025; 1-11. Epub ahead of print. PMID: 40111060. Full Text

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INTRODUCTION: Enhancer of zeste homolog 2 (EZH2) is a histone methyltransferase that orchestrates gene expression via epigenetic and non-epigenetic mechanisms. EZH2 performs epigenetic functions by methylating histones and/or non-histone proteins and suppressing or activating target genes. Moreover, non-epigenetic functions involve dysregulation of target genes independent of histone methylation, thereby impacting multiple signaling pathways. AREAS COVERED: EZH2 has emerged as a pivotal player in the initiation of various cancers. EZH2 overexpression facilitated by H3K27me3 is the principal driver. However, the consequent dysregulation of target genes resulting from EZH2 overexpression has emerged as a secondary instigator of tumorigenesis, leading to metastasis and poor prognosis. Further complexity arises from somatic mutations in EZH2 and downstream target genes such as BRAF and RASSF1A. However, understanding its effects on endocrine tumors/cancers remains an underexplored with the potential to significantly enhance clinical outcomes and contribute to human health. Therefore, the present review focuses on the multifaceted functions of EZH2 and its pathophysiological mechanisms in tumor proliferation, with a specific emphasis on endocrine tumors. EXPERT OPINION: Investigating EZH2 mechanisms and targeting with inhibitors and drugs is an active area of research that could offer a promising avenue for treatment and a better understanding of molecular therapeutic interventions.

Family Medicine

Yousif A, **Ngo J**, Abdel-Gadir D, Rocconi RP, Timmins P, Lachance J, Michael Straughn J, Jr., Dewdney S, Lachance J, Mize B, and Chefetz I. ASO Visual Abstract: Conversion from Minimally Invasive Surgical Approaches to Open Surgery Among Endometrial Cancer Patients in the SGO Clinical Outcomes Registry. *Ann Surg Oncol* 2025; Epub ahead of print. PMID: 40126716. Full Text

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Gastroenterology
Abusuliman M, **Jamali T**, **Nimri F**, **Chaudhary AJ**, Elfert K, **Saleem A**, **Alomari A**, **Faisal MS**, **Shamaa O**, **Obri M**, Salem AE, Abusuliman A, **Watson A**, **Pompa R**, **Dang D**, **Piraka C**, **Elatrache M**, **Singla S**, and **Zuchelli T**. Analysis of Adverse Events of Endoscopic Ultrasound-Guided Lumen-Apposing Metal Stent Placement: Insights Across Various Indications and Techniques. *Gastroenterology Res* 2025; 18(1):1-11. PMID: 40051887. Full Text

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BACKGROUND: Endoscopic ultrasound (EUS)-guided lumen-apposing metal stent (LAMS) placement is increasingly being used in lieu of surgery for multiple procedures, including transmural fluid drainage. However, few studies have evaluated adverse events (AEs) associated with LAMS placement. Our aim was to characterize the rates of AEs associated with several LAMS placement strategies across different procedures and indications. METHODS: A single-center retrospective cross-sectional study was conducted on patients who underwent EUS-guided LAMS placement between 2015 and 2023 at a single institution. Technical and clinical success rates and rates of early and late AEs were analyzed. Comparisons of AE rates were determined for patients who had LAMS dilation versus those without dilation, patients who had plastic stent placement in addition to LAMS placement versus those with no plastic stents, and patients who had combined dilation and plastic stent procedures versus those with LAMS dilation only. RESULTS: A total of 243 patients underwent EUS-guided LAMS interventions: 110 (45.3%) women and 133 (54.7%) men (mean age 53.7 ± 15.9 years). There were 96 (39.5%) patients who had at least one AE. Abdominal pain was the most common early and late AE. Plastic stent placement alongside LAMS placement was associated with a significantly higher rate of overall AEs (48.3% vs 29.9%; P = 0.009), late AEs (33% vs 17.9%; P = 0.021), and stent occlusion (5.7% vs 0%; P = 0.046). LAMS dilation was associated with higher rates of late AEs (34.2% vs 20.6%; P = 0.022) and stent occlusion (6.2% vs 1.0%; P = 0.049). CONCLUSIONS: LAMS placement showed high technical and clinical success rates across different indications with mostly mild AEs, suggesting that LAMSs may be safe and effective for pancreatic and biliary drainage.

Gastroenterology
Alkhouri N, Cheuk-Fung Yip T, Castera L, Takawy M, Adams LA, Verma N, Arab JP, **Jafri SM**, Zhong B, Dubourg J, Chen VL, Singal AK, Díaz LA, Dunn N, Nadeem R, Wai-Sun Wong V, Abdelmalek MF, Wang Z, Duseja A, Almahanna Y, **Omeish HA**, Ye J, Harrison SA, Cristiu J, Arrese M, Robert S, Lai-Hung Wong G, Bajunayd A, Shao C, Kubina M, and Dunn W. ALADDIN: A Machine Learning Approach to Enhance the Prediction of Significant Fibrosis or Higher in MASLD. *Am J Gastroenterol* 2025; Epub ahead of print. PMID: 40146016. Full Text

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INTRODUCTION: The recent FDA-approval of resmetirom for treating metabolic dysfunction-associated steatohepatitis (MASH) in patients necessitates patient selection for significant fibrosis or higher (≥F2). No existing vibration-controlled transient elastography (VCTE) algorithm targets ≥F2. METHODS: The ALADDIN study addressed this gap by introducing a machine-learning-based web calculator that estimates the likelihood of significant fibrosis using routine laboratory parameters with and without VCTE. Our study included a Training set of 827 patients, a Testing Set of 504 patients with biopsy-confirmed MASLD from six centers, and an External Validation Set of 1,299 patients from 9 centers. Five algorithms were compared using AUC in the Test Set: ElasticNet (EN), Random Forest (RF), Gradient Boosting Machines (GBM), XGBoost (XGB), and Neural Networks (NN). The top three (RF, GBM, and XGB) formed an ensemble model. RESULTS: In the external validation set, the ALADDIN-F2-VCTE model, using routine laboratory parameters with VCTE (AUC 0.791, 95% CI: 0.764-0.819), outperformed VCTE alone (0.745, 95% CI 0.717-0.772, p<0.0001)FAST (0.710, 0.679-0.748, p<0.0001) and Agile-3 model (0.740, 0.710-0.770, p<0.0001) in terms of the AUC, Decision Curve Analysis, and calibration. The ALADDIN-F2-Lab model, using routine laboratory parameters without VCTE, achieved an AUC of 0.706 (95% CI: 0.668-0.749), outperfored Fibrosis-4 (FIB-4), steatosis-associated fibrosis estimator (SAFE), and LiverRisk scores. CONCLUSIONS: Along with the SAFE model developed to target significant fibrosis or higher, ALADDIN-F2-VCTE (https://aihepatology.shinyapps.io/ALADDIN1) uniquely supports a refined non-invasive approach to patient selection for resmetirom without the need for liver biopsy. Additionally, ALADDIN-F2-Lab (https://aihepatology.shinyapps.io/ALADDIN2) offers an effective alternative when VCTE is unavailable.

Gastroenterology
Boortalary T, Tran T, McDonald N, Kahaleh M, Tyberg A, Shahid H, Sarkar A, Pawa R, Pawa S, Ventura F, Cohen EM, Krafft M, Thakkar S, Singh S, Nasr J, **Nimri F**, **Zuchelli T**, **Dang D**, **Piraka C**, Hassan KM, Sharaiha RZ, Kumar A, Schlachterman A, Kowalski T, and Kamal F. Success of Different Closure Modalities of Gastro-gastric or Jejunal-gastric Fistulas after Endoscopic Ultrasound-directed Transgastric Intervention. *Gastrointest Endosc* 2025; Epub ahead of print. PMID: 40120863. Full Text

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Gastroenterology
Mitchell MC, Lee BP, **Mellinger J**, and Nagy LE. Reply to 'Incorporating genetic variations in alcohol-associated liver disease trials for East Asian populations'. *Nat Rev Gastroenterol Hepatol* 2025; Epub ahead of print. PMID: 40128360. Full Text

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Gastroenterology
Truong E, **Alnimer L**, Gornbein JA, Yang JD, Alkhouri N, Harrison SA, and Noureddin M. Agile 3+ and 4 Scores Accurately Predict Major Adverse Liver Outcomes, Liver Transplant, Progression of MELD Score, the Development of Hepatocellular Carcinoma, and Death in NAFLD. *Dig Dis Sci* 2025; Epub ahead of print. PMID: 40126753. Full Text

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BACKGROUND AND AIMS: Based on liver stiffness measurement by vibration controlled transient elastography (LSM by VCTE), the Agile 3+ and 4 are novel noninvasive scores that accurately identify advanced fibrosis (≥ F3) and cirrhosis (F4), respectively. We investigated and compared the Agile 3+ and 4 scores' performances in predicting adverse events to LSM alone, FIB-4 and Fibroscan-AST (FAST) score. METHOD: This retrospective analysis included NAFLD patients with LSM by VCTE and laboratory testing from a tertiary care center from 2013 to 2022. Adverse events were defined as major adverse liver outcomes (MALO), hepatocellular carcinoma, liver transplant, and death. MALO was defined as ascites, hepatic encephalopathy, or esophageal variceal bleeding. We used the Cox proportional hazard rate model and the Harrell's concordance (C) statistic to compare predictive performances. RESULTS: 733 total subjects with median follow-up of 27.0 months were included. Average age was 58.1 years and 32.8% had type 2 diabetes. Average alanine aminotransferase was 46.6 IU/L, aspartate aminotransferase: 34.5 IU/L, albumin: 4.4 g/dL, and platelets: 241.1 × 10(9)/L. Fourteen subjects had 21 adverse outcomes, including 10 MALO, 5 HCC, 4 liver transplants, 3 progression of MELD score, and 6 deaths. Agile 3+ and 4 respectively had the highest C stats of 0.911 (C stat SE 0.028) and 0.909 (C stat SE 0.029) compared to LSM (C stat 0.857, C stat SE 0.045), FIB-4 (C stat 0.843, C stat SE 0.037) or FAST (C stat 0.703, C stat SE 0.085). CONCLUSION: The Agile 3+ and 4 scores had the highest likelihood of accurately predicting adverse outcomes including MALO and death compared to LSM alone, FIB-4 or FAST score.

Gastroenterology
Winder GS, and **Mellinger JL**. Substance Use Disorders and Interprofessional Management in the Pre and Post Liver Transplant Settings. *Clin Liver Dis* 2025. PMID: Not assigned. Full Text

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Hematology-Oncology

Ghimire B, **Zimmer M**, and **Donthireddy V**. TP53-Mutated Acute Myeloid Leukemia: Review of Treatment and Challenges. *Eur J Haematol* 2025; Epub ahead of print. PMID: 40035191. Full Text

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Patients with acute myeloid leukemia (AML) harboring mutations in TP53 (TP53-MT) have poor responses to current therapies and unfavorable prognoses. Despite the recognition of variant TP53 as an adverse feature of AML, an optimal treatment regimen has not yet been established, underlining a critical need for new, more effective therapeutic combinations and novel treatments. We present the case of a patient with TP53-MT AML and marked myelodysplasia who developed primary refractory disease after induction therapy with the intensive chemotherapy regimen of liposomal daunorubicin and cytarabine. Our patient's optimal response to second induction chemotherapy with FLAG-Ida prompted an exploration of established and investigational treatment regimens for this specific high-risk AML subtype. Therefore, we performed a comprehensive literature review of findings from studies exploring AML therapies, focusing on outcomes for patients with TP53-MT AML. The summary provided here reveals the complexity of defining the therapeutic responses of patients with the heterogeneous TP53-MT genetic background and the challenges in treating this high-risk form of AML. Future work must continue to investigate novel therapies and combinations to improve patient outcomes in this vulnerable population.

Hematology-Oncology

Graboyes EM, Maurer SN, Kistner-Griffin E, Armeson K, Starr E, McLeod T, Balliet WE, Doenges J, **Slavin-Spenny O**, Vanderlan JR, Day A, Pipkorn P, Puram SV, **Tam SH**, Ruggiero KJ, and Sterba KR. Protocol for a multisite, parallel-group, randomized clinical trial comparing a brief tele-cognitive behavioral therapy intervention (BRIGHT) with attention control for the reduction of body image-related distress among head and neck cancer survivors. *Contemp Clin Trials* 2025; 153:107888. PMID: 40139457. Full Text

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One in four head and neck cancer (HNC) survivors experience clinically significant body image distress (BID), a devastating psychosocial morbidity that adversely affects quality of life. To date, effective interventions for these patients are lacking. BRIGHT (Building a Renewed ImaGe after Head and neck cancer Treatment), a brief cognitive behavioral treatment (CBT), has shown potential efficacy as a novel treatment paradigm for HNC survivors with BID. The primary objective of this randomized clinical trial (RCT) is to test the hypothesis that BRIGHT improves BID among HNC survivors relative to an Attention Control (AC) intervention. In this multisite RCT, N = 180 HNC survivors with BID will be randomized 1:1 to six weeks of BRIGHT or AC of dose and delivery-matched survivorship education. Outcomes are assessed at baseline and 2, 3, 6, and 9-months post-randomization. The primary endpoint is the IMAGE-HN (Inventory to Measure and Assess imaGe disturbancE-Head and Neck) score, a validated patient-reported outcome of HNC-related BID. Secondary endpoints include the HN Shame and Stigma Scale, the PROMIS SF v1.0-Depression 8a, Anxiety 8a, and Ability to Participate in Social Activities 8a, the Beck Scale for Suicidal Ideation, and the EORTC QLQ-HN35 Trouble with Social Eating and Trouble with Social Contact subscales. The trial will also evaluate whether the effect of BRIGHT on BID is mediated through improvements in automatic thinking and body image coping strategies. Findings from this multisite RCT will provide a rigorous test of the efficacy of BRIGHT as the first evidence-based strategy to manage BID among HNC survivors. TRIAL REGISTRATION ID: NCT05442957.

Hematology-Oncology

Gutta R, Teslow E, Jaeger E, Stoppler MC, Chao C, **Rous FA**, **Potguari B**, and **Gadgeel S**. Racial Diversity and Co-Mutational Analysis of Biologically Relevant Alterations in EGFR Mutant Lung Cancers. *Clin Lung Cancer* 2025; Epub ahead of print. PMID: 40064574. Full Text

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BACKGROUND: EGFR alterations have significant therapeutic implications in lung cancer (LCa), yet their prevalence and co-mutational patterns in African American populations remain understudied. This study analyzes EGFR-mutant LCa across races using the Tempus database. METHODS: De-identified records sequenced via Tempus xT assay, (595 to 648 gene DNA panel) were included if they had ≥ 1 pathogenic EGFR mutation (short variants (SVs), copy number amplifications (CNAs), or fusions). Race was determined based on recorded clinical records. Co-mutations were restricted to genes with ≥ 5% frequency in at least 1 race. Statistical analyses were performed using chi-squared tests with Bonferroni or false discovery rate adjustments for multiple testing. RESULTS: Among 17,482 LCa samples, EGFR alterations occurred in 8.9% of CA, 7.6% of BAA, 39% of API, 15% of other races, and 12% of unknown races. Exon 19 deletions (P = .017) and L858R mutations (P < .001) varied by race, with higher L858R frequency in CA compared to BAA (P = .034) and in API compared to CA (P = .006). EGFR copy number variants (CNVs) were highest in BAA (P < .001). TP53 alterations occurred at a higher frequency in patients with a history of smoking, those with high tumor mutational burden (TMB), and high PD-L1. KMT2C co-mutations were significantly more common in BAA (13%) compared to CA (3%) and API (4%) (q = 0.003). Similarly, GLI1 co-mutations were most frequent in BAA (5.8%) compared to 1.5% in CA and 0% in API patients (q = 0.025). CONCLUSIONS: EGFR mutation subtypes and co-mutations differ by race. KMT2C may influence TMB and immunotherapy response, while GLI1 is linked to TKI resistance. TP53 alterations were more commen in smokers, and patients with high PDL-1 and TMB, highlighting additional factors that drive tumors with these alterations.

Hematology-Oncology

Kulkarni R, Zeine E, **Potugari B**, **Gadgeel S**, **Montecalvo J**, and **Rous FA**. Small Cell Lung Cancer With de novo BRAF V600E Mutation and Durable Response to Targeted Therapy: A Case Report. *Clin Lung Cancer* 2025; Epub ahead of print. PMID: 40133188. Full Text

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Hematology-Oncology
Lin EP, Hsu CY, Mishra S, Griffiths EA, Segal BH, **Hwang C**, **Singh SRK**, **Balanchivadze N**, Jani C, Mariano MG, Bhatt PS, Vieira K, Yu PP, Oligino EJ, Wise-Draper T, Ferrara EK, McKay RR, Nonato TK, Labaki C, Saad E, Saliby RM, Morgans AK, Nohria A, Puc M, Accordino MK, Bodin BE, Nanchal R, Singh H, Berg S, Mavromatis B, McManus HD, Halabi S, Choueiri TK, Warner JL, and Shyr Y. Associations of COVID-19 vaccination with risks for post-infectious cardiovascular complications: an international cohort study in cancer patients with SARS-CoV-2 infection. *Lancet Reg Health Am* 2025; 44:101038. PMID: 40124588. Full Text

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BACKGROUND: Whether COVID-19 vaccination is associated with risks for cardiovascular complications after SARS-CoV-2 infection in patients with cancer is unknown. The objective of this study was to investigate the associations between the two. METHODS: This registry (COVID-19 and Cancer Consortium)-based retrospective cohort study included patients with laboratory-confirmed SARS-CoV-2 infection from the United States, Canada, and Mexico between April 2021 and December 2022. Patients without COVID-19 vaccination were assigned to the unvaccinated group and patients with ≥2 doses of COVID-19 vaccination were assigned to the fully-vaccinated group. The primary outcome was a composite of post-infectious cardiac complications, including acute myocardial infarction, other ischemic heart disease, atrial fibrillation, ventricular fibrillation, other arrhythmias, cardiomyopathy, and congestive heart failure. The secondary outcome was a composite measure of post-infectious cardiovascular events,

comprising of the cardiac complications along with pulmonary embolism, deep vein thrombosis, superficial vein thrombosis, other thrombosis, and cerebrovascular stroke. Multivariable logistic regression was used for data analysis. FINDINGS: A total of 2729 patients were included for analyses, with 1382 in the unvaccinated group and 1347 in the fully-vaccinated group. The median age of the study population was 65 (interquartile range (IQR), 55-74) years. Overall, 1534 (56.0%) were women; 1272 (47%) were never smokers; 1639 (60%) were not obese; 2043 (75%) had stable cancer, and 446 (16%) took anticoagulants at baseline. The primary and secondary analyses showed lower risks of cardiac complications and cardiovascular events in the fully-vaccinated group, with adjusted odds ratios (aOR) of 0.66 (95% confidence interval (CI), 0.48-0.89) and 0.76 (95% CI, 0.59-0.99), respectively. The protective trend with COVID-19 vaccination was observed across infections with different dominant SARS-CoV-2 strains and in patients with or without anticoagulant use. INTERPRETATION: COVID-19 vaccination was associated with a reduced risk of cardiac complications and cardiovascular events by 34% and 24%, respectively, after SARS-CoV-2 infection in patients with cancer. FUNDING: National Institutes of Health USA; National Science and Technology Council of Taiwan.

Hematology-Oncology

Loveless IM, Kemp SB, **Hartway KM**, Mitchell JT, Wu Y, **Zwernik SD**, **Salas-Escabillas DJ**, **Brender S**, **George M**, **Makinwa Y**, **Stockdale T**, **Gartrelle K**, **Reddy RG**, **Long DW**, **Wombwell A**, **Clark JM**, **Levin AM**, **Kwon D**, **Huang L**, **Francescone R**, **Vendramini-Costa DB**, Stanger BZ, Alessio A, Waters AM, Cui Y, Fertig EJ, Kagohara LT, **Theisen B**, **Crawford HC**, and **Steele NG**. Human Pancreatic Cancer Single-Cell Atlas Reveals Association of CXCL10+ Fibroblasts and Basal Subtype Tumor Cells. *Clin Cancer Res* 2025; 31(4):756-772. PMID: 39636224. Full Text

Department of Public Health Sciences, Center for Bioinformatics, Henry Ford Health, Detroit, Michigan.
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PURPOSE: Pancreatic ductal adenocarcinoma (PDAC) patients with tumors enriched for the basal-like molecular subtype exhibit enhanced resistance to standard-of-care treatments and have significantly worse overall survival compared with patients with classic subtype-enriched tumors. It is important to develop genomic resources, enabling identification of novel putative targets in a statistically rigorous

manner. EXPERIMENTAL DESIGN: We compiled a single-cell RNA sequencing (scRNA-seq) atlas of the human pancreas with 229 patient samples aggregated from publicly available raw data. We mapped cell type-specific scRNA-seq gene signatures in bulk RNA-seq (n = 744) and spatial transcriptomics (ST; n = 22) and performed validation using multiplex immunostaining. RESULTS: Analysis of tumor cells from our scRNA-seq atlas revealed nine distinct populations, two of which aligned with the basal subtype, correlating with worse overall survival in bulk RNA-seq. Deconvolution identified one of the basal populations to be the predominant tumor subtype in nondissociated ST tissues and in vitro tumor cell and patient-derived organoid lines. We discovered a novel enrichment and spatial association of CXCL10+ cancer-associated fibroblasts with basal tumor cells. We identified that besides immune cells, ductal cells also express CXCR3, the receptor for CXCL10, suggesting a relationship between these cell types in the PDAC tumor microenvironment. CONCLUSIONS: We show that our scRNA-seq atlas (700,000 cells), integrated with ST data, has increased statistical power and is a powerful resource, allowing for expansion of current subtyping paradigms in PDAC. We uncovered a novel signaling niche marked by CXCL10+ cancer-associated fibroblasts and basal tumor cells that could be explored for future targeted therapies.

Hematology-Oncology

Nwosu ZC, Giza HM, Nassif M, Charlestin V, Menjivar RE, Kim D, Kemp SB, Sajjakulnukit P, Andren A, Zhang L, Lai WK, **Loveless I**, **Steele N**, Hu J, Hu B, Wang S, Pasca di Magliano M, and Lyssiotis CA. Multidimensional analyses identify genes of high priority for pancreatic cancer research. *JCI Insight* 2025; 10(4). PMID: 39774001. Full Text

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Department of Pharmacology and Toxicology, Michigan State University, East Lansing, Michigan, USA.
Department of Internal Medicine, Medical School.
Department of Pharmacology, Medical School.
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Pancreatic ductal adenocarcinoma (PDAC) is a drug-resistant and lethal cancer. Identification of the genes that consistently show altered expression across patient cohorts can expose effective therapeutic targets and strategies. To identify such genes, we separately analyzed 5 human PDAC microarray datasets. We defined genes as "consistent" if upregulated or downregulated in 4 or more datasets (adjusted $P < 0.05$). The genes were subsequently queried in additional datasets, including single-cell RNA-sequencing data, and we analyzed their pathway enrichment, tissue specificity, essentiality for cell viability, and association with cancer features, e.g., tumor subtype, proliferation, metastasis, and poor survival outcome. We identified 2,010 consistently upregulated and 1,928 downregulated genes, of which more than 50% to our knowledge were uncharacterized in PDAC. These genes spanned multiple processes, including cell cycle, immunity, transport, metabolism, signaling, and transcriptional/epigenetic regulation - cell cycle and glycolysis being the most altered. Several upregulated genes correlated with cancer features, and their suppression impaired PDAC cell viability in prior CRISPR/Cas9 and RNA interference screens. Furthermore, the upregulated genes predicted sensitivity to bromodomain and extraterminal (epigenetic) protein inhibition, which, in combination with gemcitabine, disrupted amino acid

metabolism and in vivo tumor growth. Our results highlight genes for further studies in the quest for PDAC mechanisms, therapeutic targets, and biomarkers.

Hematology-Oncology
Phillips MJ, Alese OB, Horvat NK, Greene E, Gbolahan OB, Coleman K, Doxie DB, Parihar V, Mahdi ZK, McCook-Veal A, Switchenko JM, **Diab M**, Herting CJ, Paulos CM, El-Rayes BF, and Lesinski GB. XL888 and pembrolizumab modulate the immune landscape of colorectal tumors in a phase Ib/II clinical trial. *Oncoimmunology* 2025; 14(1):2475620. PMID: 40079916. Full Text

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Department of Medicine, University of Alabama at Birmingham, Birmingham, AL, USA.

We conducted a phase Ib/II clinical trial to evaluate the safety, feasibility, and clinical activity of combining pembrolizumab (anti-PD-1) with XL888 (Hsp90 inhibitor) in patients with advanced colorectal cancer (CRC). We hypothesized that this regimen would modulate soluble and cellular immune mediators and enhance clinical outcomes. The trial employed a 3 + 3 open-label design, with an expansion cohort at the recommended phase II dose (RP2D) in treatment-refractory, mismatch repair-proficient CRC patients. Comprehensive analyses of plasma cytokines, peripheral blood mononuclear cells (PBMCs), and spatial immune cell patterns in liver biopsies were performed to identify unique immune signatures resulting from the combined therapy. The combination of pembrolizumab and XL888 proved to be safe and feasible, with a subset of patients achieving stable disease, although no objective responses were observed in this heavily pre-treated population. Correlative studies revealed immunomodulatory effects in tumors and circulation, including a reduction in IL6(+) cells and macrophages (CD68(+)) within metastatic liver tissue, alterations in blood CD3(+) cells, and upregulation of numerous inflammatory plasma cytokines. These findings suggest local and systemic immune activation by the combination of pembrolizumab and XL888. While clinical activity was modest in treatment-refractory CRC patients, there were notable effects on the tumor immune environment and systemic immune modulation.

Hematology-Oncology
Rajdev L, King GG, Lieu CH, Cohen SA, Pant S, Uboha NV, Deming D, Malla M, Kasi A, Klute K, Spencer KR, Dasari A, Morris VK, Botta G, Lowy AM, O'Hara MH, Eads J, King D, Shah MA, Hong TS, Parikh A, Klempner SJ, Jabbour SK, Chawla A, Molena D, George TJ, Gibson MK, Allegra C, Goodman K, Eng C, and **Philip PA**. Incorporating Circulating Tumor DNA Testing Into Clinical Trials: A Position Paper by the National Cancer Institute GI Oncology Circulating Tumor DNA Working Group. *JCO Precis Oncol* 2025; 9:e2400489. PMID: 40048671. Full Text

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MD Anderson Cancer Center, Houston, TX.
University of Wisconsin, Madison, WI.
University of Alabama, Birmingham, AL.
University of Kansas Medical Center, Kansas City, KS.
University of Nebraska Medical Center, Omaha, NE.
New York University Grossman School of Medicine, New York, NY.
University of California San Diego, San Diego, CA.
University of Pennsylvania, Philadelphia, PA.
Feinstein Institutes for Medical Research Northwell Health, Manhasset, NY.
Weil-Cornell Medical College New York Presbyterian, New York, NY.
Massachusetts General Hospital, Harvard Medical School, Boston, MA.

Rutgers University, New Brunswick, NJ.
Feinberg School of Medicine, Northwestern University, Chicago, IL.
Memorial Sloan Kettering Cancer Center, New York, NY.
University of Florida Health Cancer Center, Gainesville, FL.
Division Hematology & Oncology, Vanderbilt-Ingram Cancer Center, Nashville, TN.
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PURPOSE: Circulating tumor DNA (ctDNA) is an emerging tool in the evaluation of GI cancers. Challenges remain in defining its utility and role as a primary end point in therapeutic trials. The National Cancer Institute (NCI) ctDNA GI working group was created to evaluate current data and provide guidance on the inclusion of ctDNA in GI cancer trials. METHODS: The NCI GI steering committee assigned four task force members to serve as co-chairs for the working group. Co-chairs identified experts within each GI disease group to form a panel that convened to review data and provide recommendations. The group focused on ctDNA's role as a potential surrogate for assessing prognosis and guiding treatment decisions that may enhance GI cancer trials. A manuscript was drafted, circulated, revised, and voted on by the panel. The final draft was reviewed by the Cancer Therapy Evaluation Program. RESULTS: Further data are required to support ctDNA as a primary end point for late-phase therapeutic trials, particularly in studies that could change the standard-of-care. However, the group supports ctDNA as a primary efficacy end point for phase II studies and as a noninvasive evaluation strategy for new drug development. Incorporation of ctDNA as a biomarker in trial design must consider the specific context of disease biology of the GI cancer subtypes. ctDNA should be incorporated as an exploratory end point across a variety of disease settings and indications. Several practical considerations were identified to optimize the incorporation of ctDNA in future trial design. CONCLUSION: Prospective trials are required to clarify the role of ctDNA as a valid surrogate end point for progression-free or overall survival in GI cancers.

Hematology-Oncology

Saeed A, Colby S, Oberstein PE, Duda DG, Park R, Agarwal R, Figueroa-Moseley C, Vaidya R, Unger JM, Guthrie KA, Rocha FG, Senthil M, Safyan RA, Wainberg ZA, Iqbal S, Chiorean EG, and **Philip PA**. S2303: phase II/III trial of paclitaxel + ramucirumab ± nivolumab in gastric and esophageal adenocarcinoma (PARAMUNE). *Future Oncol* 2025; 1-7. Epub ahead of print. PMID: 40155326. Full Text

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Department of Surgery, Division of Surgical Oncology, University of California Irvine Cancer Center, Irvine, CA, USA.
Department of Medicine, Fred Hutchinson Cancer Center, University of Washington, Seattle, WA, USA.
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Department of Medicine, Division of Hematology & Oncology, University of Southern California Norris Comprehensive Cancer Center, Los Angeles, CA, USA.
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Nct06203600.
Cancer of the stomach and esophagus is aggressive with poor patient outcomes. Historically, the treatment for such patients has involved the use of combined chemotherapy. In recent years, the addition of immunotherapy to the treatment of patients with advanced cancers of the stomach and esophagus has led to patients living longer with a longer period without tumor growth. However, whether continuing the immunotherapy after the tumor has grown while on treatment is beneficial or not is a question that has not been answered. The standard treatment after patients' tumor has grown on their initial treatment involves a drug called ramucirumab, which blocks the ability of cancer cells to create abnormal blood vessels around itself to support its own growth. Recent research suggests that drugs like ramucirumab make immunotherapy more effective. To test whether continuing immunotherapy in combination with this "second-line" treatment that includes ramucirumab, we have designed a study to compare whether one group who will receive immunotherapy will live longer versus another group who will not receive immunotherapy.
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Hematology-Oncology
Scarano WR, Guerra MT, Perobelli JE, Fernandes GSA, Arena AC, **de Aquino AM**, Rocha VA, Magosso N, Souza PV, and Barbisan LF. IMPACT OF REAL-LIFE ENVIRONMENTAL EXPOSURES ON REPRODUCTION: Phthalate exposure and reproductive effects in rodents: a model for approaches on the protective role of natural products. *Reproduction* 2025; 169(1). PMID: 39499862. Full Text

IN BRIEF: Exposure to phthalates, alone or in mixtures, at different periods of development alters the reproductive function of males and females, especially in rodents, where they have been most studied. This review addressed the most recent data (last 10 years) on exposure to phthalates in different scenarios and how the use of natural products could mitigate the harmful effects caused by exposure at different stages of development. ABSTRACT: This review article summarizes the experimental findings in rodents published between 2014 and 2024 concerning phthalates exposure and reproductive outcomes. Rodents were chosen for this review because most studies that have focused on developmental aspects in different phases of exposure and that address more in-depth reproductive mechanisms have been carried out in mice and rats. The evidence of adverse effects of phthalates on fetal development and human and animal reproduction is extensive, with impacts ranging from gene expression to physiological alterations. Despite the large volume of scientific papers pointing out the harmful effects of exposure to phthalates, isolated or in mixtures, at different developmental periods, most of them are associated with the maternal exposure and long-term effects in the offspring. Regular vegetables, fruits, fish, dairy products, and whole grains intake rich in bioactive compounds can mitigate the adverse effects of endocrine-disrupting chemicals in humans and animals at different developmental periods. Various food bioactive compounds (FBCs), such as genistein, resveratrol, lycopene, vitamin E, curcumin, selenium, and plant secondary metabolites (PSMs), present antioxidant, anti-inflammatory, antitumor, and other biological properties with the potential to reduce deleterious effects of phthalates on the reproductive tract. In this review, we aimed to summarize the main studies carried out in the last decade about phthalate exposure and reproductive disorders in males and females (at different developmental critical windows). In addition, we proposed some FBCs and PSMs that could attenuate the main adverse effects caused by phthalate exposure on male reproduction because there is a lack of studies with females.

Hospital Medicine
Alrayes H, **Chakfeh E**, **Lai LKL**, **Fram G**, **Zweig B**, **Lee JC**, **O'Neill B**, **Frisoli T**, **O'Neill W**, **Villablanca P**, and **Engel Gonzalez P**. Impromptu SVC Caval Implantation During Tricuspid Transcatheter Valve-in-Ring. *JACC Case Rep* 2025. PMID: Not assigned. Full Text

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An 84-year-old man with a history of tricuspid valve regurgitation after repair with an incomplete annuloplasty band presented with worsening tricuspid regurgitation. He underwent a transcatheter valve-

in-ring procedure, which was complicated by proximal valve embolization. The procedure was salvaged by performing an ad hoc caval implantation, followed by an additional valve implantation within the tricuspid band, with an excellent result.

Hospital Medicine
Cook AV, **LeRoy DI**, and **Konja CT**. A Breathtaking Case of Chemotherapy-Induced Pneumonitis. *Cureus* 2025; 17(2):e78791. PMID: 40078233. Full Text

Internal Medicine, Henry Ford Health System - Warren, Warren, USA.

Medication-induced pulmonary toxicity is a rare adverse event that may occur with many chemotherapeutic agents, including etoposide. This agent has been found to cause various toxicities, including anaphylaxis, angioedema, hypotension, and pneumonitis. Etoposide is used in chemotherapy regimens for multiple cancers, including germ-cell tumors. Proper diagnosis of chemotherapy-induced pulmonary toxicity is imperative and should be considered in patients who develop acute respiratory failure during or after chemotherapy. Here, we discuss an unexpected case of etoposide-induced pneumonitis after a short course of IV etoposide in a patient with metastatic seminoma.

Hospital Medicine
Tsaftaridis N, **Cholagh A**, **Kaatz S**, and Spyropoulos AC. Venous Thromboembolism Prevention in the Hospitalized Medical Patient. *Med Clin North Am* 2025. PMID: Not assigned. Full Text

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Infectious Diseases
Arena CJ, **Van Horn BT**, **Kenney RM**, **Parke DM**, **Suleyman G**, **Davis SL**, and **Veve MP**. A Retrospective Cohort Study of Oral Antimicrobial Therapy Offers in Hospitalized People Who Inject Drugs Who Elect for Self-directed Discharge. *J Addict Med* 2025; Epub ahead of print. PMID: 40096193. Full Text

OBJECTIVES: To evaluate infection management in people who inject drugs (PWID) who elect for self-directed discharge (SDD) and to identify characteristics associated with an oral antimicrobial therapy offer (OATO). METHODS: This was a retrospective cohort of hospitalized adult PWID with an injection drug use (IDU)-related infection who elected for SDD between January 1, 2014, to January 31, 2024, at a five-hospital health system in southeast Michigan. Patients were excluded if they were hospitalized for <24 hours or if antimicrobial treatment was completed before SDD. The primary outcome was the proportion of patients with an OATO at or before SDD. Secondary outcomes at 30 days included retreatment, infection-related readmission, and all-cause mortality. RESULTS: One hundred fifty patients were included; 55 (37%) received an OATO, 95 (63%) did not receive an offer. Patient outcomes were not different between the OATO and no offer groups: infection retreatment 19 (34%) versus 32 (34%); infection-related readmission 14 (25%) versus 31 (33%); and all-cause mortality 1 (2%) versus 3 (3%). In multivariable logistic regression, variables independently associated with OATO included prescribing/continuing medications for opioid use disorder (MOUD) (adjusted odds ratio [aOR], 2.8; 95% CI: 1.36-5.92), infection source control (aOR, 2.3; 95% CI: 1.10-4.84), and early-career clinician care (aOR, 2.8; 95% CI: 1.01-7.89). CONCLUSIONS: Most hospitalized PWID with IDU-related infections with SDD did not receive an OATO. Early career clinicians more commonly offered oral antimicrobials in PWID with less complicated infection types. Standardizing OATO in PWID at risk for SDD should be considered as a future direction to improve health outcomes.

Infectious Diseases
Bhargava A, **Klamer K**, **Sharma M**, **Ortiz D**, and **Saravolatz L**. Candida auris: A Continuing Threat. *Microorganisms* 2025; 13(3). PMID: 40142543. Full Text

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Candida auris is a World Health Organization critical-priority fungal pathogen that has variable resistance to antifungal treatments. Multiple clades have been identified through genomic analysis and have appeared in different geographic locations simultaneously. Due to a combination of factors including antifungal resistance, ability to colonize and persist in the environment, and thermotolerance, it can thrive. Infected patients are associated with a high mortality rate, especially those with multiple health risk factors like those associated with other Candida species. This review highlights the current situation of this pathogen to help provide guidance for future work.

Infectious Diseases

Veve MP, **Kenney RM**, **Aljundi AM**, Dierker MS, Athans V, **Shallal AB**, and Patel N. Multicenter, retrospective cohort study of antimycobacterial treatment-related harms among patients with non-tuberculosis Mycobacterium infections in the United States. *Antimicrob Agents Chemother* 2025; Epub ahead of print. PMID: 40035548. Full Text

Department of Pharmacy, Henry Ford Hospital, Detroit, Michigan, USA. RINGGOLD: 24016
Department of Pharmacy Practice, Eugene Applebaum College of Pharmacy and Health Sciences, Wayne State University, Detroit, Michigan, USA. RINGGOLD: 15538
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Non-tuberculosis mycobacteria (NTM) are extensively drug-resistant organisms that require long-term therapy. The study purpose was to quantify the incidence of and risk factors for antimycobacterial-associated adverse drug events (ADEs) in persons with NTM infections receiving outpatient therapy. A multicenter, retrospective cohort was performed of persons with NTM infections who received antimycobacterial treatment from 2013 to 2024. Inclusion criteria were age ≥18 years, ≥1 month of outpatient treatment, and ≥1 follow-up outpatient visit within 3 months of index encounter. Mycobacterium avium complex and Mycobacterium tuberculosis complex were excluded. The primary outcome was development of pre-specified treatment-related ADE or acute kidney injury (AKI), thrombocytopenia, and/or Clostridioides difficile infection (CDI) through 12 months of therapy. Secondary outcomes included therapy discontinuation due to any treatment-related ADEs. Two hundred patients were included: 14% developed a pre-specified ADE. Mycobacterium abscessus (29%) was the most common pathogen; most initial regimens included a macrolide (54%), systemic aminoglycoside (24%), β-lactam (24%), or tetracycline derivative (22%). The most common pre-specified ADEs were thrombocytopenia (9%), AKI (8%), and CDI (<1%). The median (IQR) time-to-ADE was 25 (18-38) days from initial outpatient regimen; patients who received aminoglycoside- or oxazolidinone-based therapies were more likely to develop a pre-specified ADE (adjOR, 3.9; 95% CI, 1.7-9.2). Therapy discontinuation due to any ADE occurred in 35% of patients; the median (IQR) time-to-any ADE was 32 (21-58) days. ADEs in persons with NTM infections are common and occur near the first month of outpatient treatment. Intensified monitoring and/or use of more tolerable antimycobacterial regimens early in treatment may be an appropriate approach to avoid harms.Treatment of non-tuberculosis mycobacteria is complicated by adverse drug events (ADEs). This work quantified the incidence and time course of pre-determined, clinically relevant ADEs (acute kidney injury, thrombocytopenia, and C. difficile infection), which occurred in 14% of patients within 30 days of outpatient treatment.

Internal Medicine

Abusuliman M, **Jamali T**, **Nimri F**, **Chaudhary AJ**, Elfert K, **Saleem A**, **Alomari A**, **Faisal MS**, **Shamaa O**, **Obri M**, Salem AE, Abusuliman A, **Watson A**, **Pompa R**, **Dang D**, **Piraka C**, **Elatrache M**, **Singla S**, and **Zuchelli T**. Analysis of Adverse Events of Endoscopic Ultrasound-Guided Lumen-Apposing Metal Stent Placement: Insights Across Various Indications and Techniques. *Gastroenterology Res* 2025; 18(1):1-11. PMID: 40051887. Full Text

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Department of Gastroenterology, Henry Ford Hospital, Detroit, MI, USA.
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BACKGROUND: Endoscopic ultrasound (EUS)-guided lumen-apposing metal stent (LAMS) placement is increasingly being used in lieu of surgery for multiple procedures, including transmural fluid drainage. However, few studies have evaluated adverse events (AEs) associated with LAMS placement. Our aim was to characterize the rates of AEs associated with several LAMS placement strategies across different procedures and indications. METHODS: A single-center retrospective cross-sectional study was conducted on patients who underwent EUS-guided LAMS placement between 2015 and 2023 at a single institution. Technical and clinical success rates and rates of early and late AEs were analyzed. Comparisons of AE rates were determined for patients who had LAMS dilation versus those without dilation, patients who had plastic stent placement in addition to LAMS placement versus those with no plastic stents, and patients who had combined dilation and plastic stent procedures versus those with LAMS dilation only. RESULTS: A total of 243 patients underwent EUS-guided LAMS interventions: 110 (45.3%) women and 133 (54.7%) men (mean age 53.7 ± 15.9 years). There were 96 (39.5%) patients who had at least one AE. Abdominal pain was the most common early and late AE. Plastic stent placement alongside LAMS placement was associated with a significantly higher rate of overall AEs (48.3% vs 29.9%; P = 0.009), late AEs (33% vs 17.9%; P = 0.021), and stent occlusion (5.7% vs 0%; P = 0.046). LAMS dilation was associated with higher rates of late AEs (34.2% vs 20.6%; P = 0.022) and stent occlusion (6.2% vs 1.0%; P = 0.049). CONCLUSIONS: LAMS placement showed high technical and clinical success rates across different indications with mostly mild AEs, suggesting that LAMSs may be safe and effective for pancreatic and biliary drainage.

Internal Medicine
Cook AV, **LeRoy DI**, and **Konja CT**. A Breathtaking Case of Chemotherapy-Induced Pneumonitis. *Cureus* 2025; 17(2):e78791. PMID: 40078233. Full Text

Internal Medicine, Henry Ford Health System - Warren, Warren, USA.

Medication-induced pulmonary toxicity is a rare adverse event that may occur with many chemotherapeutic agents, including etoposide. This agent has been found to cause various toxicities, including anaphylaxis, angioedema, hypotension, and pneumonitis. Etoposide is used in chemotherapy regimens for multiple cancers, including germ-cell tumors. Proper diagnosis of chemotherapy-induced pulmonary toxicity is imperative and should be considered in patients who develop acute respiratory failure during or after chemotherapy. Here, we discuss an unexpected case of etoposide-induced pneumonitis after a short course of IV etoposide in a patient with metastatic seminoma.

Internal Medicine
El Meski N, El Ayoubi LW, Hassani S, Bidikian N, **Zakhour J**, Bou Khalil J, Kanafani ZA, and Kanj SS. Clinical Spectrum of Toxocariasis: A Retrospective Study From a Tertiary Care Center in Lebanon. *Future Microbiol* 2025; 1-9. Epub ahead of print. PMID: 40080036. Full Text

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AIMS: Toxocariasis is a prevalent zoonotic disease worldwide caused primarily by Toxocara canis and Toxocara cati. Despite its prevalence, studies focusing on clinical manifestations, and laboratory findings

of toxocariasis in the Middle East North African (MENA) region are limited, highlighting a significant gap in research. The aim of this study is to describe the spectrum of toxocariasis observed at a tertiary center in Lebanon and review the geographic distribution of infected individuals and their demographics. METHODS: The medical records of 225 patients who tested positive for Toxocara IgG via ELISA between 2002 and 2022 at the American University of Beirut Medical Center (AUBMC) were reviewed. RESULTS: 141/225 patients had confirmed positive Toxocara-specific IgG by Western blot. These patients were mostly middle-aged, with a mean of 46 years and predominantly males. Most were Lebanese (95.3%), residing in Mount Lebanon or Beirut governates. Patients were mainly symptomatic (78.5%), and the most common presenting symptoms were neurological complaints. For those with Toxocara myelitis (23 patients), spine magnetic resonance imaging (MRI) findings showed focal lesions (54.5%) mostly at the thoracic vertebrae. CONCLUSIONS: Given the challenges associated with diagnosing this disease, further studies are essential to enhance our understanding of toxocariasis in the region.
Toxocariasis is a common parasitic disease caused by Toxocara worms. These worms infect dogs and cats. Our study looked at the cases of toxocariasis at a hospital in Lebanon between 2002 and 2022 and reported 141 cases. Most patients (78.5%) had symptoms on presentation, with many complaining of neurological symptoms including headache, numbness or weakness. Among these patients, 23 had signs of infection in their spine. The majority of the infected patients were Lebanese (95.3%) and lived in specific areas of Lebanon. Because diagnosing this disease can be difficult, more research is needed to better understand toxocariasis in Lebanon and the wider Middle East and North Africa (MENA) region.
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Internal Medicine

Henry A, Mo X, Finan C, Chaffin MD, Speed D, Issa H, Denaxas S, Ware JS, Zheng SL, Malarstig A, Gratton J, Bond I, Roselli C, Miller D, Chopade S, Schmidt AF, Abner E, Adams L, Andersson C, Aragam KG, Ärnlöv J, Asselin G, Raja AA, Backman JD, Bartz TM, Biddinger KJ, Biggs ML, Bloom HL, Boersma E, Brandimarto J, Brown MR, Brunak S, Bruun MT, Buckbinder L, Bundgaard H, Carey DJ, Chasman DI, Chen X, Cook JP, Czuba T, de Denus S, Dehghan A, Delgado GE, Doney AS, Dörr M, Dowsett J, Dudley SC, Engström G, Erikstrup C, Esko T, Farber-Eger EH, Felix SB, Finer S, Ford I, Ghanbari M, Ghasemi S, Ghouse J, Giedraitis V, Giulianini F, Gottdiener JS, Gross S, Guðbjartsson DF, **Gui H**, Gutmann R, Hägg S, Haggerty CM, Hedman Å K, Helgadottir A, Hemingway H, Hillege H, Hyde CL, Aagaard Jensen B, Jukema JW, Kardys I, Karra R, Kavousi M, Kizer JR, Kleber ME, Køber L, Koekemoer A, Kuchenbaecker K, Lai YP, **Lanfear D**, Langenberg C, Lin H, Lind L, Lindgren CM, Liu PP, London B, Lowery BD, Luan J, Lubitz SA, Magnusson P, Margulies KB, Marston NA, Martin H, März W, Melander O, Mordi IR, Morley MP, Morris AP, Morrison AC, Morton L, Nagle MW, Nelson CP, Niessner A, Niiranen T, Noordam R, Nowak C, O'Donoghue ML, Ostrowski SR, Owens AT, Palmer CNA, Paré G, Pedersen OB, Perola M, Pigeyre M, Psaty BM, Rice KM, Ridker PM, Romaine SPR, Rotter JI, Ruff CT, Sabatine MS, Sallah N, Salomaa V, Sattar N, Shalaby AA, Shekhar A, Smelser DT, Smith NL, Sørensen E, Srinivasan S, Stefansson K, Sveinbjörnsson G, Svensson P, Tammesoo ML, Tardif JC, Teder-Laving M, Teumer A, Thorgeirsson G, Thorsteinsdottir U, Torp-Pedersen C, Tragante V, Trompet S, Uitterlinden AG, Ullum H, van der Harst P, van Heel D, van Setten J, van Vugt M, Veluchamy A, Verschuuren M, Verweij N, Vissing CR, Völker U, Voors AA, Wallentin L, Wang Y, Weeke PE, Wiggins KL, **Williams LK**, Yang Y, Yu B, Zannad F, Zheng C, Asselbergs FW, Cappola TP, Dubé MP, Dunn ME, Lang CC, Samani NJ, Shah S, Vasan RS, Smith JG, Holm H, Shah S, Ellinor PT, Hingorani AD, Wells Q, and Lumbers RT. Genome-wide association study meta-analysis provides insights into the etiology of heart failure and its subtypes. *Nat Genet* 2025; Epub ahead of print. PMID: 40038546. Full Text

Heart failure (HF) is a major contributor to global morbidity and mortality. While distinct clinical subtypes, defined by etiology and left ventricular ejection fraction, are well recognized, their genetic determinants remain inadequately understood. In this study, we report a genome-wide association study of HF and its subtypes in a sample of 1.9 million individuals. A total of 153,174 individuals had HF, of whom 44,012 had a nonischemic etiology (ni-HF). A subset of patients with ni-HF were stratified based on left ventricular systolic function, where data were available, identifying 5,406 individuals with reduced ejection fraction and 3,841 with preserved ejection fraction. We identify 66 genetic loci associated with HF and its subtypes, 37 of which have not previously been reported. Using functionally informed gene prioritization methods, we predict effector genes for each identified locus, and map these to etiologic disease clusters through phenome-wide association analysis, network analysis and colocalization. Through heritability

enrichment analysis, we highlight the role of extracardiac tissues in disease etiology. We then examine the differential associations of upstream risk factors with HF subtypes using Mendelian randomization. These findings extend our understanding of the mechanisms underlying HF etiology and may inform future approaches to prevention and treatment.

Internal Medicine
Jaan A, Zubair A, Farooq U, Nadeem H, **Chaudhary AJ**, Shahzil M, Dhawan A, Zafar H, Rahman AU, and Shah T. Impact of frailty on outcomes and biliary drainage strategies in acute cholangitis: A retrospective cohort analysis. *Clin Res Hepatol Gastroenterol* 2025; 49(4):102568. PMID: 40043797. Full Text

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BACKGROUND: Acute cholangitis (AC) is a potentially fatal infection of the biliary tract characterized by varying degrees of severity, with endoscopic retrograde cholangiopancreatography (ERCP) serving as the primary drainage modality. Though frailty is linked to poor outcomes in general, its implications for AC patients remain unexplored. METHODS: Using the National Inpatient Sample Database 2017-2020, we identified adult AC hospitalizations, which were further stratified based on frailty. A multivariate regression model was used for analysis. RESULTS: We included 32,310 AC patients, out of whom 11,230 (34.76 %) were frail. Frail patients had elevated AC severity as well as in-hospital mortality (adjusted odds ratio [aOR] 6.89; P < 0.01). Additionally, frail patients were found to have significantly higher odds of complications including septic shock (aOR 15.87), acute renal failure (aOR 5.67), acute respiratory failure (aOR 11.11) and need for mechanical ventilation (aOR 13.80). From a procedural viewpoint, frail patients had higher odds of undergoing percutaneous biliary drainage (PBD) but lower odds of undergoing "early" ERCP (ERCP within 24 h of admission). When compared to non-frail counterparts, frail patients were more likely to undergo PBD as opposed to early ERCP (aOR 1.46; P = 0.01). CONCLUSION: Frailty independently predicts poor AC outcomes and has a notable impact on the choice of biliary drainage procedure. Recognizing frailty instead of age alone as a determinant of AC outcomes can aid clinicians in risk stratification and guide tailored interventions in this population.

Internal Medicine
Ogedegbe OJ, Ntukidem OL, **Bai S**, Sukhera AB, and Atencah SN. EPR25-120: Second Primary Malignancy in Multiple Myeloma Survivors: A Population-Based Retrospective Cohort Study. *J Natl Compr Canc Netw* 2025; 23(3.5). PMID: 40154498. Full Text

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Internal Medicine
Qureshi MA. Letter to the Editor: "Accurate diagnosis of ischemic heart disease without exposure to radiation using non-stress unshielded magnetocardiography (MCG)". *Am Heart J Plus* 2025; 52:100519. PMID: 40129619. Full Text

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Internal Medicine

Saleem A, Hussain M, Schechter S, and Sturm MB. Colonic malakoplakia. *BMJ Case Rep* 2025; 18(3). PMID: 40132942. Full Text

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Colonic malakoplakia is a rare granulomatous inflammatory condition that can cause abdominal pain, diarrhoea and rectal bleeding and be associated with colon adenocarcinoma. Chronic bacterial infections with defective lysosomal activity in macrophages are possible causes for malakoplakia. We present a case report of asymptomatic colonic malakoplakia in an otherwise healthy woman undergoing a screening colonoscopy for colorectal cancer. Limited case reports and treatment guidance are available for colonic malakoplakia with only a few dozen cases in the literature. Given the potential morbidity and mortality associated with this condition, we emphasise the importance of thorough diagnostic and therapeutic evaluation even in asymptomatic patients.

Internal Medicine

Shahzil M, Hasan F, Kazmi SK, Gangwani MK, Shabbar U, **Chaudhary AJ**, Khaqan MA, **Faisal MS**, Williams KN, Mohan BP, and Tofani C. Evaluating the Effectiveness of Pegbelfermin in MASH-Associated Hepatic Fibrosis A Meta-Analysis and Systematic Review of Randomized Controlled Trials. *JGH Open* 2025; 9(3):e70131. PMID: 40104016. Full Text

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INTRODUCTION: Metabolic dysfunction-associated steatohepatitis (MASH), an advanced form of fatty liver disease, is characterized by liver inflammation and fibrosis, with an emerging interest in fibroblast growth factor (FGF)-21 analogs, particularly pegbelfermin (PGBF). This study evaluates the efficacy and safety of PGBF in treating MASH-associated hepatic fibrosis. METHODS: This meta-analysis followed Cochrane guidelines and PRISMA standards. A comprehensive search of databases up to January 2023 focused on randomized controlled trials (RCTs) comparing PGBF to placebo for MASH. Meta-analyses were performed with RevMan 5.4 using a random-effects model. RESULTS: Data from 452 participants across three RCTs were analyzed. Significant improvements in adiponectin concentration were observed in both the 10 mg [MD = 18.23, 95% CI (6.35, 30.11), p = 0.003] and 20 mg [MD = 18.09, 95% CI (5.88, 30.31), p = 0.004] PGBF groups compared to placebo. Significant reductions in PRO-C3 concentration were noted in both the 10 mg [MD = -25.50, 95% CI (-43.95, -7.05), p = 0.007] and 20 mg [MD = -19.54, 95% CI (-33.33, -5.76), p = 0.005] groups. Significant improvement in MASH was seen in the 10 mg group [RR = 2.84, 95% CI (1.18, 6.78), p = 0.02] but not in the 20 mg group. No significant improvements in liver stiffness, Modified Ishak scores, collagen proportionate area, ALT and AST levels, or treatment-emergent adverse events (TEAEs) were observed in either dosage group. CONCLUSIONS: Pegbelfermin, a promising therapy for MASH fibrosis, has demonstrated effectiveness at 10 mg, significantly improving MASH and biomarkers including adiponectin and PRO-C3, while maintaining a generally safe profile.

Internal Medicine

Shaikh S, Khan AR, Saini S, Naimat A, Amudha C, Bannur D, **Ajayi E**, Rehman A, Shah S, Fakhruddin NM, Kormath N, and Mylavarapu M. Cryoneurolysis: A Comprehensive Review of Applications in Pain Management. *Cureus* 2025; 17(2):e79448. PMID: 40130111. Full Text

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Pain management is an integral part of healthcare, and cryoneurolysis, a technique that uses extreme cold to disrupt nerve conduction, has demonstrated potential in managing both acute and chronic pain. It is an alternative for patients who do not respond to traditional pain management therapies. This review examines the efficacy, application, mechanism, limitations, challenges, and advancements in cryoneurolysis. Cryoneurolysis has broad applications, including acute pain management, reducing opioid dependency, and shortening hospital stays. It effectively treats chronic pain conditions like lumbar facet syndrome, phantom limb pain, occipital neuralgia, and, in some cases, unresponsiveness to traditional therapies. Furthermore, it offers values in tumor-induced neuropathies and postoperative pain. Cryoneurolysis has a favorable safety profile, presenting a low risk of minor complications such as infection and bruising, which resolve with proper care. Comparative studies indicate that cryoneurolysis, which induces Wallerian degeneration, is as effective as cooled radiofrequency ablation (CRFA), which achieves thermal nerve degradation to block pain transmission, particularly in knee osteoarthritis. However, its potential limitations impede widespread adoption, including small sample sizes, study heterogeneity, and the lack of standardized protocols. Future research should focus on large-scale trials, comparative studies with other pain management modalities, and developing standardized guidelines to enhance clinical outcomes.

Internal Medicine

Tabassum S, Azhar F, Hussain F, Naeem A, **Sheffeh MA**, and Asghar MS. Trends in ischemic heart disease-related mortality in obese population in the United States. *Cardiovasc Endocrinol Metab* 2025; 14(2):e00325. PMID: 40051885. Full Text

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Obesity affects approximately 72 million Americans and is a significant contributor to ischemic heart disease (IHD). Given the scarcity of data, this observational study examines trends and disparities in IHD-related mortality among obese individuals in the United States from 2003 to 2019 using Centers for Disease Control and Prevention's Wide-Ranging Online Data for Epidemiologic Research data. Age-adjusted mortality rates (AAMRs) were calculated for IHD as the underlying cause of death and obesity as a contributing cause of death, revealing an increase in IHD-related mortality among obese adults.

AAMR rose from 2.1 in 2003 to 3.9 in 2019, with higher rates in men, non-Hispanic Black individuals, the elderly, and those in nonmetropolitan and Midwest regions. These findings underscore significant sex, racial, and regional disparities in mortality, suggesting a need for targeted health policies and resource allocation, improving overall cardiovascular health outcomes.

Internal Medicine

Tsaftaridis N, **Cholagh A**, **Kaatz S**, and Spyropoulos AC. Venous Thromboembolism Prevention in the Hospitalized Medical Patient. *Med Clin North Am* 2025. PMID: Not assigned. Full Text

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Neurology

Andrews J, Paganoni S, Macklin EA, Chibnik LB, Quintana M, Saville BR, Detry MA, Vestrucci M, Marion J, McGlothlin A, Young E, Chase M, Pothier L, Harkey B, Yu H, Sherman A, Shefner J, Hall M, Kittle G, Connolly MR, Berry JD, D'Agostino D, Tustison E, Giacomelli E, Scirocco E, Alameda G, Locatelli E, Ho D, Quick A, Heitzman D, Ajroud-Driss S, Appel SH, Shroff S, Katz J, Felice K, Maragakis NJ, Simmons Z, Goutman SA, Olney N, Miller T, Fernandes JA, Ilieva H, Jawdat O, Weiss MD, Foster L, Vu T, Ladha S, Owegi MA, **Newman DS**, **Arcila-Londono X**, Jackson CE, Swenson A, Heiman-Patterson T, Caress J, Fee D, Peltier A, Lewis R, Rosenfeld J, Walk D, Johnson K, Elliott M, Kasarskis EJ, Rutkove S, McIlduff CE, Bedlack R, Elman L, Goyal NA, Rezania K, Twydell P, Benatar M, Glass J, Cohen JA, Jones V, Zilliox L, Wymer JP, Beydoun SR, Shah J, Pattee GL, Martinez-Thompson J, Nayar S, Granit V, Donohue M, Grossman K, Campbell DJ, Qureshi IA, Cudkowicz ME, and Babu S. Verdiperstat in Amyotrophic Lateral Sclerosis: Results From the Randomized HEALEY ALS Platform Trial. *JAMA Neurol* 2025; Epub ahead of print. PMID: 40067754. Full Text

IMPORTANCE: Myeloperoxidase is one of the most abundant peroxidase enzymes in activated myeloid cells. Myeloperoxidase inhibitors may have a clinical benefit in amyotrophic lateral sclerosis (ALS) by slowing neurodegeneration via reduced neuroinflammation and oxidative stress. OBJECTIVE: To determine the safety, tolerability, and efficacy of verdiperstat, a selective myeloperoxidase inhibitor, in ALS. DESIGN, SETTINGS, AND PARTICIPANTS: Verdiperstat was tested as a regimen of the HEALEY ALS Platform Trial, a multicenter, double-blind, perpetual platform design, randomized clinical trial, with sharing of trial infrastructure and placebo data across multiple regimens. The study was conducted at 54 ALS referral centers across the US from July 2020 to April 2022. Adult participants with a diagnosis of clinically possible, probable, laboratory-supported probable, or definite ALS defined by the revised El Escorial criteria were randomized to verdiperstat or regimen-specific placebo. An additional group of participants concurrently randomized to placebo from other regimens was included in the analyses. INTERVENTIONS: Eligible participants were randomized in a 3:1 ratio to receive oral verdiperstat, 600 mg, twice daily or matching placebo for a planned placebo-controlled duration of 24 weeks. MAIN OUTCOMES AND MEASURES: The primary efficacy outcome was change from baseline through week 24 in disease severity, as measured by a joint model of ALS Functional Rating Scale-Revised and survival, with the treatment effect quantified by the disease rate ratio (DRR), with DRR less than 1 indicating a slowing in disease progression of verdiperstat relative to placebo. RESULTS: A total of 167 participants (mean [SD] age, 58.5 [11.4] years; 59 [35.3%] female; 108 [64.6%] male) were randomized to either verdiperstat (126 [75.4%]) or to placebo (41 [25.6%]). Among the participants randomized to the verdiperstat regimen, 130 (78%) completed the trial. The estimated DRR was 0.98 (95% credible interval, 0.77-1.24; posterior probability = 0.57 for slowing of disease progression [DRR <1]). Verdiperstat was estimated to slow progression by 2% vs placebo (95% credible interval, -23% to 24%; posterior probability 0.57). Verdiperstat was overall safe and well tolerated. Common adverse events in the verdiperstat group were nausea, insomnia, and elevated thyrotropin levels. CONCLUSIONS AND RELEVANCE: Results demonstrate that treatment with verdiperstat was unlikely to alter disease progression in ALS. TRIAL REGISTRATION: Clinical Trial Identifiers: NCT04297683 and NCT04436510.

Neurology

Berry JD, Maragakis NJ, Macklin EA, Chibnik LB, Quintana M, Saville BR, Detry MA, Vestrucci M, Marion J, McGlothlin A, Stommel EW, Chase M, Pothier L, Harkey BA, Yu H, Sherman A, Shefner J, Hall M, Kittle G, Babu S, Andrews J, D'Agostino D, Tustison E, Scirocco E, Giacomelli E, Alameda G, Locatelli E, Ho D, Quick A, Ajroud-Driss S, Katz J, Heitzman D, Appel SH, Shroff S, Felice KJ, Simmons Z, Miller T, Olney N, Weiss MD, Goutman SA, Fernandes JA, Jr., Jawdat O, Owegi MA, Foster L, Vu T, Ilieva H, **Newman DS**, **Arcila-Londono X**, Jackson C, Ladha S, Heiman-Patterson T, Caress J, Swenson A, Peltier A, Lewis R, Fee D, Elliott M, Bedlack R, Kasarskis EJ, Elman L, Rosenfeld J, Walk D, McIlduff CE, Twydell P, Young E, Johnson K, Rezania K, Goyal NA, Cohen JA, Benatar M, Jones V, Glass J, Shah J, Beydoun SR, Wymer JP, Zilliox L, Nayar S, Pattee GL, Martinez-Thompson J, Rynders A, Evan J, Evan J, Hartford A, Sepassi M, Ho KS, Glanzman R, Greenberg B, Hotchkin MT, Paganoni S, and Cudkowicz ME. CNM-Au8 in Amyotrophic Lateral Sclerosis: The HEALEY ALS Platform Trial. *JAMA* 2025; Epub ahead of print. PMID: 40067821. Full Text

IMPORTANCE: Bioenergetic failure has been proposed as a driver of amyotrophic lateral sclerosis (ALS). CNM-Au8 is a suspension of gold nanocrystals that catalyzes the conversion of nicotinamide adenine dinucleotide hydride into NAD+, resulting in an increase of cellular adenosine triphosphate production. OBJECTIVE: To determine the effects of CNM-Au8 on ALS disease progression. DESIGN, SETTING, AND PARTICIPANTS: CNM-Au8 was tested as a regimen of the HEALEY ALS Platform Trial, a phase 2/3, multicenter, randomized, double-blind platform trial. The study was conducted at 54 sites in the US from July 2020 to March 2022 (final follow-up, March 17, 2022). A total of 161 participants with ALS were randomized to receive CNM-Au8 (n = 120) or regimen-specific placebo (n = 41). Data from 123 concurrently randomized placebo participants in other regimens were combined for analyses. INTERVENTIONS: Eligible participants were randomized in a 3:3:2 ratio to receive CNM-Au8 60 mg daily (n = 61), CNM-Au8 30 mg daily (n = 59), or matching placebo (n = 41) for 24 weeks. MAIN OUTCOMES AND MEASURES: The primary efficacy outcome was change from baseline through week 24 in ALS disease severity measured by a bayesian shared parameter model of function (based on the Revised Amyotrophic Lateral Sclerosis Functional Rating Scale) and survival, which provided an estimate of the rate of disease progression measured by the disease rate ratio (DRR), with a DRR of less than 1 indicating treatment benefit. Secondary end points included a Combined Assessment of Function and Survival using a joint-rank test, rate of decline in slow vital capacity (percent predicted), and survival free of permanent assisted ventilation. RESULTS: Among 161 participants who were randomized within the CNM-Au8 regimen (mean age, 58.4 years; 61 [37.9%] female), 145 (90%) completed the trial. In the primary analysis comparing the combined CNM-Au8 dosage groups vs the combined placebo groups, the primary end point (DRR, 0.97 [95% credible interval, 0.783-1.175]; posterior probability of DRR <1, 0.65) and the 3 secondary end points suggested no benefit or harm of CNM-Au8. In the active (n = 120) vs placebo (n = 163) groups, the most common adverse events were diarrhea (23 [19%] vs 12 [7%]), nausea (17 [14.2%] vs 14 [8.6%]), fatigue (12 [10.8%] vs 30 [18.4%]), and muscular weakness (24 [20%] vs 45 [27.6%]). CONCLUSIONS AND RELEVANCE: No benefit of CNM-Au8 on ALS disease progression was observed at 24 weeks. TRIAL REGISTRATION: ClinicalTrials.gov Identifiers: NCT04297683, NCT04414345.

Neurology

Chu I, **Kokash A**, Li SP, and Vendrame M. Grapheme-color synesthesia in patients with epilepsy: A pilot study. *Epilepsy Behav* 2025; 166:110378. PMID: 40081148. Full Text

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BACKGROUND: Synesthesia is a condition in which the stimulation of one sensory modality triggers unusual experiences in a second sensory modality such as colors or shapes. Synesthesia has been linked to specific conditions such as autism spectrum disorder, although the mechanisms underlying synesthesia remain largely unclear. OBJECTIVE: This pilot study aimed to investigate the prevalence of grapheme-color synesthesia (GCS) in patients with epilepsy and to characterize the epilepsy features associated with GCS experiences. METHODS: Participants were asked whether they reported experiences suggesting GCS. Those reporting GCS underwent a standard online consistency and congruency battery test (http://www.synesthete.org). Epilepsy features, electroencephalogram (EEG) findings, and magnetic resonance imaging (MRI) findings were collected and analyzed. RESULTS: Of the 40 study participants, 21 reported GCS experiences and 3 (7.5 %) resulted synesthetes from the battery test. Analysis of the test results showed that participants with focal seizures had lower median consistency scores (indicating they were less consistent in their color assignments) and higher congruency scores (indicating they were more accurate in quickly identifying matching color and letter/number combinations) compared to patients with generalized-onset seizures (2.9 and 51.4 respectively; $p = 0.006$, $p = 0.001$). Participants with non-motor seizures had lower median consistency scores (1.1) and higher congruency scores (79.2) compared to patients with motor seizures (2.8 and 52.8, respectively; $p = 0.011$, $p = 0.036$). CONCLUSION: GCS may be more prevalent in patients with epilepsy than the general population. Focal and non-motor seizures may be associated with predisposition to GCS. Further larger scale studies are needed to confirm and expand these observations.

Neurology

Shefner JM, Oskarsson B, Macklin EA, Chibnik LB, Quintana M, Saville BR, Detry MA, Vestrucci M, Marion J, McGlothlin A, Heiman-Patterson T, Chase M, Pothier L, Harkey BA, Yu H, Sherman AV, Hall M, Kittle G, Berry JD, Babu S, Andrews J, D'Agostino D, Tustison E, Scirocco E, Giacomelli E, Alameda G, Locatelli E, Ho D, Quick A, Ajroud-Driss S, Katz J, Heitzman D, Appel SH, Shroff S, Felice K, Maragakis NJ, Simmons Z, Miller TM, Olney N, Weiss MD, Goutman SA, Fernandes JA, Jawdat O, Owegi MA, Foster LA, Vu T, Ilieva H, **Newman DS**, **Arcila-Londono X**, Jackson CE, Ladha S, Caress JB, Swenson A, Peltier A, Lewis RA, Fee D, Elliott M, Bedlack R, Kasarskis EJ, Elman L, Rosenfeld J, Walk D, McIlduff C, Twydell P, Young E, Johnson K, Rezania K, Goyal NA, Cohen JA, Benatar M, Jones V, Shah J, Beydoun SR, Wymer JP, Zilliox L, Nayar S, Pattee GL, Martinez-Thompson J, Leitner ML, Chen K, Goldberg YP, Cohen Y, Geva M, Hayden MR, Paganoni S, and Cudkowicz ME. Pridopidine in Amyotrophic Lateral Sclerosis: The HEALEY ALS Platform Trial. *JAMA* 2025; Epub ahead of print. PMID: 40067755. Full Text

IMPORTANCE: Amyotrophic lateral sclerosis (ALS) is a fatal disease. The sigma-1 (σ1) receptor emerged as a target for intervention. OBJECTIVE: To determine the effects of pridopidine, a σ1-receptor agonist, in ALS. DESIGN, SETTINGS, AND PARTICIPANTS: Pridopidine was tested as a regimen of the HEALEY ALS Platform Trial, a phase 2/3, multicenter, randomized, double-blind, platform trial. The study was conducted at 54 sites in the US from January 2021 to July 2022 (final follow-up, July 14, 2022). A total of 163 participants with ALS were randomized to receive pridopidine or placebo. An additional 122 concurrently randomized participants were assigned to receive placebo in other regimens and included in the analyses. INTERVENTIONS: Eligible participants were randomized 3:1 to receive oral pridopidine 45 mg twice daily (n = 121) or matching oral placebo (n = 42) for a planned duration of 24 weeks. MAIN OUTCOMES AND MEASURES: The primary efficacy outcome was change from baseline through week 24 in ALS disease severity, analyzed using a bayesian shared parameter model, which has components for function (Revised Amyotrophic Lateral Sclerosis Functional Rating Scale [ALSFRS-R]) and survival that were linked through an integrated estimate of treatment-dependent disease slowing across these 2 components. This was denoted as the disease rate ratio (DRR), with DRR less than 1 indicating a slowing in disease progression on pridopidine relative to placebo. There were 5 key secondary end points: time to 2-point or greater reduction in ALSFRS-R total score among participants with bulbar dysfunction at baseline, rate of decline in slow vital capacity among participants with bulbar dysfunction at baseline, percentage of participants with no worsening in the ALSFRS-R bulbar domain score, time to 1-point or

greater change in the ALSFRS-R bulbar domain score, and time to death or permanent assisted ventilation. RESULTS: Among 162 patients (mean age, 57.5 years; 35% female) who were randomized to receive the pridopidine regimen and included in the primary efficacy analysis, 136 (84%) completed the trial. In the primary analysis comparing pridopidine vs the combined placebo groups, there was no significant difference between pridopidine and placebo in the primary end point (DRR, 0.99 [95% credible interval, 0.80-1.21]; probability of DRR <1, 0.55) and no differences were seen in the components of ALSFRS-R or survival. There was no benefit of pridopidine on the secondary end points. In the safety dataset (pridopidine, n = 121; placebo, n = 163), the most common adverse events were falls (28.1% vs 29.3%, respectively) and muscular weakness (24.0% vs 31.7%, respectively). CONCLUSIONS AND RELEVANCE: In this 24-week study, pridopidine did not impact the progression of ALS. TRIAL REGISTRATION: ClinicalTrials.gov Identifiers: NCT04297683, NCT04615923.

Neurology

Wang M, **Liu Z**, **Wang W**, **Chopp M**, **Millman M**, **Li Y**, **Cepparulo P**, **Kemper A**, **Li C**, **Zhang L**, **Zhang Y**, and **Zhang ZG**. Enhanced Small Extracellular Vesicle Uptake by Activated Interneurons Improves Stroke Recovery in Mice. *J Extracell Biol* 2025; 4(3):e70036. PMID: 40134760. Full Text

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Neuronal circuitry remodelling, which comprises excitatory and inhibitory neurons, is critical for improving neurological outcomes after a stroke. Preclinical studies have shown that small extracellular vesicles (sEVs) have a therapeutic effect on stroke recovery. However, it is highly challenging to use sEVs to specifically target individual neuronal populations to enhance neuronal circuitry remodelling after stroke. In the present study, using a chemogenetic approach to specifically activate peri-infarct cortical interneurons in combination with the administration of sEVs derived from cerebral endothelial cells (CEC-sEVs), we showed that the CEC-sEVs were preferentially taken up by the activated neurons, leading to significant improvement of functional outcome after stroke, which was associated with augmentation of peri-infarct cortical axonal/dendritic outgrowth and of axonal remodelling of the corticospinal tract. The ultrastructural and Western blot analyses revealed that neurons with internalization of CEC-sEVs exhibited significantly reduced numbers of damaged mitochondria and proteins that mediate dysfunctional mitochondria, respectively. Together, these data indicate that the augmented uptake of CEC-sEVs by activated peri-infarct cortical interneurons facilitates neuronal circuitry remodelling and functional recovery after stroke, which has the potential to be a novel therapy for improving stroke recovery.

Neurosurgery

Bheemireddy S, Gajjar AA, Abe M, Custozzo A, Lipp S, Ringer A, Essibayi MA, Altschul D, Goren O, Oliver J, **Reese JC**, **Entezami P**, Chaudry I, Manos S, Turk ASt, Sagues E, Gudino A, Samaniego EA, Kühn AL, Singh J, Puri AS, Roy JM, ElNaamani K, Gooch MR, Jaikumar V, Siddiqui AH, Boulos AS, Dalfino JC, and Paul AR. Multicenter study of association between socioeconomic status and treatment of ruptured cerebral aneurysms compared to unruptured cerebral aneurysms: insights from 4,517 patients using the area deprivation index. *J Neurointerv Surg* 2025; Epub ahead of print. PMID: 40157743. Full Text

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BACKGROUND: Socioeconomic status influences health outcomes, including cerebrovascular diseases. Patients from socioeconomically deprived areas may present with more severe conditions due to delayed access to care. This study evaluates the association between neighborhood-level deprivation, measured by the Area Deprivation Index (ADI), and the treatment of ruptured intracranial aneurysms (RIAs) compared with unruptured intracranial aneurysms (UIAs) across multiple centers. METHODS: This retrospective cohort study analyzed data from 4517 patients treated for cerebral aneurysms at 10 US comprehensive stroke centers between 2018 and 2024. Patients were stratified by national ADI decile based on their residential addresses. Multivariable logistic regression was used to examine the relationship between ADI and aneurysm rupture (reference being unruptured aneurysms) and controlled for age, sex, smoking history, family history, and race. RESULTS: Of 4517 total patients, 1260 (27.9%) underwent treatment of RIAs. Multivariable analysis confirmed ADI as an independent predictor of presentation for treatment of RIA (odds ratio (OR)=1.100, 95% confidence interval (CI)=1.068-1.133, P<0.0001) after adjusting for age, sex, smoking history, and race. This corresponds to a 10% increase in likelihood of presenting for treatment of a ruptured vs unruptured intracranial aneurysm with each ADI decile. CONCLUSION: Socioeconomic deprivation independently predicts treatment of RIAs compared with the treatment of UIAs. These findings highlight disparities in aneurysm detection and management, emphasizing the need for targeted preventive care and accessible screening programs to mitigate the impact of socioeconomic disadvantage on cerebral aneurysm outcomes.

Neurosurgery

Cheok SK, Ruzevick J, Briggs RG, Cote DJ, Shah I, Gomez D, Bove I, Feng JJ, Pangal DJ, Strickland BA, Shiroishi M, Zavros Y, Hurth KM, Mathew A, Garrett NE, Little AS, Laws ER, **Castro AV**, Horbinski CM, Carmichael JD, and Zada G. A contemporary, multiinstitutional analysis of transcription factor lineage in pituitary adenomas: comparative study of neuroimaging, histopathology, and clinical outcomes. *J Neurosurg* 2025; 1-9. Epub ahead of print. PMID: 40085941. Full Text

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OBJECTIVE: Pituitary adenomas (PAs) are common lesions that often present with endocrinopathy and/or visual symptoms. Classification of PAs has historically been based on functional status and histopathological staining of anterior pituitary hormones. In 2017, the WHO revised the classification of PAs, establishing cell lineages identified by the transcription factors (TFs) PIT1, TPIT, and SF1. The clinical behavior of PA subtypes based on TF typing, including growth patterns, response to treatment, and recurrence rates, is unknown. The authors aimed to assess clinical presentation and outcomes according to TF lineage in a contemporary series of PAs. METHODS: A retrospective multicenter clinical study of patients undergoing resection of PAs between June 2017 and August 2021 was performed. Included tumors underwent immunohistochemical staining for WHO-defined TFs (TPIT, PIT1, and SF1). Clinical data including demographics, tumor characteristics, extent of resection, and clinical outcomes

pertaining to tumor control and hormonal remission were assessed. RESULTS: A total of 238 patients were included in the analysis, with the following clinical breakdown of PA subtypes: nonfunctional PAs (n = 150, 63.0%); growth hormone-secreting PAs causing acromegaly (n = 53, 22.3%); adrenocorticotropic hormone-secreting PAs causing Cushing's disease (n = 30, 12.6%); and prolactinomas (n = 2, 0.8%). The most common TFs identifying cell lineages were SF1 (n = 104 samples, 43.7%), TPIT (n = 53, 22.3%), and PIT1 (n = 46, 19.3%). Thirty-five samples (14.7%) were positive for two TFs. Prevalence of suprasellar extension was highest in SF1 tumors (91.3%) and lowest in PIT1 tumors (54.3%), and varied significantly across groups ($p < 0.001$). Cavernous sinus and clival/sphenoid invasion also varied among TF subtypes, with the highest rates seen in PIT1 PAs ($p = 0.002$). Although no significant differences in progression-free survival (PFS) were noted across TF subtypes, among nonfunctional PAs the median PFS for SF1, PIT1, and TPIT TFs were 83 months, 26 months, and 45 months, respectively ($p = 0.002$). Nonfunctional PIT1 PAs had a significantly shorter PFS/recurrence-free survival compared to functional PIT1 tumors (HR 59.45, 95% CI 2.54-1394, $p = 0.01$). CONCLUSIONS: The modern WHO diagnosis of PAs incorporates pituitary TF staining to standardize classification according to PA cell lineage. TF designation is associated with major clinical and endocrine variables including PA extension, extrasellar growth patterns, Ki-67 labeling index, and PFS among patients with PA subtypes.

Neurosurgery

Lu-Emerson C, Chowdhary S, Kotecha R, Sharma A, Odia Y, Vaillant B, Redfern C, Mammoser A, Shih K, Kesari S, Peterson R, Friday B, Edenfield WJ, Koga S, **Snyder J**, Jaboin J, Melguizo-Gavilanes I, McCabe M, Humeniuk M, Ambady P, and Dunbar E. A pilot survey into the landscape of neuro-oncology care in the community. *Oncologist* 2025; 30(3). PMID: 40163684. Full Text

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BACKGROUND: The complexities of the field of neuro-oncology require multidisciplinary collaboration in order to deliver contemporary comprehensive care. There is increasing awareness that much of neuro-oncology care occurs in the community setting. In 2022, the Society for Neuro-Oncology (SNO) created the Community Neuro-Oncology Committee (CNO) in an inaugural attempt to formally acknowledge community neuro-oncology practitioners. METHODS: A 19 question survey was developed by SNO-CNO

to gather initial data on the current landscape of neuro-oncology care in the community. The survey was distributed via the SNO newsletter and email blasts as well as through partnerships with multiple advocacy groups. Results were analyzed and tabulated through R2. RESULTS: There were 112 responses from providers in the United States and Canada. Most providers were physicians and represented multiple disciplines including neurology, neuro-oncology, medical oncology, neurosurgery, and radiation oncology. Sixty-four (57%) described themselves as neuro-oncology-focused. Eighty-eight (79%) reported access to neuro-oncology tumor boards. Sixty-eight (73%) stated they had access to molecular tumor boards. Most respondents felt that they were adequately supported to manage neuro-oncology patients. When dividing responses based on a neuro-oncology-focused practice compared to a less neuro-oncology-focused practice, there were significant differences between access to molecular tumors boards (85% vs 63%, P = .023) and access to clinical trials (98% vs 82%, P = .022). CONCLUSION: This qualitative and quantitative hypothesis-generating data is the start of understanding the challenges faced by community neuro-oncology providers. These results will guide future studies and recommendations aimed toward better supporting them and their patients.

Neurosurgery

Mackie H, Eide JG, Yassin-Kassab A, **Wilson C**, **Ray A**, **Robin AM**, **Asmaro K**, **Rock JP**, and **Craig JR**. Rapid Intrathecal Fluorescein Injection During Cerebrospinal Fluid Leak Repair Is Safe and Effective. *Laryngoscope* 2025; Epub ahead of print. PMID: 40110730. Full Text

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OBJECTIVE: Intrathecal fluorescein (IF) is effective for localizing nasal cerebrospinal fluid (CSF) leaks along the skull base during endoscopic exploration, with largest studies reporting sensitivities ranging from 66%-93%. Due to reports of intraoperative and postoperative neurologic complications such as seizures and paralysis, surgeons often dilute the fluorescein and inject it intrathecally slowly over a variable amount of time. However, no study has assessed whether rapid IF administration causes the aforementioned risks or whether it affects its accuracy in identifying CSF leaks intraoperatively. METHODS: A prospective study was conducted from 2015 to 2024, where all patients undergoing endoscopic exploration and/or repair of CSF rhinorrhea had 0.1 mL of 10% fluorescein (10 mg) mixed with 3-5 mL of patients' CSF injected rapidly via the lumbar drain over a few seconds. RESULTS: Of the 82 included patients, the mean age was 53.8 ± 15.2 years, and 84% were female. Sixty-nine patients underwent successful endoscopic CSF leak repairs, and 13 had negative endoscopic explorations. Rapid IF injection was 80% sensitive (20% false negative rate) and 100% specific for identifying CSF leaks, and it caused no seizures, paralysis, or other neurologic complications. CONCLUSION: Compared to prior reports of slow low-dose IF injection for CSF leak localization, rapid IF injection yielded similar efficacy (80% sensitivity) with no IF-related complications. Rapid IF injection was safe and effective but should be corroborated by future studies.

Neurosurgery

Mansouri A, Ozair A, Bhanja D, Wilding H, Mashiach E, Haque W, Mikolajewicz N, de Macedo Filho L, Mahase SS, Machtay M, Metellus P, Dhermain F, Sheehan J, Kondziolka D, Lunsford LD, Niranjan A, Minniti G, Li J, **Kalkanis SN**, Wen PY, Kotecha R, McDermott MW, Bettegowda C, Woodworth GF, Brown PD, Sahgal A, and Ahluwalia MS. Stereotactic radiosurgery for patients with brain metastases: current principles, expanding indications and opportunities for multidisciplinary care. *Nat Rev Clin Oncol* 2025; Epub ahead of print. PMID: 40108412. Full Text

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The management of brain metastases is challenging and should ideally be coordinated through a multidisciplinary approach. Stereotactic radiosurgery (SRS) has been the cornerstone of management for most patients with oligometastatic central nervous system involvement (one to four brain metastases), and several technological and therapeutic advances over the past decade have broadened the indications for SRS to include polymetastatic central nervous system involvement (>4 brain metastases), preoperative application and fractionated SRS, as well as combinatorial approaches with targeted therapy and immune-checkpoint inhibitors. For example, improved imaging and frameless head-immobilization technologies have facilitated fractionated SRS for large brain metastases or postsurgical cavities, or lesions in proximity to organs at risk. However, these opportunities come with new challenges and questions, including the implications of tumour histology as well as the role and sequencing of concurrent systemic treatments. In this Review, we discuss these advances and associated challenges in the context of ongoing clinical trials, with insights from a global group of experts, including recommendations for current clinical practice and future investigations. The updates provided herein are meaningful for all practitioners in clinical oncology.

Neurosurgery

Walbert T. When survival is not enough-Quality of life as a decision endpoint for patients. *Neurooncol Pract* 2025; 12(2):177-178. PMID: 40110069. Full Text

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Ophthalmology and Eye Care Services
Salem Z, Mubeen A, Sridhara R, Toiv A, Williams P, Gappy C, Jacobson A, Wang G, **Segar S**, Jakpor O, Freedman SF, and Killeen OJ. Cost as a barrier to eyeglasses in pediatric population: a cross-sectional survey analysis. *J AAPOS* 2025; 104171. Epub ahead of print. PMID: 40058566. Full Text

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Eyeglasses are an essential medical device to maximize visual potential and learning in children. We surveyed parents and pediatric ophthalmologists regarding their perspectives on the cost of pediatric eyeglasses. Parents and ophthalmologists identified cost as a barrier to obtaining eyeglasses. Despite over 80% of patients having some insurance coverage for eyeglasses, less than 1 in 4 reported that insurance fully covered the cost, and parents most frequently spent $100-200 per pair. More than 1 in 4 parents deferred purchasing recommended eyeglasses due to cost. Although over 80% of parents felt comfortable discussing the price of eyeglasses with the ophthalmologist, less than half of ophthalmologists felt comfortable discussing cost.

Orthopedics/Bone and Joint Center
Castle JP, **Gaudiani MA**, **Abbas MJ**, **Halkias EL**, **Pratt BA**, **Gasparro MA**, **Wager SG**, **Moutzouros V**, and **Makhni EC**. Preoperative depression screening using PHQ-2 is associated with worse outcomes after ACL reconstruction. *J Orthop* 2025; 70:63-69. PMID: Not assigned. Full Text

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Purpose: To determine how screening positive for depression preoperatively can affect patient reported outcomes after anterior cruciate ligament reconstruction (ACLR). Methods: Primary ACLR patients between May 2020–September 2022 with a PHQ-2 score prior to their surgery were retrospectively reviewed. Patients older than 13 years of age and with minimum 6-months of follow-up were included for analysis. Patients were categorized as PHQ(+) (PHQ-2 ≥2) or PHQ2(−) (PHQ-2 < 2). Demographics, preoperative and postoperative Patient Reported Outcome Information System (PROMIS) -Physical Function (PF) and Pain Interference (PI) scores, Patient Acceptable Symptomatic State (PASS), surgical clinical outcomes, and complications were collected and compared. Chi-square tests and independent t-tests were used for categorical and continuous variables, respectively. Results: A total of 127 patients were analyzed, with 32 PHQ2(+) and 95 PHQ2(−). The PHQ2(+) group had a lower proportion responding “yes” to PASS preoperatively (6.5 % vs. 25.3 %, p = 0.03), at 9 months (47.4 % vs. 72.4 %, p = 0.05), and 12 months postoperatively (42.9 % vs 79.5 %, p = 0.009). PHQ2(+) reported worse PROMIS-PI scores preoperatively, at 6 months, and at 9 months. The PHQ2(+) group reported worse PROMIS-PF preoperatively, at 6 months, at and 12 months. The PHQ2(+) group had worse IKDC scores preoperatively at 9 months and at 12 months. Those screening positive for depression also demonstrated a higher incidence of postoperative complications (34.4 % vs. 9.5 %, p = 0.001) and reoperation rates (21.9 % vs. 4.2 %; p = 0.002). Conclusion: A brief preoperative survey, such as the PHQ-2, can provide prognostic value for patient outcomes after ACLR. Level of evidence: III-Retrospective cohort study.

Orthopedics/Bone and Joint Center
Chatterji R, Fisher BT, Arapovic A, Xing Y, and Wiater JM. Serum Metal Ion Levels in Patients with Failed Total Shoulder Arthroplasty. *J Shoulder Elbow Surg* 2025; Epub ahead of print. PMID: 40032063. Full Text

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BACKGROUND: Shoulder arthroplasty systems are transitioning towards modular prosthesis options with the goal of reducing complication profiles and increasing range of motion. Modularity may increase the potential for fretting, corrosion, and subsequent release of metal ions. The purpose of this study was to identify associations between implant designs, metallurgy, patient characteristics, and serum metal ion levels in patients undergoing revision shoulder arthroplasty. METHODS: 51 patients that underwent revision shoulder arthroplasty were retrospectively reviewed based on prospectively collected data. All patients had serum metal ion levels (titanium, cobalt, chromium) measured in parts per billion (ppb) prior to their revision arthroplasty. Trends and correlations to serum ion levels were examined based on implant materials, number of modular components, and patient characteristics. RESULTS: 21 patients had prior anatomic total shoulder arthroplasty (ATSA) and 30 had prior reverse total shoulder arthroplasty (RTSA). The average age at primary arthroplasty was 64.7 years (49.0-84.0). The average term of implant was 4.83 years (0.18-21.0). 46 patients (90%) had titanium based humeral stems. 21 (100 %) ATSA humeral heads were comprised of cobalt chrome. 5 patients with prior ATSA had hybrid titanium and polyethylene glenoid components. In those with RTSA, 30 (100 %) had glenoid components composed of titanium baseplates and cobalt chrome glenospheres. Titanium ion levels were significantly higher in patients with greater than 7 total modular components (12.6 vs. 6.09 ppb, p=0.008). Titanium ion levels were significantly higher in patients with greater than 4 modular components when excluding screws (12.1 vs. 5.06, p = 0.038). The number of modular components did not have a statistically significant effect on cobalt or chromium serum ion levels. Patients with intraoperative metallosis during revision surgery had titanium ion levels 10.51 units higher on average (p = 0.009) than those without metallosis. There was no difference in titanium (p=0.63), cobalt (p=0.29), or chromium (p=0.58) levels in those patients with a proven infection compared to those without. CONCLUSIONS: Increasing modularity in primary TSA should be weighed with the potential for increased serum metal ion levels, particularly titanium. While the systemic effects of elevated serum titanium remain largely unknown, it may be a predictor for occult corrosion or need for revision. Metallosis poses challenges in the revision setting; however, the implications of increased serum metal ion levels on clinical outcomes after revision shoulder arthroplasty requires further studies.

Orthopedics/Bone and Joint Center

Chauhan D, **DeYoung JK**, **Goodrich E**, Templeton K, and **Day CS**. Gender-Based Disparities in Academic Orthopaedic Surgery Physician Compensation in 2023. *J Am Acad Orthop Surg* 2025; Epub ahead of print. PMID: 40073068. Full Text

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BACKGROUND: Orthopaedic surgery remains one of the least diverse specialties in medicine. Parity in opportunity and recognition are key factors in attracting and retaining a diverse group of individuals in the field. The primary purpose of this study was to assess gender-based discrepancies in total salary compensation by rank for academic orthopaedic surgery faculty. METHODS: Aggregate data were obtained from the Association of American Medical Colleges for fiscal year 2023. Mean compensation was compared for orthopaedic surgery faculty and total surgery faculty at all academic ranks based on

gender and race. RESULTS: Men received markedly higher total compensation for all ranks except chair within orthopaedic surgery. At the instructor level, men earned an average annual income of $554,245 while women received $229,204, demonstrating a significant pay gap (P = 0.0019). At the assistant professor (men: $628,346; women: $475,857), associate professor (men: $732,381; women: $575,877), and professor (men: $743,822; women: $472,140) levels, there existed significant pay disparities (P < 0.0001 for all three academic levels, respectively). At the chief position, men earned an average of $1,185,873 annually while women received $596,270 (P = 0.0006). Aggregate data for other surgical specialties demonstrated similar results, with women receiving lower total compensation at all ranks compared with men. CONCLUSION: This analysis of the 2023 American Medical Colleges Faculty Salary Report demonstrates a notable pay differential between men and women in orthopaedic surgery and surgical specialties, in general, across multiple academic levels including instructor, assistant professor, associate professor, professor, and chief of division. Although there has been increasing awareness of gender-based compensation disparities within surgical specialties, particularly in orthopaedic surgery, these disparities are still clearly present.

Orthopedics/Bone and Joint Center

Harley JD, **Braman JP**, Harrison AK, and Rao AJ. A Novel Process to Reduce the Cost of Admission for Treatment of Infected Shoulder Arthroplasty. *J Shoulder Elbow Surg* 2025; Epub ahead of print. PMID: 40120640. Full Text

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BACKGROUND: With the rapidly increasing volume of total joint arthroplasty (TJA) procedures, the incidence of periprosthetic joint infection (PJI) and its associated economic burden are expected to rise. Two-stage reimplantation, a common strategy for PJI management, is costly, as it requires multiple surgeries and hospitalizations, with total costs ranging from $35,000 to $42,000. Given the long hospital stays required for these patients, a quality improvement project was undertaken at the authors' institution to reduce admission costs (COA) and length of stay (LOS). METHODS: We conducted a retrospective review of patients treated for PJI of the shoulder at a single hospital within a large health system. Patients were included if they had a biopsy-proven shoulder PJI treated with one of two protocols: a conventional, inpatient focused approach, or a new, outpatient focused approach. Conventional management involved prosthesis explantation with intraoperative cultures, antibiotic spacer placement, inpatient infectious disease (ID) consultation, and inpatient peripherally inserted central catheter (PICC) placement. The new protocol consisted of outpatient ID clinic referral and PICC placement prior to explantation and spacer placement. COA and LOS were compared between the two groups. RESULTS: 16 patients were included, 8 in each group. Patients managed with the outpatient focused protocol had a significantly reduced COA ($17,711 ± 4078) compared to the conventional protocol ($24,233 ± 4,967) with a mean difference of $6521, representing a 26.9% cost reduction per patient (p = 0.006). LOS was significantly reduced in the outpatient focused group (Median: 1.35 days, IQR: 1.21-1.89) compared to the conventional protocol group (Median: 2.52 days, IQR: 1.81-3.21) (U = 10.50, Z = -2.26, p = 0.024). CONCLUSIONS: The pilot quality improvement initiative resulted in a 27% reduction in COA and a significantly reduced LOS for patients with shoulder PJI. This has broad implications across orthopedics for the management of periprosthetic joint replacement and potential for tremendous impact of reducing health care costs.

Orthopedics/Bone and Joint Center

Jildeh TR, and **Castle JP**. Establishing a Successful Research Infrastructure for Orthopaedic Surgery Residents. *J Am Acad Orthop Surg* 2025; 33(6):e319-e326. PMID: 39820193. Full Text

Research among orthopaedic surgery residents provides numerous benefits, which include but are not limited to development of critical thinking skills, greater understanding of study design and statistical

analysis, strengthened fellowship applications, networking, and the ability to practice evidence based medicine. Research has been increasingly emphasized among orthopaedic surgery residency directors, and residency programs have uniformly implemented protected research time into their formal clinical training. Despite this, there are few resources describing the ability to conduct research effectively during residency. The purpose of this review is to provide an outline for implementing a successful, productive, high-output, resident-centric, research infrastructure leveraging resources available at clinical orthopaedic surgery residencies.

Orthopedics/Bone and Joint Center

Jurayj A, **Nerys-Figueroa J**, Espinal E, **Gaudiani MA**, **Baes T**, **Mahylis J**, and **Muh S**. Evaluating if ChatGPT Can Answer Common Patient Questions Compared With OrthoInfo Regarding Rotator Cuff Tears. *J Am Acad Orthop Surg Glob Res Rev* 2025; 9(3). PMID: 40080671. Full Text

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PURPOSE: To evaluate ChatGPT's (OpenAI) ability to provide accurate, appropriate, and readable responses to common patient questions about rotator cuff tears. METHODS: Eight questions from the OrthoInfo rotator cuff tear web page were input into ChatGPT at two levels: standard and at a sixth-grade reading level. Five orthopaedic surgeons assessed the accuracy and appropriateness of responses using a Likert scale, and the Flesch-Kincaid Grade Level measured readability. Results were analyzed with a paired Student t-test. RESULTS: Standard ChatGPT responses scored higher in accuracy (4.7 ± 0.47 vs. 3.6 ± 0.76; $P < 0.001$) and appropriateness (4.5 ± 0.57 vs. 3.7 ± 0.98; $P < 0.001$) compared with sixth-grade responses. However, standard ChatGPT responses were less accurate (4.7 ± 0.47 vs. 5.0 ± 0.0; $P = 0.004$) and appropriate (4.5 ± 0.57 vs. 5.0 ± 0.0; $P = 0.016$) when compared with OrthoInfo responses. OrthoInfo responses were also notably better than sixth-grade responses in both accuracy and appropriateness ($P < 0.001$). Standard responses had a higher Flesch-Kincaid grade level compared with both OrthoInfo and sixth-grade responses ($P < 0.001$). CONCLUSION: Standard ChatGPT responses were less accurate and appropriate, with worse readability compared with OrthoInfo responses. Despite being easier to read, sixth-grade level ChatGPT responses compromised on accuracy and appropriateness. At this time, ChatGPT is not recommended as a standalone source for patient information on rotator cuff tears but may supplement information provided by orthopaedic surgeons.

Orthopedics/Bone and Joint Center

Weaver MJ, Khan U, **Puri S**, Lamiha S, **Swanson K**, **Rababa I**, **Olson A**, and **Best B**. Risk factors associated with surgical site infection after internal fixation of ballistic diaphyseal fractures. *Injury* 2025; 56(6):112302. PMID: 40163958. Full Text

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OBJECTIVES: Management of civilian gunshot wound (GSW) fractures is controversial, with limited data on infection risk and controversy regarding treatment. While lower-energy GSWs are considered lower risk than other open fractures, complication rates remain high. This study aimed to identify risk factors for infection in operatively treated ballistic fractures. METHODS: After institutional review board approval, we

identified 2136 GSW-related fractures from 01/01/2012 to 12/31/2021 at our level one trauma center. After excluding articular, hand, foot, injuries through viscera and pre-existing infections, 110 patients with 125 long bone fractures were retrospectively reviewed. The primary outcome was infection requiring reoperation. Statistical analysis included Mann-Whitney U, T-tests, Pearson's Chi-square, ROC analysis, and Youden's index. RESULTS: Sixteen patients (14.5 %) developed infections requiring reoperation. The cohort had a mean age of 30 years, 90 % male, BMI 27.7 ± 7.2 kg/m², Charlson comorbidity index <1, and 37 % smokers. Increased infection risk was associated with admission glucose ($p < 0.001$) and length of stay ($p < 0.001$). Admission glucose >156 mg/dL increased odds of infection sixfold (OR 6.1, 95 % CI 2.0-19.0), while a hospital stay >10 days increased odds of infection twentyfold (OR 21.1, 95 % CI 5.3-82.7). Transfusion ($p = 0.004$), abdominal ($p = 0.007$), and chest trauma ($p = 0.010$) also correlated with infection risk. No significant associations were found with nicotine use, Charlson comorbidity index, or BMI. CONCLUSIONS: Operatively treated long bone injuries had a 14.5 % infection rate. Elevated admission glucose and prolonged hospital stay significantly increased infection risk, particularly in polytrauma patients. Identifying high-risk patients, promoting early mobilization, and ensuring glycemic control may help reduce infections. Further research is needed to develop targeted prevention strategies. LEVEL OF EVIDENCE: 3 (Retrospective Comparative Study).

Otolaryngology – Head and Neck Surgery

Bernacchi V, Hirko K, **Boakye EA**, **Tam S**, Lucas T, and Moss JL. Lung cancer disparities in rural, persistent poverty counties: a secondary data analysis. *BMC Public Health* 2025; 25(1):878. PMID: 40045229. Full Text

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BACKGROUND: In the US, lung cancer burden is greater in counties that are either rural or in persistent poverty. This study examined lung cancer risk (e.g., smoking), incidence, and mortality across four county types defined by cross-classification of rurality and persistent poverty. METHODS: We conducted a secondary analysis of county characteristics and lung cancer risk, incidence and mortality. We used data from USDA to classify counties according to rurality (using rural-urban continuum codes) and persistent poverty (i.e., 20% + of residents living below the poverty line for 30 + years). We used publicly-available data to calculate mean county-level prevalence of smoking among adults (in 2019), lung cancer incidence (2015-2019), and lung cancer mortality (2015-2019) across county types. Beta and binomial regression models assessed differences in smoking, lung cancer incidence, and lung cancer mortality by rurality and persistent poverty. RESULTS: Among U.S. counties, 1,115 were urban, non-persistent poverty, 1,675 were rural, non-persistent poverty, 52 were urban, persistent poverty, and 301 were rural, persistent poverty. Smoking, lung cancer incidence, and lung cancer mortality were higher in rural counties and in persistent poverty counties than in their comparison counties. Counties that were both rural and persistent poverty had the highest rates of smoking, lung cancer incidence, and lung cancer mortality. Persistent poverty and rurality interacted in their relationship with smoking prevalence ($p < 0.01$), and lung cancer mortality ($p < 0.10$). CONCLUSIONS: Smoking, lung cancer incidence, and lung cancer mortality are highest in counties that are both rural and persistent poverty, suggesting an urgent need to develop targeted lung cancer interventions in these communities.

Otolaryngology – Head and Neck Surgery

Donaldson LB, and **Deeb RH**. Office-Based Facial Plastic Surgery. *Otolaryngol Clin North Am* 2025; Epub ahead of print. PMID: 40121164. Full Text

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Office-based facial plastic surgery involves a wide array of procedures from esthetic surgeries such as facelifting and blepharoplasty to reconstructive procedures including scar revision and local tissue flaps. The cornerstone to a successful outcome is a thorough history and physical examination with an emphasis on assessment of a patient's ability to tolerate an office-based procedure. Room set-up, equipment, and personnel play an especially important role in these procedures. Anesthetic considerations as well as a heightened attention to safety are paramount in ensuring an excellent patient experience and an optimal result.

Otolaryngology – Head and Neck Surgery

Graboyes EM, Maurer SN, Kistner-Griffin E, Armeson K, Starr E, McLeod T, Balliet WE, Doenges J, **Slavin-Spenny O**, Vanderlan JR, Day A, Pipkorn P, Puram SV, **Tam SH**, Ruggiero KJ, and Sterba KR. Protocol for a multisite, parallel-group, randomized clinical trial comparing a brief tele-cognitive behavioral therapy intervention (BRIGHT) with attention control for the reduction of body image-related distress among head and neck cancer survivors. *Contemp Clin Trials* 2025; 153:107888. PMID: 40139457. Full Text

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One in four head and neck cancer (HNC) survivors experience clinically significant body image distress (BID), a devastating psychosocial morbidity that adversely affects quality of life. To date, effective interventions for these patients are lacking. BRIGHT (Building a Renewed ImaGe after Head and neck cancer Treatment), a brief cognitive behavioral treatment (CBT), has shown potential efficacy as a novel treatment paradigm for HNC survivors with BID. The primary objective of this randomized clinical trial (RCT) is to test the hypothesis that BRIGHT improves BID among HNC survivors relative to an Attention Control (AC) intervention. In this multisite RCT, N = 180 HNC survivors with BID will be randomized 1:1 to six weeks of BRIGHT or AC of dose and delivery-matched survivorship education. Outcomes are

assessed at baseline and 2, 3, 6, and 9-months post-randomization. The primary endpoint is the IMAGE-HN (Inventory to Measure and Assess imaGe disturbancE-Head and Neck) score, a validated patient-reported outcome of HNC-related BID. Secondary endpoints include the HN Shame and Stigma Scale, the PROMIS SF v1.0-Depression 8a, Anxiety 8a, and Ability to Participate in Social Activities 8a, the Beck Scale for Suicidal Ideation, and the EORTC QLQ-HN35 Trouble with Social Eating and Trouble with Social Contact subscales. The trial will also evaluate whether the effect of BRIGHT on BID is mediated through improvements in automatic thinking and body image coping strategies. Findings from this multisite RCT will provide a rigorous test of the efficacy of BRIGHT as the first evidence-based strategy to manage BID among HNC survivors. TRIAL REGISTRATION ID: NCT05442957.

Otolaryngology – Head and Neck Surgery
Grewal JS, Bouzaher MH, Mojica CR, Shokri T, and Ducic Y. Open Treatment of Mandible Angle Fractures and the Role for Maxillomandibular Fixation. *J Craniofac Surg* 2025; Epub ahead of print. PMID: 40029620. Full Text

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BACKGROUND: Maxillomandibular fixation (MMF) remains a mainstay in the treatment algorithm of bony injuries involving the lower facial skeleton to help restore premorbid occlusion. PURPOSE: To compare postoperative open reduction and internal fixation outcomes in dentate patients with noncomminuted, isolated angle fractures of the mandible between patients that underwent postoperative MMF and those who did not. METHODS: Retrospective review of 224 patients treated for isolated, noncomminuted mandible angle fractures between January 1997 and December 2023. Patients were either kept in occlusion with intraoperative maxillomandibular (MMF) or with bimanual reduction. Patients either remained in MMF or not postoperatively. RESULTS: There was not a significant overall association of surgery group on complications (P=0.44). The odds of complications were lower for the intraoperative bimanual reduction group without MMF compared with patients that underwent intraoperative and postoperative MMF (odds ratio=0.48, P=0.26). CONCLUSION: This study describes similar surgical outcomes after open reduction and internal fixation of isolated, noncomminuted mandible angle fractures with or without postoperative MMF. This study helps show that in appropriately selected cases, postoperative MMF may not be necessary in this specific mandible fracture pattern.

Otolaryngology – Head and Neck Surgery
Kondamuri NS, Dedhia RC, and **Yaremchuk KL**. Ten-Year Update: The State of Sleep Surgery Training for Otolaryngologists. *Otolaryngol Head Neck Surg* 2025; Epub ahead of print. PMID: 40134210. Full Text

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A decade ago, the field of sleep surgery was on the brink of extinction after changes in certification requirements. Though improving, many otolaryngology programs still do not have dedicated sleep faculty, and residents feel they have not received adequate sleep medicine experience. The field of sleep surgery can expand on a pipeline of sleep-trained otolaryngology fellows by increasing residency exposure to faculty with subcertification in sleep medicine and increasing visibility of fellowship opportunities. Mini-mentorship programs for residents without sleep programs/faculty and inclusion of sleep surgery procedures as key indicator cases during residency may increase interest and exposure to sleep procedures. Maintaining current lists of sleep medicine fellowship programs that include Otolaryngology-Head and Neck Surgery faculty is critical to ensuring accessibility and transparency. Without intervention, the field may be limited to selecting sleep surgery fellows from programs with established sleep surgeons and/or training programs, creating a narrow path for future growth.

Otolaryngology – Head and Neck Surgery

Mackie H, Eide JG, Yassin-Kassab A, **Wilson C**, **Ray A**, **Robin AM**, **Asmaro K**, **Rock JP**, and **Craig JR**. Rapid Intrathecal Fluorescein Injection During Cerebrospinal Fluid Leak Repair Is Safe and Effective. *Laryngoscope* 2025; Epub ahead of print. PMID: 40110730. Full Text

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OBJECTIVE: Intrathecal fluorescein (IF) is effective for localizing nasal cerebrospinal fluid (CSF) leaks along the skull base during endoscopic exploration, with largest studies reporting sensitivities ranging from 66%-93%. Due to reports of intraoperative and postoperative neurologic complications such as seizures and paralysis, surgeons often dilute the fluorescein and inject it intrathecally slowly over a variable amount of time. However, no study has assessed whether rapid IF administration causes the aforementioned risks or whether it affects its accuracy in identifying CSF leaks intraoperatively. METHODS: A prospective study was conducted from 2015 to 2024, where all patients undergoing endoscopic exploration and/or repair of CSF rhinorrhea had 0.1 mL of 10% fluorescein (10 mg) mixed with 3-5 mL of patients' CSF injected rapidly via the lumbar drain over a few seconds. RESULTS: Of the 82 included patients, the mean age was 53.8 ± 15.2 years, and 84% were female. Sixty-nine patients underwent successful endoscopic CSF leak repairs, and 13 had negative endoscopic explorations. Rapid IF injection was 80% sensitive (20% false negative rate) and 100% specific for identifying CSF leaks, and it caused no seizures, paralysis, or other neurologic complications. CONCLUSION: Compared to prior reports of slow low-dose IF injection for CSF leak localization, rapid IF injection yielded similar efficacy (80% sensitivity) with no IF-related complications. Rapid IF injection was safe and effective but should be corroborated by future studies.

Otolaryngology – Head and Neck Surgery

Mayerhoff R, and Jahan-Parwar B. Implementation of Office-Based Procedures in Large Institutions. *Otolaryngol Clin North Am* 2025; Epub ahead of print. PMID: 40069055. Full Text

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This article discusses the background of office-based procedures in otolaryngology, including definitions of important terms related to office-based procedures. Using a framework of safety, functional logistics, and economics, this article can serve as a guide for how to implement office-based procedures at a large institution.

Pathology and Laboratory Medicine

Bui J, **Chalom T**, **Nathanson SD**, **Schwartz TL**, **Hunt K**, **Alkhoory W**, and **Xu Z**. Invasive ductal carcinoma at the site of a cosmetic nipple piercing. *J Surg Case Rep* 2025; 2025(3):rjaf132. PMID: 40079036. Full Text

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We report a young female patient diagnosed with an invasive ductal carcinoma at the site of a prior cosmetic nipple piercing. She had no significant familial, genetic, or other carcinogenic risk factors to account for her presentation. A review of the literature confirms that trauma can occasionally be associated with invasive breast cancer, but such a connection has not previously been related to nipple piercing procedures.

Pathology and Laboratory Medicine
Ghirardelli Smith OC, Tsai AK, Zhong M, **Dejban P**, Nelson AC, Dolan M, Antonarakis ES, and Murugan P. Case Report: Prepubertal-type testicular teratoma with local metastasis in a postpubertal patient. *Front Oncol* 2025; 15:1547258. PMID: 40071092. Full Text

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INTRODUCTION: We report for the first time a case of a postpubertal patient presenting with a metastatic prepubertal-type testicular teratoma. CASE DISCUSSION: A 29-year-old male with a history of corrected unilateral cryptorchidism presented with progressive bilateral lower extremity edema. Imaging revealed an inferior vena cava thrombus associated with a complex mass. A left testicular ultrasound identified a solid lesion suggestive of a germ cell tumor, leading to a left radical orchiectomy, which revealed a mature pure teratoma with no evidence of germ cell neoplasia in situ (GCNIS). Excision of the retroperitoneal mass confirmed the presence of mature teratomatous elements without evidence of non-teratomatous germ cell tumor elements or cytological atypia. Fluorescence in situ hybridization (FISH) showed no evidence of gain of 12p, and next-generation sequencing showed no alterations in genes known to be associated with GCT. CONCLUSION: This case illustrates that pure mature teratomas lacking chromosome 12p abnormalities, GCNIS, and other dysgenetic features, occurring in postpubertal males, cannot invariably be classified into the benign prepubertal-type teratoma category. Contrary to current paradigm, in rare cases these may represent tumors with metastatic potential.

Pathology and Laboratory Medicine
Kulkarni R, Zeine E, **Potugari B**, **Gadgeel S**, **Montecalvo J**, and **Rous FA**. Small Cell Lung Cancer With de novo BRAF V600E Mutation and Durable Response to Targeted Therapy: A Case Report. *Clin Lung Cancer* 2025; Epub ahead of print. PMID: 40133188. Full Text

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Pathology and Laboratory Medicine
Loveless IM, Kemp SB, **Hartway KM**, Mitchell JT, Wu Y, **Zwernik SD**, **Salas-Escabillas DJ**, **Brender S**, **George M**, **Makinwa Y**, **Stockdale T**, **Gartrelle K**, **Reddy RG**, **Long DW**, **Wombwell A**, **Clark JM**, **Levin AM**, **Kwon D**, **Huang L**, **Francescone R**, **Vendramini-Costa DB**, Stanger BZ, Alessio A, Waters AM, Cui Y, Fertig EJ, Kagohara LT, **Theisen B**, **Crawford HC**, and **Steele NG**. Human Pancreatic Cancer Single-Cell Atlas Reveals Association of CXCL10+ Fibroblasts and Basal Subtype Tumor Cells. *Clin Cancer Res* 2025; 31(4):756-772. PMID: 39636224. Full Text

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PURPOSE: Pancreatic ductal adenocarcinoma (PDAC) patients with tumors enriched for the basal-like molecular subtype exhibit enhanced resistance to standard-of-care treatments and have significantly worse overall survival compared with patients with classic subtype-enriched tumors. It is important to develop genomic resources, enabling identification of novel putative targets in a statistically rigorous manner. EXPERIMENTAL DESIGN: We compiled a single-cell RNA sequencing (scRNA-seq) atlas of the human pancreas with 229 patient samples aggregated from publicly available raw data. We mapped cell type-specific scRNA-seq gene signatures in bulk RNA-seq (n = 744) and spatial transcriptomics (ST; n = 22) and performed validation using multiplex immunostaining. RESULTS: Analysis of tumor cells from our scRNA-seq atlas revealed nine distinct populations, two of which aligned with the basal subtype, correlating with worse overall survival in bulk RNA-seq. Deconvolution identified one of the basal populations to be the predominant tumor subtype in nondissociated ST tissues and in vitro tumor cell and patient-derived organoid lines. We discovered a novel enrichment and spatial association of CXCL10+ cancer-associated fibroblasts with basal tumor cells. We identified that besides immune cells, ductal cells also express CXCR3, the receptor for CXCL10, suggesting a relationship between these cell types in the PDAC tumor microenvironment. CONCLUSIONS: We show that our scRNA-seq atlas (700,000 cells), integrated with ST data, has increased statistical power and is a powerful resource, allowing for expansion of current subtyping paradigms in PDAC. We uncovered a novel signaling niche marked by CXCL10+ cancer-associated fibroblasts and basal tumor cells that could be explored for future targeted therapies.

Pathology and Laboratory Medicine

Veve MP, **Kenney RM**, **Aljundi AM**, Dierker MS, Athans V, **Shallal AB**, and Patel N. Multicenter, retrospective cohort study of antimycobacterial treatment-related harms among patients with non-tuberculosis Mycobacterium infections in the United States. *Antimicrob Agents Chemother* 2025; Epub ahead of print. PMID: 40035548. Full Text

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Non-tuberculosis mycobacteria (NTM) are extensively drug-resistant organisms that require long-term therapy. The study purpose was to quantify the incidence of and risk factors for antimycobacterial-associated adverse drug events (ADEs) in persons with NTM infections receiving outpatient therapy. A multicenter, retrospective cohort was performed of persons with NTM infections who received antimycobacterial treatment from 2013 to 2024. Inclusion criteria were age ≥18 years, ≥1 month of outpatient treatment, and ≥1 follow-up outpatient visit within 3 months of index encounter. Mycobacterium avium complex and Mycobacterium tuberculosis complex were excluded. The primary outcome was development of pre-specified treatment-related ADE or acute kidney injury (AKI), thrombocytopenia, and/or Clostridioides difficile infection (CDI) through 12 months of therapy. Secondary outcomes included therapy discontinuation due to any treatment-related ADEs. Two hundred patients were included: 14% developed a pre-specified ADE. Mycobacterium abscessus (29%) was the most common pathogen; most initial regimens included a macrolide (54%), systemic aminoglycoside (24%), β-lactam (24%), or tetracycline derivative (22%). The most common pre-specified ADEs were thrombocytopenia (9%), AKI (8%), and CDI (<1%). The median (IQR) time-to-ADE was 25 (18-38) days from initial outpatient regimen; patients who received aminoglycoside- or oxazolidinone-based therapies were more likely to develop a pre-specified ADE (adjOR, 3.9; 95% CI, 1.7-9.2). Therapy discontinuation due to any ADE occurred in 35% of patients; the median (IQR) time-to-any ADE was 32 (21-58) days. ADEs in persons with NTM infections are common and occur near the first month of outpatient treatment. Intensified monitoring and/or use of more tolerable antimycobacterial regimens early in treatment may be an appropriate approach to avoid harms.Treatment of non-tuberculosis mycobacteria is complicated by adverse drug events (ADEs). This work quantified the incidence and time course of pre-determined, clinically relevant ADEs (acute kidney injury, thrombocytopenia, and C. difficile infection), which occurred in 14% of patients within 30 days of outpatient treatment.

Pathology and Laboratory Medicine

Wang M, **Liu Z**, **Wang W**, **Chopp M**, **Millman M**, **Li Y**, **Cepparulo P**, **Kemper A**, **Li C**, **Zhang L**, **Zhang Y**, and **Zhang ZG**. Enhanced Small Extracellular Vesicle Uptake by Activated Interneurons Improves Stroke Recovery in Mice. *J Extracell Biol* 2025; 4(3):e70036. PMID: 40134760. Full Text

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Neuronal circuitry remodelling, which comprises excitatory and inhibitory neurons, is critical for improving neurological outcomes after a stroke. Preclinical studies have shown that small extracellular vesicles (sEVs) have a therapeutic effect on stroke recovery. However, it is highly challenging to use sEVs to specifically target individual neuronal populations to enhance neuronal circuitry remodelling after stroke. In the present study, using a chemogenetic approach to specifically activate peri-infarct cortical interneurons in combination with the administration of sEVs derived from cerebral endothelial cells (CEC-sEVs), we showed that the CEC-sEVs were preferentially taken up by the activated neurons, leading to significant improvement of functional outcome after stroke, which was associated with augmentation of peri-infarct cortical axonal/dendritic outgrowth and of axonal remodelling of the corticospinal tract. The ultrastructural and Western blot analyses revealed that neurons with internalization of CEC-sEVs exhibited significantly reduced numbers of damaged mitochondria and proteins that mediate dysfunctional mitochondria, respectively. Together, these data indicate that the augmented uptake of CEC-sEVs by activated peri-infarct cortical interneurons facilitates neuronal circuitry remodelling and functional recovery after stroke, which has the potential to be a novel therapy for improving stroke recovery.

Pharmacy

Ammar A, **Edwin SB**, Whitney R, **Lipari M**, and **Giuliano C**. Updates in chronic kidney disease management: A systematic review. *Pharmacotherapy* 2025; Epub ahead of print. PMID: 40152479. Full Text

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Chronic kidney disease (CKD) is a significant global health challenge that impacts both patients and the health care system. This systematic review aims to evaluate the efficacy and safety of emerging therapeutic strategies for CKD management, including sodium-glucose cotransporter 2 inhibitors (SGLT2i), glucagon-like peptide-1 receptor agonists (GLP-1RA), finerenone, sacubitril/valsartan, and potassium binders. We conducted searches in databases including PubMed, Scopus, CINAHL Complete, and Web of Science Core Collection to identify experimental and observational studies pertaining to each of these agents. Included studies were those that enrolled adult patients with CKD who evaluated SGLT2i, GLP-1RA, finerenone, sacubitril/valsartan, and potassium binders compared to other medications or placebo and evaluated renal-related outcomes as a primary or secondary outcome. Methodological quality and risk of bias were assessed using the Cochrane Risk of Bias (version 2) tool for experimental studies and ROBINS-I for observational studies. After screening 2135 unique studies, 138 studies were eligible for this review. These studies describe a substantial and growing body of evidence focused on improving the management of CKD beyond renin-angiotensin system inhibitors (RASi), such as angiotensin-converting enzyme inhibitors (ACEi) and angiotensin receptor blockers (ARBs). Currently, SGLT2i have demonstrated consistent benefits with large effect sizes in preventing the progression of CKD, solidifying this class as a first-line treatment along with RASi. Subsequent consideration for GLP-1RA, finerenone, and sacubitril/valsartan should be dependent on patient-specific comorbidities, while potassium binders may allow for longer use of RASi.

Pharmacy

Arena CJ, **Van Horn BT**, **Kenney RM**, **Parke DM**, **Suleyman G**, **Davis SL**, and **Veve MP**. A Retrospective Cohort Study of Oral Antimicrobial Therapy Offers in Hospitalized People Who Inject Drugs Who Elect for Self-directed Discharge. *J Addict Med* 2025; Epub ahead of print. PMID: 40096193. Full Text

OBJECTIVES: To evaluate infection management in people who inject drugs (PWID) who elect for self-directed discharge (SDD) and to identify characteristics associated with an oral antimicrobial therapy offer (OATO). METHODS: This was a retrospective cohort of hospitalized adult PWID with an injection drug use (IDU)-related infection who elected for SDD between January 1, 2014, to January 31, 2024, at a five-hospital health system in southeast Michigan. Patients were excluded if they were hospitalized for <24 hours or if antimicrobial treatment was completed before SDD. The primary outcome was the proportion of patients with an OATO at or before SDD. Secondary outcomes at 30 days included retreatment, infection-related readmission, and all-cause mortality. RESULTS: One hundred fifty patients were included; 55 (37%) received an OATO, 95 (63%) did not receive an offer. Patient outcomes were not different between the OATO and no offer groups: infection retreatment 19 (34%) versus 32 (34%); infection-related readmission 14 (25%) versus 31 (33%); and all-cause mortality 1 (2%) versus 3 (3%). In multivariable logistic regression, variables independently associated with OATO included prescribing/continuing medications for opioid use disorder (MOUD) (adjusted odds ratio [aOR], 2.8; 95% CI: 1.36-5.92), infection source control (aOR, 2.3; 95% CI: 1.10-4.84), and early-career clinician care (aOR, 2.8; 95% CI: 1.01-7.89). CONCLUSIONS: Most hospitalized PWID with IDU-related infections with SDD did not receive an OATO. Early career clinicians more commonly offered oral antimicrobials in PWID with less complicated infection types. Standardizing OATO in PWID at risk for SDD should be considered as a future direction to improve health outcomes.

Pharmacy

Veve MP, **Kenney RM**, **Aljundi AM**, Dierker MS, Athans V, **Shallal AB**, and Patel N. Multicenter, retrospective cohort study of antimycobacterial treatment-related harms among patients with non-tuberculosis Mycobacterium infections in the United States. *Antimicrob Agents Chemother* 2025; Epub ahead of print. PMID: 40035548. Full Text

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Non-tuberculosis mycobacteria (NTM) are extensively drug-resistant organisms that require long-term therapy. The study purpose was to quantify the incidence of and risk factors for antimycobacterial-associated adverse drug events (ADEs) in persons with NTM infections receiving outpatient therapy. A multicenter, retrospective cohort was performed of persons with NTM infections who received antimycobacterial treatment from 2013 to 2024. Inclusion criteria were age ≥18 years, ≥1 month of outpatient treatment, and ≥1 follow-up outpatient visit within 3 months of index encounter. Mycobacterium avium complex and Mycobacterium tuberculosis complex were excluded. The primary outcome was development of pre-specified treatment-related ADE or acute kidney injury (AKI), thrombocytopenia, and/or Clostridioides difficile infection (CDI) through 12 months of therapy. Secondary outcomes included therapy discontinuation due to any treatment-related ADEs. Two hundred patients were included: 14% developed a pre-specified ADE. Mycobacterium abscessus (29%) was the most common pathogen; most initial regimens included a macrolide (54%), systemic aminoglycoside (24%), β-lactam (24%), or tetracycline derivative (22%). The most common pre-specified ADEs were thrombocytopenia (9%), AKI (8%), and CDI (<1%). The median (IQR) time-to-ADE was 25 (18-38) days from initial outpatient regimen; patients who received aminoglycoside- or oxazolidinone-based therapies were more likely to develop a pre-specified ADE (adjOR, 3.9; 95% CI, 1.7-9.2). Therapy discontinuation due to any ADE occurred in 35% of patients; the median (IQR) time-to-any ADE was 32 (21-58) days. ADEs in persons with NTM infections are common and occur near the first month of outpatient treatment. Intensified monitoring and/or use of more tolerable antimycobacterial regimens early in treatment may be an appropriate approach to avoid harms.Treatment of non-tuberculosis mycobacteria is complicated by adverse drug events (ADEs). This work quantified the incidence and time course of pre-determined, clinically relevant ADEs (acute kidney injury, thrombocytopenia, and C. difficile infection), which occurred in 14% of patients within 30 days of outpatient treatment.

Plastic Surgery

Donaldson LB, and **Deeb RH**. Office-Based Facial Plastic Surgery. *Otolaryngol Clin North Am* 2025; Epub ahead of print. PMID: 40121164. Full Text

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Office-based facial plastic surgery involves a wide array of procedures from esthetic surgeries such as facelifting and blepharoplasty to reconstructive procedures including scar revision and local tissue flaps. The cornerstone to a successful outcome is a thorough history and physical examination with an emphasis on assessment of a patient's ability to tolerate an office-based procedure. Room set-up, equipment, and personnel play an especially important role in these procedures. Anesthetic considerations as well as a heightened attention to safety are paramount in ensuring an excellent patient experience and an optimal result.

Public Health Sciences

Geller R, Wesselink AK, Claus Henn B, Upson K, Vinceti M, Harmon QE, Baird DD, **Wegienka G**, and **Wise LA**. A prospective ultrasound study of whole blood metals and incidence of uterine leiomyomata. *Environ Health Perspect* 2025; Epub ahead of print. PMID: 40063901. Full Text

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BACKGROUND: Uterine leiomyomata (UL), hormone-dependent neoplasms, are a major source of gynecologic morbidity. Metals are hypothesized to influence UL risk through endocrine disruption, and their effects may vary by vitamin D status. OBJECTIVE: We estimated associations of a metal mixture with incident UL, overall and by vitamin D status. METHODS: We analyzed data from the Study of Environment, Lifestyle and Fibroids, a Detroit-area prospective cohort study of 1,693 Black women aged 23-35 years. We measured concentrations of 17 metals/metalloids in whole blood and 25-hydroxyvitamin D (25[OH]D) in serum collected at baseline (2010-2012). Participants underwent ultrasonography at baseline and after 20 months to detect UL. We used Bayesian Kernel Machine Regression to estimate adjusted associations (β) of the metal mixture with probit of incident UL. We also ran Cox regression models with interaction terms to estimate incidence rate ratios (IRR) by vitamin D status. RESULTS: Among 1,132 UL-free participants at baseline, 832 (73%) had vitamin D deficiency (25[OH]D<20 ng/mL) and 117 (10%) developed UL within 20 months. Increasing all metals from their 50(th) to 75(th) percentiles was weakly positively associated with UL overall (β=0.06, 95% credible interval [CrI]: -0.03, 0.16) and among vitamin D-deficient participants (β=0.13, 95% CrI: 0.01, 0.24), driven by cadmium (overall and vitamin D-deficient) and mercury (vitamin D-deficient only). Increasing cadmium from its 25(th) to 75(th) percentile was positively associated with UL overall (β=0.03, 95% CrI: -0.05, 0.11) and among vitamin D-deficient participants (β=0.13, 95% CrI: 0.02, 0.24). In Cox models, cadmium (IRR=1.55, 95% confidence interval [CI]: 1.07, 2.24, per 1-unit increase in standardized concentration) and mercury (IRR=1.38, 95% CI: 0.99, 1.92) were positively associated with UL among vitamin D-deficient participants. DISCUSSION: The metal mixture was positively associated with incident UL, but the association was weak and imprecise. We observed a stronger association among vitamin D-deficient participants that was driven by cadmium and mercury. https://doi.org/10.1289/EHP15218.

Public Health Sciences

Gui H, Lessard CJ, Liu J, Li M, and **Adrianto I**. Editorial: Integrative genetics and multi-omics of complex human disorders. *Front Genet* 2025; 16:1574431. PMID: 40061127. Full Text

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Public Health Sciences

Kim RY, Rendle KA, Mitra N, **Neslund-Dudas C**, Greenlee RT, Honda SA, Schapira MM, **Simoff MJ**, Jeon J, Meza R, Ritzwoller DP, and Vachani A. Adherence to Annual Lung Cancer Screening and Rates of Cancer Diagnosis. *JAMA Netw Open* 2025; 8(3):e250942. PMID: 40100218. Full Text

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IMPORTANCE: Adherence to annual lung cancer screening (LCS) is a proposed quality metric for LCS programs, but data linking annual adherence to lung cancer outcomes are lacking. OBJECTIVE: To investigate annual LCS adherence rates across 2 subsequent LCS rounds among adults undergoing baseline LCS and examine the association of adherence with lung cancer diagnosis rates. DESIGN, SETTING, AND PARTICIPANTS: This retrospective cohort study included adults aged 55 to 75 years who formerly or currently smoked and underwent baseline LCS between January 1, 2015, and December 31, 2018, across 5 US health care systems in the Population-Based Research to Optimize the Screening Process-Lung Consortium. Participants with missing Lung Computed Tomography Screening Reporting & Data System scores or a lung cancer diagnosis prior to LCS initiation were excluded. Data were analyzed from October 2023 to October 2024. EXPOSURES: For negative baseline screening results, T1 and T2 screening adherence was defined as chest computed tomography (CT) between 10 and 18 months and 22 and 30 months after baseline, respectively. For positive baseline screening results, T1 and T2 adherence was defined as chest CT between 11 and 21 months and 28 and 36 months after baseline, respectively. MAIN OUTCOMES AND MEASURES: The main outcomes were annual T1 and T2 LCS adherence rates and associations between T1 and T2 screening adherence; annual incident lung cancer diagnoses in rounds T0 (0-12 months after baseline), T1 (>12 to 24 months after baseline), and T2 (>24 to 36 months after baseline); and cancer stage distribution. RESULTS: A total of 10 170 individuals received baseline LCS (median age, 65 years [IQR, 60-69 years]; 5415 [53.2%] male). During round T1, 6141 of 10 033 eligible patients (61.2% [95% CI, 60.2%-62.2%]) were adherent, and during round T2, 5028 of 9966 eligible patients (50.5% [95% CI, 49.5%-51.4%]) were adherent. T1 adherence was significantly associated with T2 adherence (adjusted relative risk, 2.40; 95% CI, 2.06-2.79). Across 36 months of follow-up, 279 patients (2.7%; 95% CI, 2.4%-3.1%) were diagnosed with lung cancer. Incident lung cancer diagnosis rates were 1.3% (95% CI, 1.1%-1.6%), 0.7% (95% CI, 0.5%-0.8%), and 0.8% (95%

CI, 0.6%-0.9%) during rounds T0, T1, and T2, respectively. Lung cancer diagnosis rates were higher among individuals who were LCS adherent vs nonadherent during both rounds T1 (59 of 6141 [1.0%; 95% CI, 0.7%-1.2%] vs 8 of 3892 [0.2%; 95% CI, 0.1%-0.4%]; P < .001) and T2 (63 of 5028 [1.3%; 95% CI, 1.0%-1.6%] vs 12 of 4938 [0.2%; 95% CI, 0.1%-0.4%]; P < .001). A greater proportion of early-stage lung cancers were diagnosed among individuals adherent to screening at T2 compared with those who were not (46 of 63 [73.0%] vs 3 of 12 [25.0%]; P = .006). CONCLUSIONS AND RELEVANCE: In this multicenter cohort study of adults undergoing LCS, screening adherence was associated with increased overall and early-stage lung cancer detection rates; however, adherence decreased annually after baseline screening, suggesting that it is an important LCS quality metric.

Public Health Sciences

Loveless IM, Kemp SB, **Hartway KM**, Mitchell JT, Wu Y, **Zwernik SD**, **Salas-Escabillas DJ**, **Brender S**, **George M**, **Makinwa Y**, **Stockdale T**, **Gartrelle K**, **Reddy RG**, **Long DW**, **Wombwell A**, **Clark JM**, **Levin AM**, **Kwon D**, **Huang L**, **Francescone R**, **Vendramini-Costa DB**, Stanger BZ, Alessio A, Waters AM, Cui Y, Fertig EJ, Kagohara LT, **Theisen B**, **Crawford HC**, and **Steele NG**. Human Pancreatic Cancer Single-Cell Atlas Reveals Association of CXCL10+ Fibroblasts and Basal Subtype Tumor Cells. *Clin Cancer Res* 2025; 31(4):756-772. PMID: 39636224. Full Text

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PURPOSE: Pancreatic ductal adenocarcinoma (PDAC) patients with tumors enriched for the basal-like molecular subtype exhibit enhanced resistance to standard-of-care treatments and have significantly worse overall survival compared with patients with classic subtype-enriched tumors. It is important to develop genomic resources, enabling identification of novel putative targets in a statistically rigorous manner. EXPERIMENTAL DESIGN: We compiled a single-cell RNA sequencing (scRNA-seq) atlas of the human pancreas with 229 patient samples aggregated from publicly available raw data. We mapped cell type-specific scRNA-seq gene signatures in bulk RNA-seq (n = 744) and spatial transcriptomics (ST; n = 22) and performed validation using multiplex immunostaining. RESULTS: Analysis of tumor cells from our scRNA-seq atlas revealed nine distinct populations, two of which aligned with the basal subtype,

correlating with worse overall survival in bulk RNA-seq. Deconvolution identified one of the basal populations to be the predominant tumor subtype in nondissociated ST tissues and in vitro tumor cell and patient-derived organoid lines. We discovered a novel enrichment and spatial association of CXCL10+ cancer-associated fibroblasts with basal tumor cells. We identified that besides immune cells, ductal cells also express CXCR3, the receptor for CXCL10, suggesting a relationship between these cell types in the PDAC tumor microenvironment. CONCLUSIONS: We show that our scRNA-seq atlas (700,000 cells), integrated with ST data, has increased statistical power and is a powerful resource, allowing for expansion of current subtyping paradigms in PDAC. We uncovered a novel signaling niche marked by CXCL10+ cancer-associated fibroblasts and basal tumor cells that could be explored for future targeted therapies.

Public Health Sciences

Mackie H, Eide JG, Yassin-Kassab A, **Wilson C**, **Ray A**, **Robin AM**, **Asmaro K**, **Rock JP**, and **Craig JR**. Rapid Intrathecal Fluorescein Injection During Cerebrospinal Fluid Leak Repair Is Safe and Effective. *Laryngoscope* 2025; Epub ahead of print. PMID: 40110730. Full Text

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OBJECTIVE: Intrathecal fluorescein (IF) is effective for localizing nasal cerebrospinal fluid (CSF) leaks along the skull base during endoscopic exploration, with largest studies reporting sensitivities ranging from 66%-93%. Due to reports of intraoperative and postoperative neurologic complications such as seizures and paralysis, surgeons often dilute the fluorescein and inject it intrathecally slowly over a variable amount of time. However, no study has assessed whether rapid IF administration causes the aforementioned risks or whether it affects its accuracy in identifying CSF leaks intraoperatively. METHODS: A prospective study was conducted from 2015 to 2024, where all patients undergoing endoscopic exploration and/or repair of CSF rhinorrhea had 0.1 mL of 10% fluorescein (10 mg) mixed with 3-5 mL of patients' CSF injected rapidly via the lumbar drain over a few seconds. RESULTS: Of the 82 included patients, the mean age was 53.8 ± 15.2 years, and 84% were female. Sixty-nine patients underwent successful endoscopic CSF leak repairs, and 13 had negative endoscopic explorations. Rapid IF injection was 80% sensitive (20% false negative rate) and 100% specific for identifying CSF leaks, and it caused no seizures, paralysis, or other neurologic complications. CONCLUSION: Compared to prior reports of slow low-dose IF injection for CSF leak localization, rapid IF injection yielded similar efficacy (80% sensitivity) with no IF-related complications. Rapid IF injection was safe and effective but should be corroborated by future studies.

Public Health Sciences

Miller RL, Schuh H, Chandran A, Habre R, Angal J, Aris IM, Aschner JL, Bendixsen CG, Blossom J, Bosquet-Enlow M, Breton CV, Camargo CA, Jr., Carroll KN, Commodore S, Croen LA, Dabelea DM, Deoni SCL, Ferrara A, Fry RC, Ganiban JM, Geiger SD, Gern JE, Gilliland FD, Gogcu S, Gold DR, Hare ME, Harte RN, Hartert TV, Hertz-Picciotto I, Hipwell AE, Jackson DJ, Karagas MK, Khurana Hershey GK, **Kim H**, Litonjua AA, Marsit CJ, McEvoy CT, Mendonça EA, Moore PE, Nguyen AP, Nkoy FL, O'Connor TG, Oken E, Ownby DR, Perzanowski M, Rivera-Spoljaric K, Sathyanarayana S, Singh AM, Stanford JB, Stroustrup A, Towe-Goodman N, Wang VA, Woodruff TJ, Wright RO, Wright RJ, Zanobetti A, **Zoratti EM**, and **Johnson CC**. Child Opportunity Index at Birth and Asthma with Recurrent Exacerbations in the U.S. ECHO Program. *J Allergy Clin Immunol* 2025; Epub ahead of print. PMID: 40089117. Full Text

BACKGROUND: Environmental exposures and social determinants likely influence specific childhood asthma phenotypes. OBJECTIVE: We hypothesized that the Child Opportunity Index (COI) at birth, measuring multiple neighborhood opportunities, influences incidence rates (IRs) for asthma with recurrent exacerbations (ARE). METHODS: We tested for COI associations with ARE incidence rates in 15,877 children born between 1990-2018 in the Environmental Influences on Child Health Outcomes (ECHO) program. Parent-reported race and ethnicity and other demographics were assessed as effect modifiers.

RESULTS: The IR of ARE for children born in very low COI neighborhoods was higher (IR=10.98; 95% Confidence Intervals (CI) 9.71, 12.25) than for other COI categories. Rates for Non-Hispanic Black children (NHB) were significantly higher than Non-Hispanic White (NHW) children in every COI category. The ARE IRs for children born in very low COI neighborhoods were several-fold higher for NHB and Hispanic Black (HB) children (IR=15.30; 95% CI 13.10, 17.49; IR=18.48; 95% CI 8.80, 28.15 respectively) when compared to White children. Adjusting for individual-level characteristics, children born in very low COI neighborhoods demonstrated an ARE incidence rate ratio (IRR) of 1.26 (95% CI 0.99,1.59) with a higher incidence of cases among children ages 2-4 years and with a parental history of asthma. CONCLUSIONS: Rates of ARE were higher among children born in under-resourced communities and this relationship is strongest for young minoritized children with a parental history of asthma. Higher rates for NHB even in the highest COI categories suggest that risk associated with race persists regardless of social disadvantage.

Public Health Sciences

Nwosu ZC, Giza HM, Nassif M, Charlestin V, Menjivar RE, Kim D, Kemp SB, Sajjakulnukit P, Andren A, Zhang L, Lai WK, **Loveless I**, **Steele N**, Hu J, Hu B, Wang S, Pasca di Magliano M, and Lyssiotis CA. Multidimensional analyses identify genes of high priority for pancreatic cancer research. *JCI Insight* 2025; 10(4). PMID: 39774001. Full Text

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Pancreatic ductal adenocarcinoma (PDAC) is a drug-resistant and lethal cancer. Identification of the genes that consistently show altered expression across patient cohorts can expose effective therapeutic targets and strategies. To identify such genes, we separately analyzed 5 human PDAC microarray datasets. We defined genes as "consistent" if upregulated or downregulated in 4 or more datasets (adjusted $P < 0.05$). The genes were subsequently queried in additional datasets, including single-cell RNA-sequencing data, and we analyzed their pathway enrichment, tissue specificity, essentiality for cell viability, and association with cancer features, e.g., tumor subtype, proliferation, metastasis, and poor survival outcome. We identified 2,010 consistently upregulated and 1,928 downregulated genes, of which more than 50% to our knowledge were uncharacterized in PDAC. These genes spanned multiple processes, including cell cycle, immunity, transport, metabolism, signaling, and transcriptional/epigenetic regulation - cell cycle and glycolysis being the most altered. Several upregulated genes correlated with cancer features, and their suppression impaired PDAC cell viability in prior CRISPR/Cas9 and RNA interference screens. Furthermore, the upregulated genes predicted sensitivity to bromodomain and extraterminal (epigenetic) protein inhibition, which, in combination with gemcitabine, disrupted amino acid metabolism and in vivo tumor growth. Our results highlight genes for further studies in the quest for PDAC mechanisms, therapeutic targets, and biomarkers.

Public Health Sciences

Redding A, **Copeland L**, **Murphy D**, Clemmons-Lloyd K, Cummings K, Doyle J, Kesavan S, Mitchell V, Riley D, Stechison L, and **Santarossa S**. Bridging the gap: empowering patients as research partners through a structured training program. *Res Involv Engagem* 2025; 11(1):17. PMID: 40038786. Full Text

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BACKGROUND: Engaging patients as partners in the research process is a mutually beneficial endeavor. However, patients may need skills training in order to meaningfully contribute to a project. The present paper describes the training program "A Front Row SEAT to Research," which equipped patient partners to independently lead focus groups and interpret their associated data. The focus groups were an aim of a larger project evaluating the face validity of a scale measuring patient engagement in research. MAIN BODY: The nine-week training program, created by Patient Engaged Research Center qualitative research experts, empowered patient partners to conduct qualitative research. The structure of the program included asynchronous video lessons, workbook exercises, and live sessions for practice. Topics covered included a comprehensive overview of the scientific process, qualitative research methods, focus group moderation, planning, coding, data interpretation, and dissemination of findings. A hands-on approach to learning, coupled with the collection of continuous feedback, were hallmarks of the program. CONCLUSION: The training program emphasized clear expectations, accessibility, and providing resources to build the capacity of patient partners. Trust was established through a dedicated support person, a collaborative group dynamic, and regular engagement, ensuring patient partners felt valued and empowered. This approach allowed patients to meaningfully contribute to the research and develop a sense of shared ownership in the project.
This paper describes a training program called “A Front Row SEAT to Research,” which taught patient partners how to lead focus groups and analyze the data on their own. These focus groups were part of a larger project that aimed to check if a tool measuring patient engagement in research was working as intended. The nine-week training program, developed by experts at the Patient Engaged Research Center, prepared patient partners to conduct qualitative research. The training program included pre-recorded video lessons, workbook activities, and live practice sessions. It covered topics such as how research works, qualitative research methods, steps involved in planning and moderating focus groups, analyzing data, and sharing findings. The program focused on hands-on learning and collected ongoing feedback from participants to improve their experience. The program prioritized clear communication, accessibility, and providing the resources needed to build the patient partners’ skills. Trust was strengthened through a supportive team, a collaborative environment, and regular interaction, ensuring patient partners felt respected and empowered. This approach allowed patient partners to contribute meaningfully to the research and feel a sense of shared ownership in the project.

Public Health Sciences

Salut N, Gamallat Y, Seyedi S, Felipe Lima J, **Ghosh S**, and Bismar TA. Unraveling the Prognostic Significance of BRCA1-Associated Protein 1 (BAP1) Expression in Advanced and Castrate-Resistant Prostate Cancer. *Biology (Basel)* 2025; 14(3). PMID: 40136571. Full Text

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Prostate cancer (PCa) is ranked as one of the top cancers affecting men in Western societies. BRCA1-associated protein 1 (BAP1) expression significance has been observed in various cancers, including prostate cancer. The search for prognostic models allowing better risk stratification and prediction of disease progression in prostate cancer patients is still of major clinical need. Our data showed that nuclear BAP1 expression is the most associated with cancer clinical outcomes and other biomarkers. The data confirmed that decreased BAP1 nuclear expression is linked to aggressive tumors and poorer prognosis. We assessed BAP1 expression in 202 cases, including advanced and castrate-resistant PCa (CRPCa). Our data indicated low BAP1 nuclear expression in advanced and castrate-resistant disease (CRPCa). Furthermore, there was a significant difference between high and low BAP1 nuclear expression relative to the patient's clinical outcome. In the present cohort, decreased BAP1 intensity exhibited a significant association with unfavorable overall survival (OS) (HR 2.31, CI: 1.38-3.86, p = 0.001) and cause-specific survival (CSS) (HR 2.44, CI: 1.24-4.78, p = 0.01). Additionally, this association was more pronounced when low BAP1 expression (high risk) was combined with other common PCa genomic alterations such as phosphatase and tensin homolog (PTEN) loss or ETS-related gene (ERG)-positive cases, resulting in higher unfavorable OS and CSS. Conversely, high BAP1 nuclear expression (moderate and high intensity) combined with no ERG expression or PTEN (moderate or high expression), p53 (wild type), and androgen receptor (AR) (low/moderate intensity) showed better association with higher survival rates. All these data support the notion that BAP1 functions as a tumor suppressor. Integrating BAP1 status with other genomic alterations offers a more comprehensive understanding of disease aggressiveness.

Public Health Sciences
Schildroth S, Claus Henn B, Geller RJ, Wesselink AK, Upson K, Vines AI, Vinceti M, Harmon QE, Baird DD, **Wegienka G**, and Wise LA. A prospective study of a whole blood metal mixture and depressive symptoms among Black women from Detroit, Michigan. *Neurotoxicology* 2025; 108:94-104. PMID: 40032041. Full Text

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Exposure to metals has been previously associated with depressive symptoms, but few studies have considered potential effects of metal mixtures. In addition, few previous studies have been conducted

among Black women, who are disproportionately at risk for exposure to some metals and greater depression incidence and severity. We analyzed data from the Study of Environment, Lifestyle, and Fibroids (SELF), a prospective cohort study of reproductive-aged Black women from Detroit, to examine associations between a mixture of metals, metalloids, and trace elements ("metals") and depressive symptoms (n = 1450). SELF participants self-identified as Black or African American and were 23-34 years of age at enrollment. We collected covariate information on structured questionnaires and whole blood samples at baseline. We quantified 17 metals in whole blood using inductively coupled plasma mass spectrometer triple quadruple or Direct Mercury Analyzer-80. Participants reported depressive symptoms on the Center for Epidemiologic Studies Depression Scale (CES-D) at the 20-month follow-up visit, where higher CES-D scores reflected greater depressive symptoms. We used quantile-based g-computation to estimate the cumulative association of the metal mixture with CES-D scores, adjusting for age, household income, educational attainment, body mass index, smoking status, alcohol intake, and parity. We estimated beta coefficients (with 95 % confidence intervals [CI]) as the percent difference in CES-D scores per quartile increase in all metals. A one-quartile increase in the metal mixture was associated with 14.8 % lower (95 % CI=-26.7 %, -1.1 %) CES-D scores, reflecting lower depressive symptoms. The mixture association was driven by nickel, copper, cesium, molybdenum, and lead. Other neurotoxic metals (cadmium, arsenic, mercury, chromium) were associated with greater depressive symptoms. Findings from this study suggest that exposure to a mixture of metals may affect depressive symptoms in Black women, with individual metals acting in opposing directions.

Public Health Sciences

Tinsley SA, **Stephens A**, **Morrison C**, **Richard C**, **Hares K**, **Lutchka J**, **Rogers C**, and **Abdollah F**. Utilization and Cancer Control Outcomes of Active Surveillance Amongst Black and White Men with Intermediate Risk Prostate Cancer in a Population-Based Analysis. *J Racial Ethn Health Disparities* 2025; Epub ahead of print. PMID: 40048083. Full Text

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INTRODUCTION: To assess the utilization and prostate cancer (PCa)-specific mortality (PCSM) between non-Hispanic Black (NHB) and non-Hispanic White (NHW) on active surveillance (AS) with intermediate risk PCa (iPCa). METHODS: The Surveillance, Epidemiology, and End Results database was queried between 2010-2016. The rate of AS was calculated per year between NHB and NHW using univariable logistic analysis (UVA) and multivariable logistic analysis (MVA). Next, inverse probability of treatment weighting was performed on those that underwent watchful waiting (WW) and competing-risks cumulative incidence function (CIF) and MVA were used to assess the impact of race on other-cause mortality (OCM) and PCSM. Statistical significance defined as $p < 0.05$, but some observations were deemed non-statistically significant per our Benjamini-Hochberg procedures, RESULTS: 50,315 patients had iPCa, and 3,310 underwent AS/WW. The rate of AS increased amongst NHB (+ 3.1%) and NHW (+ 5.7%) from 2010 - 2016. UVA did not show an association with race, but MVA showed a negative association, based on our Benjamini-Hochberg correction, between NHB and AS [OR 0.68 (95% CI: 5.4-0.87; $p = 0.002$)]. On CIF, NHB and NHW had non-significant differences in OCM in the weighted cohort ($p = 0.03$), due to the Benjamini-Hochberg correction, and that was confirmed with MVA with a HR of 1.23 (95% CI: 1.02-1.49; $p = 0.03$). However, the CIF on PCSM showed NHB had a higher risk of PCSM ($p < 0.0001$), and that was confirmed with MVA with a HR of 3.01 (95% CI: 2.00-4.53; $p < 0.001$). CONCLUSION: The utilization of AS for iPCa increased amongst NHB and NHW patients. Unfortunately, NHB race was associated with increased risk of PCSM from one year to the next compared to NHW patients.

Public Health Sciences

Venkateswaran VR, **She R**, Gardell SJ, **Luzum JA**, **Gupta R**, **Zhang K**, **Williams LK**, **Sabbah HN**, and **Lanfear DE**. Association of plasma metabolites and cardiac mitochondrial function with heart failure progression. *ESC Heart Fail* 2025; Epub ahead of print. PMID: 40064034. Full Text

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AIMS: Plasma metabolites are prognostic in heart failure with reduced ejection fraction (HFrEF), with citric acid cycle metabolites linked to ejection fraction (EF) changes. We investigated these mechanisms in a canine chronic HFrEF model. We tested associations between changes in plasma metabolites, left ventricular (LV) end-diastolic volume and cardiomyocyte mitochondrial function. METHODS: Eighteen dogs underwent microembolization to induce moderate HFrEF (target LVEF 35%-40%). Plasma metabolites, LV size and mitochondrial function were assessed over 12 months. RESULTS: Plasma metabolite heatmap showed acylcarnitine changes, with early alterations in organic acids and amino acids predicting later adverse LV remodelling. Using either baseline or change over time, 13 metabolites correlated with 12 month LV enlargement. This is mostly often at 3 months (11 of 13), notably C18:2 ($r = -0.58$, $P = 0.003$) and cardiac anaplerotic substrates like glutamine ($r = -0.52$, $P = 0.009$) and 3-HBA ($r = -0.43$, $P = 0.035$). Impaired cardiomyocyte mitochondrial function correlated with LV enlargement (max ATP synthesis 12.7 vs. 19.9 nmol/min/mg, $P = 0.0036$; ADP-stimulated respiration 224 vs. 308 nAtom O/min/mg protein; $P = 0.0064$). Plasma metabolites correlated with mitochondrial parameters at 12 month, particularly with MAX ATP: malate ($r = -0.75$, $P < 0.001$), fumarate ($r = -0.6$, $P = 0.008$) and glutamine ($r = 0.51$, $P = 0.031$). CONCLUSIONS: In canine HFrEF, plasma acylcarnitines, citric acid cycle or anaplerotic metabolites predicted adverse LV remodelling. LV enlargement correlated with reduced cardiomyocyte mitochondrial function, which in turn was also associated with increased citric acid cycle metabolites. Together, these data suggest impaired cardiac energetic function drives plasma metabolite associations in HFrEF progression.

Public Health Sciences

Viganò S, **Finati M**, **Stephens A**, **Bertini A**, **Finocchiaro A**, Lughezzani G, Buffi N, Salonia A, Briganti A, Montorsi F, Rossanese M, Di Trapani E, Ficarra V, Sood A, **Rogers C**, and **Abdollah F**. Socioeconomic Disparities in Prostate Cancer Treatment: The Impact of Area Deprivation Index on Initial Treatment Type for Localized PCa in a North-American Cohort. *Prostate* 2025; Epub ahead of print. PMID: 40066656. Full Text

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BACKGROUND: Socioeconomic status and geographical location contribute to disparities in localized prostate cancer (PCa) treatment. We examined the impact of area of deprivation index (ADI) on initial treatment type for localized PCa in a North-American cohort. METHODS: We performed a retrospective analysis of patients diagnosed with localized PCa, treated within Henry Ford Health (HFH), between 1995 and 2022, with available ADI-data. ADI was assigned based on residential census block group, ranked as a national deprivation percentile. Patients were categorized into three treatment-groups: radical prostatectomy (RP), radiation therapy (RT) and "other" treatment. Using multinomial logistic regression, we assessed ADI impact on treatment choice. After excluding patients without cT, ISUP-grade and/or PSA, we stratified by D'Amico risk-classification and repeated the regression analysis in each subgroup.

RESULTS: Among 14,204 patients, 28.4% were NHB. Median (IQR) age at diagnosis was 65 (59-71) years. Median (IQR) ADI was 58 (36-83) for overall cohort and 51 (30-74), 66 (45-91), and 62 (39-88) for RP, RT, and "other" groups, respectively ($p < 0.0001$). Multivariable analysis showed ADI as an independent predictor of treatment choice ($p = 0.01$): for each 10-unit increase in ADI, patients were 3% more likely to receive RT and 10% less likely to receive RP. High ADI predicted a lower likelihood of receiving initial surgery across all risk-groups ($p < 0.001$). CONCLUSIONS: Patients in more advantaged areas were more likely to receive RP, while those in disadvantaged areas received more RT. Recognizing how neighborhood factors affect treatment choices is crucial for improving health equity and reducing disparities in PCa outcomes.

Pulmonary and Critical Care Medicine

Kim RY, Rendle KA, Mitra N, **Neslund-Dudas C**, Greenlee RT, Honda SA, Schapira MM, **Simoff MJ**, Jeon J, Meza R, Ritzwoller DP, and Vachani A. Adherence to Annual Lung Cancer Screening and Rates of Cancer Diagnosis. *JAMA Netw Open* 2025; 8(3):e250942. PMID: 40100218. Full Text

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IMPORTANCE: Adherence to annual lung cancer screening (LCS) is a proposed quality metric for LCS programs, but data linking annual adherence to lung cancer outcomes are lacking. OBJECTIVE: To investigate annual LCS adherence rates across 2 subsequent LCS rounds among adults undergoing baseline LCS and examine the association of adherence with lung cancer diagnosis rates. DESIGN, SETTING, AND PARTICIPANTS: This retrospective cohort study included adults aged 55 to 75 years who formerly or currently smoked and underwent baseline LCS between January 1, 2015, and December 31, 2018, across 5 US health care systems in the Population-Based Research to Optimize the Screening Process-Lung Consortium. Participants with missing Lung Computed Tomography Screening Reporting & Data System scores or a lung cancer diagnosis prior to LCS initiation were excluded. Data were analyzed from October 2023 to October 2024. EXPOSURES: For negative baseline screening results, T1 and T2 screening adherence was defined as chest computed tomography (CT) between 10 and 18 months and 22 and 30 months after baseline, respectively. For positive baseline screening results, T1 and T2 adherence was defined as chest CT between 11 and 21 months and 28 and 36 months after baseline, respectively. MAIN OUTCOMES AND MEASURES: The main outcomes were annual T1 and T2 LCS adherence rates and associations between T1 and T2 screening adherence; annual incident lung cancer diagnoses in rounds T0 (0-12 months after baseline), T1 (>12 to 24 months after baseline), and T2 (>24 to 36 months after baseline); and cancer stage distribution. RESULTS: A total of 10 170 individuals received baseline LCS (median age, 65 years [IQR, 60-69 years]; 5415 [53.2%] male). During round T1, 6141 of 10 033 eligible patients (61.2% [95% CI, 60.2%-62.2%]) were adherent, and during round T2, 5028 of 9966 eligible patients (50.5% [95% CI, 49.5%-51.4%]) were adherent. T1 adherence was significantly associated with T2 adherence (adjusted relative risk, 2.40; 95% CI, 2.06-2.79). Across 36 months of follow-up, 279 patients (2.7%; 95% CI, 2.4%-3.1%) were diagnosed with lung cancer. Incident lung cancer diagnosis rates were 1.3% (95% CI, 1.1%-1.6%), 0.7% (95% CI, 0.5%-0.8%), and 0.8% (95%

CI, 0.6%-0.9%) during rounds T0, T1, and T2, respectively. Lung cancer diagnosis rates were higher among individuals who were LCS adherent vs nonadherent during both rounds T1 (59 of 6141 [1.0%; 95% CI, 0.7%-1.2%] vs 8 of 3892 [0.2%; 95% CI, 0.1%-0.4%]; P < .001) and T2 (63 of 5028 [1.3%; 95% CI, 1.0%-1.6%] vs 12 of 4938 [0.2%; 95% CI, 0.1%-0.4%]; P < .001). A greater proportion of early-stage lung cancers were diagnosed among individuals adherent to screening at T2 compared with those who were not (46 of 63 [73.0%] vs 3 of 12 [25.0%]; P = .006). CONCLUSIONS AND RELEVANCE: In this multicenter cohort study of adults undergoing LCS, screening adherence was associated with increased overall and early-stage lung cancer detection rates; however, adherence decreased annually after baseline screening, suggesting that it is an important LCS quality metric.

Pulmonary and Critical Care Medicine

Yataco AC, Soghier I, Hébert PC, Belley-Cote E, Disselkamp M, Flynn D, Halvorson K, Iaccarino JM, Lim W, Lindenmeyer CC, Miller PJ, O'Neil K, Pendleton KM, Vusse LV, and **Ouellette DR**. Transfusion of Fresh Frozen Plasma and Platelets in Critically Ill Adults: An American College of Chest Physicians Clinical Practice Guideline. *Chest* 2025; Epub ahead of print. PMID: 40074060. Full Text

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BACKGROUND: Platelets and fresh frozen plasma (FFP) are frequently administered to critically ill patients. Considering the variability in indications and thresholds guiding these transfusions, a comprehensive review of current evidence was conducted to provide guidance to critical care practitioners. This American College of Chest Physicians guideline examined the literature on platelet transfusions in critically ill patients with thrombocytopenia, with and without active bleeding, as well as data on prophylactic platelet and FFP transfusions for common procedures in the critical care setting. STUDY DESIGN AND METHODS: A panel of experts developed seven Population, Intervention, Comparator, and Outcome questions addressing platelet and FFP transfusions in critically ill patients and performed a comprehensive evidence review. The panel applied the Grading of Recommendations, Assessment, Development, and Evaluations approach to assess the certainty of evidence, and to formulate and grade recommendations. A modified Delphi technique was used to reach consensus on the recommendations. RESULTS: The initial search identified a total of 7,172 studies, and after the initial screening, 100 articles were reviewed. Sixteen studies met inclusion criteria, comprising 1 randomized controlled trial and 15 observational studies. Overall, the certainty of the evidence for all questions was very low. The panel formulated seven conditional recommendations. CONCLUSIONS: In critically ill

patients with thrombocytopenia or coagulopathy, a risk/benefit assessment should be made by providers prior to transfusion of platelets or FFP. Given the known risks of blood product transfusion, and the limited data regarding the benefits from platelet or FFP transfusion, most patients will benefit from avoiding transfusion of these blood products. In patients at high risk of bleeding, or where the bleeding complication may be catastrophic, transfusion should be considered.

Radiation Oncology

Agulles-Pedrós L, MacDonald RL, Cherpak AJ, Dixit N, Dong L, Zhao T, **Thind K**, **Doemer A**, Teo BK, Su S, Moncion A, and Robar JL. Multi-institutional study on image quality for a novel CBCT solution on O-ring linac. *J Appl Clin Med Phys* 2025; Epub ahead of print. PMID: 40048322. Full Text

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INTRODUCTION: This work presents a multi-institutional study on image quality provided by a novel cone beam computed tomography (CBCT). The main goal is to investigate the consistency of imaging performance across multiple institutions. METHODS: Phantoms for measuring relative electron density (RED) and image quality were sent to six institutions for imaging on Ethos and Halcyon units equipped with HyperSight CBCT. The imaging protocols included tube potential from 100 to 140 kVp and exposure from 80 to 800 mAs. Imaging performance was evaluated with regard to RED versus Hounsfield units (HU), uniformity, contrast-to-noise ratio (CNR), slice thickness, circular symmetry, modulation transfer function (MTF), and spatial resolution. RESULTS: Among all institutions, some variability was observed among institutions in the RED-to-HU relationship, especially for RED values greater than 1, although no outliers were found (|z-score| < 2 in all cases). In this range, RED/HU slopes were 475 ± 25 10(-6) RED/HU at 100kVp, 505 ± 20 10(-6) RED/HU at 125kVp, and 550 ± 20 10(-6) RED/HU at 140kVp. Radial uniformity ranged from 1 to 7 HU, depending on protocol. Circular symmetry for two points 50 mm apart showed consistency within one-pixel dimension. Integral nonuniformity was between 1 and 10, with no difference observed between vertical and horizontal dimensions. Contrast rods with 1% gave CNR = 0.5, 1 and 2 for 100(88), 125(176), and 140(528) in kVp(mAs), and contrast rods with 0.5% had CNR = 0.2, 0.4 and 0.8 for 100(88), 125(176), and 140(528) in kVp(mAs). Spatial resolution given by MTF at 10% and 50% yielded values of 0.55 ± 0.01 mm(-1) and 0.35 ± 0.02 mm(-1), respectively. CONCLUSIONS: This multi-institutional analysis of CBCT imaging performance showed consistency in radial uniformity, circular symmetry, integral nonuniformity, contrast, and spatial resolution. Some variability was seen in the RED-to-HU relationship for RED > 1 depending on exposure. More data from different institutions would be necessary to establish more robust statistical metrics, which ensure quality parameters.

Rehabilitation Services/Physical Therapy/Occupational Health

Sebastian D, and **George P**. Correlating Movement Impairments As Potential Risk Factors for Musculoskeletal Dysfunction: A Retrospective Cross-Sectional Analysis in a Rehabilitation Setting. *Cureus* 2025; 17(2):e79841. PMID: 40161172. Full Text

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BACKGROUND: Mechanical musculoskeletal disorders diminish quality of life and increase healthcare costs but lack prevention strategies. The lack of validated risk factors may be a reason. This study supports the previously hypothesized motion impairments as one potential risk factor in causing mechanical musculoskeletal disorders. METHODS: A retrospective chart review of individuals in a

rehabilitation setting with mechanical musculoskeletal disorders was done to identify the presence of co-existing motion impairments. A correlational analysis of their co-existing presence with a description of how they may directly contribute to those disorders followed. RESULTS: All individuals with mechanical musculoskeletal disorders whose charts were reviewed, presented with co-existing motion impairments. Pearson's correlation coefficient (R) was 1 indicating a strong positive correlation between variables. Linear regression revealed a coefficient of determination (R2) of 1 suggesting that variation in the dependent variable was explained by the independent variable. CONCLUSION: The results of this study may be of value as a hypothesis generator highlighting the need for the investigation of motion impairments as a potential risk factor for musculoskeletal dysfunction.

Research Administration

Chadwick J, Hinterberg MA, Asselbergs FW, Biegel H, Boersma E, Cappola TP, Chirinos JA, Coresh J, Ganz P, Gordon DA, Kureshi N, Loupey KM, Orlenko A, Ostroff R, Sampson L, Shrestha S, Sweitzer NK, Williams SA, Zhao L, Kardys I, and **Lanfear DE**. Harnessing the Plasma Proteome to Predict Mortality in Heart Failure Subpopulations. *Circ Heart Fail* 2025; Epub ahead of print. PMID: 40052265. Full Text

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BACKGROUND: We derived and validated proteomic risk scores (PRSs) for heart failure (HF) prognosis that provide absolute risk estimates for all-cause mortality within 1 year. METHODS: Plasma samples from individuals with HF with reduced ejection fraction (HFrEF; ejection fraction <40%; training/validation n=1247/762) and preserved ejection fraction (HFpEF; ejection fraction ≥50%; training/validation n=725/785) from 3 independent studies were run on the SomaScan Assay measuring ≈5000 proteins. Machine learning techniques resulted in unique 17- and 14-protein models for HFrEF and HFpEF that predict 1-year mortality. Discrimination was assessed via C-index and 1-year area under the curve (AUC), and survival curves were visualized. PRSs were also compared with Meta-Analysis Global Group in Chronic HF (MAGGIC) score and NT-proBNP (N-terminal pro-B-type natriuretic peptide) measurements and further assessed for sensitivity to disease progression in longitudinal samples (HFrEF: n=396; 1107 samples; HFpEF: n=175; 350 samples). RESULTS: In validation, the HFpEF PRS performed significantly better (P≤0.1) for mortality prediction (C-index, 0.79; AUC, 0.82) than MAGGIC (C-index, 0.71; AUC, 0.74) and NT-proBNP (PRS C-index, 0.76 and AUC, 0.81 versus NT-proBNP C-index, 0.72 and AUC, 0.76). The HFrEF PRS performed comparably to MAGGIC (PRS C-index, 0.76 and AUC, 0.83 versus MAGGIC C-index, 0.75 and AUC, 0.84) but had a significantly better C-Index (P=0.026) than NT-proBNP (PRS C-index, 0.75 and AUC, 0.78 versus NT-proBNP C-index, 0.73 and AUC, 0.77). PRS included known HF pathophysiology biomarkers (93%) and novel proteins (7%). Longitudinal assessment revealed that HFrEF and HFpEF PRSs were higher and increased more over time in individuals who experienced a fatal event during follow-up. CONCLUSIONS: PRSs can provide valid, accurate, and dynamic prognostic estimates for patients with HF. This approach has the potential to improve longitudinal monitoring of patients and facilitate personalized care.

Research Administration

Fallahi A, Nazem-Zadeh MR, Hosseini-Tabatabaei N, Habibabadi JM, Hashemi-Fesharaki SS, and **Soltanian-Zadeh H**. Language and Memory Network Alterations in Temporal Lobe Epilepsy: A Functional and Structural Connectivity Study. *AJNR Am J Neuroradiol* 2025; Epub ahead of print. PMID: 40081848. Full Text

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BACKGROUND AND PURPOSE: This study evaluated preoperative alterations and postoperative reorganization of the joint language-memory network (LMN) from the perspective of resting-state functional and structural connectivity in Temporal lobe epilepsy (TLE). Graph theory and machine learning approaches were employed to explore automatic lateralization. MATERIALS AND METHODS: Resting-state fMRI and DTI data were obtained from 20 healthy subjects and 35 patients with TLE. Functional and structural connectivity were calculated within the LMN before and after temporal lobectomy. ANOVA was performed to identify significant connectivity differences between groups. Four local graph measures were extracted from functional and structural connectivity matrices. Standard feature selection techniques and genetic algorithm (GA) methods were applied to select the optimal features. Subsequently, the K-nearest neighbor, support vector machine (SVM), Naive Bayes, and logistic regression classification methods were used to classify healthy controls (HCs) and pre-surgical TLE groups, as well as pre-surgical left TLE (LTLE) and right TLE (RTLE) groups. Also, relationships between psychological scores and the selected features were evaluated using a linear regression method. RESULTS: The results demonstrated increased functional and decreased structural connectivity in TLE patients before surgery. After surgery, significant connections revealed reduced functional connectivity and increased structural connectivity in TLE patients. Functional analysis identified the left parahippocampal region in LTLE and the right temporal regions in RTLE as key areas. Structural connectivity analysis showed that memory-related areas in the bilateral occipital region and the left language-related area were the origins of alterations. The GA method achieved the highest classification performance using SVM for fMRI and DTI graph measures, with accuracy rates of 97% and 88% for distinguishing LTLE from RTLE, and 93% and 87% for distinguishing TLE from HC, respectively. Moreover, a significant relationship was observed between the best-selected features and memory-assisted cognitive tests. CONCLUSIONS: Pre-surgical functional hyperconnectivity and post-surgical hypoconnectivity and also newly observed bilateral postsurgical structural connectivity, highlighting functional and structural alterations in the LMN network. Additionally, the study underscores the potential of machine learning for TLE diagnosis and lateralization. A limited sample size, particularly in the postsurgical group was one of the constraints of this study. ABBREVIATIONS: TLE=Temporal lobe epilepsy; LMN=Language-memory network; GA=Genetic algorithm; HC=Healthy controls; LTLE=Left TLE; RTLE=Right TLE; AUC=Area under the curve.

Sleep Medicine

Roth T. Therapeutic Use of γ-Hydroxybutyrate: History and Clinical Utility of Oxybates and Considerations of Once- and Twice-Nightly Dosing in Narcolepsy. *CNS Drugs* 2025; 39(Suppl 1):37-51. PMID: 40111735. Full Text

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Narcolepsy is a rare and chronic hypersomnolence disorder characterized by excessive daytime sleepiness, disrupted nighttime sleep, sleep paralysis, and hypnagogic hallucinations and occurs with or without cataplexy. Orexin neuron loss has been implicated in the underlying pathophysiology of narcolepsy type 1 through dysregulation of sleep/wake patterns and rapid eye movement sleep. γ-Aminobutyric acid (GABA) has been shown to play a role in modulation of orexin neuronal activity during transitions from wakefulness to sleep. γ-Hydroxybutyrate (GHB), an endogenous analog of GABA, has demonstrated therapeutic benefit in treatment of narcolepsy through early investigations, but use has historically been limited owing to existing stigma related to illicit use and abuse risk. Initial regulatory approval of its sodium salt derivative, sodium oxybate (SXB), for cataplexy in patients with narcolepsy occurred in 2002, and additional formulations have been developed. The efficacy and safety of SXB in narcolepsy have been supported by decades of clinical use and research. This review discusses the history and clinical application of GHB and its SXB derivatives in the treatment of individuals with narcolepsy, including clinical safety and effect on sleep.

Sleep Medicine

Roth T, Thorpy MJ, Kushida CA, and Gudeman J. Efficacy of Once-Nightly Sodium Oxybate in Patients with Narcolepsy: Post Hoc Analyses of Sensitivity, Effect Size, and Numbers Needed to Treat from the Phase 3 REST-ON Trial. *CNS Drugs* 2025; 39(Suppl 1):61-70. PMID: 40111739. Full Text

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BACKGROUND: Once-nightly sodium oxybate (ON-SXB; LUMRYZ™; FT218) treatment significantly improved 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 episodes versus placebo in a randomized, placebo-controlled trial (REST-ON). The objective of these post hoc sensitivity analyses was to evaluate the robustness of treatment with ON-SXB, while accounting for missing participant data. Number needed to treat (NNT) and effect size analyses were conducted to quantify the treatment benefits. METHODS: Participants ≥ 16 years of age with narcolepsy type 1 or 2 were randomized 1:1 to receive ON-SXB (4.5 g [week 1]; 6 g [weeks 2-3]; 7.5 g [weeks 4-8]; or 9 g [weeks 9-13]) or placebo. Sensitivity analyses included completer population, placebo-based multiple imputation (MI) with a missing-not-at-random assumption, analysis of covariance (ANCOVA), and tipping-point-based MI of worsening values until $P > 0.05$. Mean differences and P-values were calculated for the MWT and number of cataplexy episodes. For CGI-I, odds ratios and P-values were calculated for completers; mean differences (1-7 points; lower values indicate greater improvement) and P-values were calculated using ANCOVA. Effect sizes were calculated using Cohen's d; NNTs were calculated as the inverse of the absolute risk reduction. RESULTS: In the completer population (ON-SXB, n = 69; placebo, n = 79), all ON-SXB doses demonstrated significant improvements versus placebo for all coprimary endpoints ($P < 0.001$). All ON-SXB doses demonstrated significant improvements ($P < 0.001$) versus placebo for all coprimary endpoints when missing values in both treatment arms were imputed from observed values in the placebo arm (i.e., missing data were replaced with placebo data) and when analyzed using ANCOVA. Tipping-point-based analysis on the change from baseline in mean sleep latency on the MWT demonstrated that implausible or nearly implausible baseline MWT assumptions were needed to render the differences between ON-SXB and placebo no longer statistically significant. All doses of ON-SXB had NNTs of three and effect sizes of 0.7-0.9 for MWT response. For the response in terms of number of cataplexy episodes, NNT was six for the 6 g dose and three for the 7.5 g and 9 g doses; the effect sizes were between -0.7 and -0.8. For the Epworth Sleepiness Scale (ESS) response, NNTs ranged from three to six, with a dose-response effect. Effect sizes were between -0.5 and -0.7 for all doses. CONCLUSIONS: These post hoc results demonstrate the robustness of the REST-ON clinical trial efficacy data. CLINICAL TRIAL ID: NCT02720744.

Sleep Medicine

Van Dongen HPA, Leary EB, **Drake C**, Bogan R, Jaeger J, Rosenberg R, Streicher C, and Tabuteau H. Results of the Solriamfetol's Effect on Cognitive Health in Apnea Participants During a Randomized Placebo-Controlled Study (SHARP): A Randomized Placebo-Controlled Double-Blind Repeated-Measures Crossover Phase IV Clinical Trial of the Effect of the Wake-Promoting Agent Solriamfetol on Cognitive Function in OSA With Excessive Daytime Sleepiness and Cognitive Impairment. *Chest* 2025; 167(3):863-875. PMID: 39528111. Full Text

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BACKGROUND: OSA causes episodes of fragmented sleep and intermittent hypoxia and leads to excessive daytime sleepiness (EDS). Deficits in cognitive function are a troublesome symptom in patients with OSA and EDS. RESEARCH QUESTION: How does solriamfetol affect cognitive function in patients with cognitive impairment associated with OSA and EDS? STUDY DESIGN AND METHODS: Solriamfetol's Effect on Cognitive Health in Apnea Participants During a Randomized Placebo-Controlled Study (SHARP) was a phase IV, randomized double-blind placebo-controlled crossover trial. Participants (N = 59) were randomized to receive placebo or solriamfetol (75 mg/d for 3 days, then 150 mg/d) for 2 weeks, with crossover separated by a 1-week washout period. Efficacy measures included the Coding subtest, comparable to the Digit Symbol Substitution Test (DSST), of the Repeatable Battery for the Assessment of Neuropsychological Status (RBANS), the British Columbia Cognitive Complaints Inventory (BC-CCI), the Patient Global Impression of Severity (PGI-S), and the Epworth Sleepiness Scale (ESS). The primary end point was change from baseline in average postdose DSST RBANS scores. Secondary end points were changes from baseline in BC-CCI, PGI-S, ESS, and DSST RBANS scores at 2, 4, 6, and 8 hours' postdose. Safety was monitored by assessment of treatment-emergent adverse events. RESULTS: Solriamfetol was shown to significantly improve postdose average DSST RBANS scores compared with placebo (P = .009; effect size [Cohen's d], 0.37). When evaluated at each 2-hour time point, cognitive function was significantly improved at 2, 6, and 8 hours after dosing (all, P < .05). During solriamfetol treatment, there were significant improvements in BC-CCI (P = .002; d = 0.45), PGI-S (P = .034; d = 0.29), and ESS (P = .004; d = 0.40) compared with placebo. The most common treatment-emergent adverse events were nausea (7%) and anxiety (3%). INTERPRETATION: SHARP showed that solriamfetol can improve objective and subjective measures of cognitive function in patients with cognitive impairment associated with OSA and EDS. CLINICAL TRIAL REGISTRATION: ClinicalTrials.gov; No.: NCT04789174; URL: www. CLINICALTRIALS: gov and EudraCT; No.: 2020-004243-92; URL: https://eudract.ema.europa.eu.

Surgery

Ayvaci MUS, Giacoma T, **Abouljoud MS**, and Tanriover B. The economic value of a transplant nephrologist: The case for improving compensation models. *Am J Transplant* 2025; Epub ahead of print. PMID: 40090416. Full Text

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This article examined the economic value of transplant nephrologists and the need for adequate compensation. Kidney transplantation is a health and lifespan-extending procedure that relies on the expertise of transplant nephrologists. However, current compensation models, primarily based on relative

value units (RVUs), often fail to capture the full scope of their work, particularly nonbillable activities essential to patient care. Additionally, regulatory compliance issues, particularly those related to the physician self-referral law (also known as the Stark law), complicate compensation structures. The Stark law mandates that physician compensation must align with fair market value to avoid conflicts of interest, adding complexity to designing compensation packages that accurately reflect the value of transplant nephrologists' contributions. This article critiques the RVU-based system, highlighting its limitations in adequately compensating these specialists and proposing solutions such as integrating customized RVUs and outcome value units to better account for nonbillable work and incentivize high-quality care. The use of Medicare organ acquisition cost reports is also suggested to align compensation more closely with the actual economic value generated. A comprehensive approach that addresses both the quantitative and qualitative aspects of transplant nephrologists' work, while navigating regulatory requirements, is essential for adequate and equitable compensation.

Surgery

Ballard ET, **Bergeson KS**, **Wisniewski SJ**, Singh S, **Ejub S**, and **Nelson RA**. Gastrointestinal Bleeds Are a Rare Event After Total Hip and Knee Arthroplasty. *J Arthroplasty* 2025; Epub ahead of print. PMID: 39892621. Full Text

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BACKGROUND: The presence of a gastrointestinal (GI) bleed after elective total hip arthroplasty and total knee arthroplasty (THA and TKA, respectively) is concerning and a potential cause for hospital readmission. This condition can also be life-threatening if not identified and treated appropriately. Many surgeons use multimodal analgesia protocols to limit opioid use and also use venous thromboembolism prophylaxis. Aspirin and nonsteroidal anti-inflammatories, often a component of these protocols, reduce prostaglandin production necessary for gastric mucosal protection. The authors hypothesized that the incidence of a GI bleed after TKA and THA would be rare. METHODS: This was a retrospective review of 8,207 patients 18 years or older who had THA or TKA at a single institution between 2015 and 2022. Patients who were evaluated for GI bleed within 90 days postoperatively were identified. Perioperative risks were analyzed based on demographics, procedures, and other risk factors. RESULTS: The incidence of GI bleeding was 0.33%, in which 27 patients sustained a GI bleed in 8,206 THA and TKA cases. The average days from the time of surgery for GI bleed were 18.6 days. There was a difference in the occurrence of GI bleeds by age, with increasing age being positively associated with an increase in the odds of GI bleeds, odds ratio = 1.15 (95% CI [confidence interval]: 1.09 to 1.21), $P < 0.01$. No statistical difference was found based on other demographic data, procedure type, or site. CONCLUSIONS: This institution's perioperative protocol, including the use of nonsteroidal anti-inflammatories and aspirin for TKA and THA, had a low incidence of GI bleeds in the perioperative setting at our community hospital over the course of 2015 to 2022.

Surgery

Bui J, **Chalom T**, **Nathanson SD**, **Schwartz TL**, **Hunt K**, **Alkhoory W**, and **Xu Z**. Invasive ductal carcinoma at the site of a cosmetic nipple piercing. *J Surg Case Rep* 2025; 2025(3):rjaf132. PMID: 40079036. Full Text

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We report a young female patient diagnosed with an invasive ductal carcinoma at the site of a prior cosmetic nipple piercing. She had no significant familial, genetic, or other carcinogenic risk factors to account for her presentation. A review of the literature confirms that trauma can occasionally be

associated with invasive breast cancer, but such a connection has not previously been related to nipple piercing procedures.

Surgery

Conte MS, Farber A, Barleben A, Chisci E, Doros G, Kashyap VS, Kayssi A, Kolh P, Moreira CC, **Nypaver T**, Rosenfield K, Rowe VL, Schanzer A, Singh N, Siracuse JJ, Strong MB, and Menard MT. Impact of Bypass Conduit and Early Technical Failure on Revascularization for Chronic Limb-Threatening Ischemia. *Circ Cardiovasc Interv* 2025; 18(3):e014716. PMID: 40100950. Full Text

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BACKGROUND: The optimal strategy for lower extremity revascularization (surgical bypass versus endovascular intervention) in patients with chronic limb-threatening ischemia (CLTI) is unclear. We examined the effectiveness of open surgical bypass using single-segment great saphenous vein conduit (SSGSV), alternative conduits (AC), or endovascular interventions (ENDO) among patients with CLTI deemed acceptable for either open surgical bypass or ENDO treatment. METHODS: This was a planned as-treated analysis of the multicenter BEST-CLI (Best Endovascular Versus Best Surgical Therapy in Patients With Critical Limb Ischemia) randomized controlled trial comparing open surgical bypass and ENDO for CLTI due to infrainguinal peripheral artery disease. Outcomes were tabulated based on the initial revascularization received: SSGSV bypass, AC bypass, and ENDO. Analyses were performed for all treated patients and then excluding those who experienced early technical failure. Multivariable Cox regression models were used. End points included the primary trial outcome (major adverse limb event [MALE] or all-cause death), major amputation, MALE at any time or perioperative (30-day) death, reintervention-amputation-death, and all-cause mortality. RESULTS: Among 1780 patients with CLTI, treatments received included SSGSV bypass (n=621), AC bypass (n=236), and ENDO (n=923) procedures. There were no significant differences in 30-day mortality, major adverse cardiovascular events, or serious adverse events; subjects treated with ENDO experienced greater MALE within 30 days (13.1% versus 2.7%, 3% for SSGSV, AC; P<0.001). On risk-adjusted analysis, SSGSV bypass was associated with reduced MALE or all-cause death (hazard ratio, 0.65 [95% CI, 0.56-0.76]; P<0.001), major amputation (hazard ratio, 0.70 [95% CI, 0.52-0.94]; P=0.017), MALE or perioperative death (hazard ratio, 0.51 [0.41-0.62]; P<0.001), and reintervention-amputation-death (hazard ratio, 0.69 [95% CI, 0.61-0.79]; P<0.001). AC bypass was associated with reduced MALE or perioperative death and reintervention-amputation-death compared with ENDO. Significant benefits of SSGSV over ENDO remained when excluding patients who experienced early technical failure. There were no significant differences in long-term mortality by initial treatment received. When analyzed by the level of disease treated, the improved outcomes of SSGSV were greatest among patients who underwent femoropopliteal revascularization. CONCLUSIONS: Analysis of as-treated outcomes from the BEST-CLI trial demonstrates the safety and clinical superiority of bypass with SSGSV among patients with CLTI who

were deemed suitable for either open surgical bypass or ENDO revascularization. Assessment of great saphenous vein quality should be incorporated into the evaluation of patients with CLTI who are surgical candidates. REGISTRATION: URL: https://www.clinicaltrials.gov; Unique identifiers: NCT02060630 and NCT02060630.

Surgery

Hans SS. A practical technique for optimal visualization of popliteal artery in patients with prior knee arthroplasty. *J Vasc Surg Cases Innov Tech* 2025; 11(3). PMID: Not assigned. Full Text

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A practical technique to visualize popliteal artery in patients with prior knee arthroplasty is described using ipsilateral lateral knee flexion and contralateral oblique position of the image intensifier. This position is well-tolerated without any risk of kinking of the femoral sheath.

Surgery

John S, Yuja Vaquiz Y, Nyayapathi N, **Kabbani L**, Nilam A, Lovell JF, Wilson NA, Yan Y, and Mehrmohammadi M. Photoacoustic Imaging for Image-Guided Gastric Tube Placement: Ex Vivo Characterization. *Sensors (Basel)* 2025; 25(5). PMID: 40096492. Full Text

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Over 250,000 gastrostomy tubes (G-tubes) are placed annually in the United States. Percutaneous endoscopic gastrostomy (PEG) is the most widely used clinical method for placing G-tubes within the stomach. However, endoscope detectability is limited due to the scattering of light by tissues. Poor organ visibility and low sensitivity of the palpation techniques cause blind needle insertions, which cause colon/liver perforations, abdominal bleeding, and gastric resections. Additionally, imaging artifacts and the poor distinguishability between water-filled tissues make ultrasound (US) imaging-based techniques incompatible with G-tube placement. The risk of ionizing radiation exposure and the confinement of fluoroscopy to radiology suites limits its bedside utility in patients. Considering these limitations, we propose to design a safe, point-of-care integrated US and photoacoustic (PA) imaging system for accurate G-tube placement procedures, for a broad spectrum of patients, and to characterize the system's effectiveness. Our proposed technology utilizes a clinically safe contrast agent and a dual-wavelength approach for precise procedures. Our ex vivo tissue studies indicated that PA imaging accurately differentiates the different organs at specific wavelengths. Our characterization studies revealed that PA imaging could detect lower concentrations of Indocyanine Green (ICG) dye coating the colon wall, minimizing the risk of ICG dye-related toxicity and providing safer G-tube placements.

Surgery

Miller-Matero LR, **Vanderziel A**, **Haley EN**, Jackson KM, Moore RS, **Hamann A**, **Carlin AM**, **Genaw J**, and **Braciszewski JM**. Alcohol use after metabolic and bariatric surgery: a qualitative investigation of the relation with mood and food. *Health Psychol Behav Med* 2025; 13(1):2478029. PMID: 40098646. Full Text

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BACKGROUND: Individuals who undergo metabolic and bariatric surgery are at increased risk for an alcohol use disorder. Clarity on the relationships between mood, food, and alcohol use could inform interventions to reduce alcohol use and mitigate risk of alcohol use disorders after metabolic and bariatric surgery (MBS). METHODS: Twenty patients who underwent MBS at a single health care system and reported engaging in post-operative alcohol use were recruited. Participants were between 6 months and 3 years post-operative and reported consuming alcohol at least 2-3 times per month. Participants engaged in a 1-hour semi-structured interview about factors influencing post-operative mood, eating behaviors, and alcohol use. All interviews were recorded, transcribed, and coded by two independent raters. RESULTS: Statements by participants were deductively coded within different themes: (1) changes in mood, (2) changes in eating patterns, and (3) unintended alcohol use and eating. Participants reported positive changes in mood and eating behaviors following MBS, but also indicated potential for negative mood states and new eating patterns. They also suggested that mood was a driver of both eating and alcohol use, including unintended (i.e. unplanned) eating and unintended alcohol use. However, most did not consume food and alcohol at the same time. DISCUSSION: Food and alcohol may be used as a coping strategy for mood, though they are not often consumed together. There is currently a lack of post-operative interventions to reduce alcohol use and findings suggest that interventions could simultaneously target mood, unintended eating, and alcohol use.

Surgery

Sawma T, **Chamseddine H**, Wehbe S, Kanbar K, Cheaib S, Haddad F, and Hoballah JJ. Ankle Peak Systolic Velocity Correlates with Toe Pressure in Patients with Peripheral Artery Disease. *Ann Vasc Surg* 2025; Epub ahead of print. PMID: 40157450. Full Text

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BACKGROUND: Conventional screening of Peripheral Artery Disease (PAD) with Ankle Brachial Index (ABI) may be limited in diabetic patients due to arterial calcification. Alternatively, Ankle Peak Systolic Velocity (APVS) may be a more accurate measure of limb perfusion in those patients. This study aims to assess the correlation between APSV and Toe Pressure (TP) in patients evaluated for PAD. METHODS: This is a single-center retrospective study examining the correlation between APSV and TP in patients evaluated for PAD at a tertiary medical center between January 2019 and August 2020. Spearman Correlation and multivariate linear regression were used to assess the association between APSV and TP. The optimal cutoffs for APSV corresponding to TP of 30 mmHg and 50 mmHg were generated using the Youden index. RESULTS: A total of 224 patients with median age 72 years were included in this study. 61% of patients were females and 54% were diabetic. The mean APSV of the overall population was 62 cm/s. APSV was significantly correlated with TP (R=0.6, p<0.001) in both diabetic and non-diabetic patients. On multivariate analysis, TP was significantly associated with APSV (Estimate B 0.41, 95% CI 0.29-0.53, p<0.001). The optimal cutoffs of APSV to detect a TP ≤ 30 mmHg and TP ≥ 50 mmHg were 35 cm/s and 44 cm/s respectively. CONCLUSION: APSV is a reliable measure for evaluating perfusion in PAD patients. Its adoption in the clinical setting can significantly improve the accuracy of PAD diagnosis, allowing earlier detection and treatment.

Surgery

Shamaa T, **Bajjoka I**, **Prashar R**, **Callaghan M**, **Serra S**, **Abouljoud M**, and **Denny J**. Donor App Increases Awareness and Overall Living Kidney Organ Donation. *Clin Transplant* 2025; 39(3):e70118. PMID: 40103548. Full Text

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Thirty-seven million adult Americans have chronic kidney disease with African Americans are significantly more likely to develop end-stage renal disease (ESRD) compared to other racial groups. Donor App was designed to help kidney transplant candidates (KTCs) identify potential living donors (LDs) by creating social media postings about their need for transplant. The purpose of this study is to evaluate the feasibility of using Donor App in improving awareness about living organ donation and rates of living donor kidney transplantation (LDKT). LD inquiries and transplant outcomes were compared between KTCs who used the Donor App with 1:3 matched historic controls from our center's waitlist. Forty-nine KTCs posted their stories using Donor App. The total views on all platforms and patients were 11 881. Ninety-three potential LD inquiries came on behalf of 26/49 KTCs (53%). KTCs with at least one potential LD inquiry were likely to have at least one donor champion ($p = 0.01$), used multiple social media outlets ($p = 0.003$), and had significantly higher median views versus candidates without inquiries (263 [interquartile range (IQR): 117-624] vs. 42 [IQR: 15-96], respectively; $p < 0.001$). To date, three underwent transplants (two LDKTs and one deceased direct donation). None of the matched controls had any potential LD inquiries ($p = 0.01$). The Donor App can significantly increase awareness and rate of living organ donation.

Surgery

Winder GS, and **Mellinger JL**. Substance Use Disorders and Interprofessional Management in the Pre and Post Liver Transplant Settings. *Clin Liver Dis* 2025. PMID: Not assigned. Full Text

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Urology

Bologna E, Wu Z, Franco A, **Abdollah F**, **Finati M**, Simone G, Tuderti G, Licari LC, Correa AF, Lee R, De Cobelli O, Ferro M, Porpiglia F, Amparore D, Checcucci E, Tufano A, Perdonà S, Bhanvadia R, Margulis V, Brönimann S, Singla N, Puri D, Derweesh IH, Mendiola DF, Gonzalgo ML, Ben-David R, Mehrazin R, Moon SC, Rais-Bahrami S, Yong C, Sundaram CP, Ghoreifi A, Moghaddam FS, Djaladat H, Ditonno F, Antonelli A, and Autorino R. Single bladder instillation of gemcitabine versus mitomycin C after minimally invasive radical nephroureterectomy: A propensity-score match analysis from the ROBUUST 2.0 collaborative group. *Asian J Urol* 2025. PMID: Not assigned. Full Text

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Objective: Radical nephroureterectomy (RNU) is considered the standard of care for patients with high-risk upper tract urothelial carcinoma. Current literature reveals a deficit in direct comparative studies evaluating the efficacy of different chemotherapeutic agents administered in single postoperative instillation following RNU. The primary aim of this study was to compare the bladder recurrence (BR) rates between patients receiving a single instillation of mitomycin C (MMC) versus gemcitabine (Gem) after RNU. Methods: The ROBUUST (ROBotic surgery for Upper tract Urothelial cancer STudy) 2.0 is an international, multicenter registry that aggregates data on patients who have undergone curative surgery for upper tract urothelial carcinoma across participating centers from January 2015 to December 2022. Data including primary baseline variables of the patients, characteristics of the tumors, surgical management, and definitive histopathological characterizations were collected and stratified based on the type of post-operative bladder instillation: MMC (the MMC group) and Gem (the Gem group). We selected variables correlated with our primary outcome to conduct a propensity-score match analysis. Results: One hundred patients in the MMC group were matched 1:1 with 100 patients in the Gem group. At 36 months of follow-up, 30 patients in the MMC group and 39 patients in the Gem group experienced BR, representing recurrence rates of 30% and 39%, respectively (p=0.2). The Cox proportional hazards model comparing BR between the groups revealed a hazard ratio of 1.58 (95 % confidence interval: 0.98–2.55)

with a non-statistically significant increased risk of BR in the Gem group compared with the MMC group (p=0.059). Conclusion: A single perioperative instillation of Gem or MMC seems to offer similar efficacy in reducing the risk of BR in patients undergoing RNU. Further research, ideally within the framework of prospective studies, is warranted to elucidate the optimal chemotherapeutic approach in this setting.

Urology

Sheybaee Moghaddam F, Sayyid RK, Ghoreifi A, Franco A, Wu Z, Wang L, Antonelli A, Ditonno F, **Abdollah F**, **Finati M**, Simone G, Tuderti G, Helstrom E, Correa AF, De Cobelli O, Ferro M, Porpiglia F, Amparore D, Tufano A, Perdonà S, Brönimann S, Singla N, Meagher MF, Derweesh IH, Mendiola DF, Gonzalgo ML, Ben-David R, Mehrazin R, Moon SC, Rais-Bahrami S, Yong C, Sundaram CP, Bhanvadia R, Margulis V, Autorino R, and Djaladat H. Neoadjuvant chemotherapy prior to radical nephroureterectomy: Survival outcomes and recurrence patterns by pathologic node status. *Urol Oncol* 2025; Epub ahead of print. PMID: 40133182. Full Text

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Department of Urology, Icahn School of Medicine at Mount Sinai Hospital, New York, NY.
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Norris Comprehensive Cancer Center, Department of Urology, University of Southern California, Los Angeles, CA. Electronic address: djaladat@med.usc.edu.

PURPOSE: To evaluate survival outcomes and recurrence patterns by pathologic nodal status in upper tract urothelial carcinoma (UTUC) patients receiving neoadjuvant chemotherapy (NAC) prior to radical nephroureterectomy (RNU) and lymph node dissection (LND). MATERIALS AND METHODS: Using the international ROBUUST 2.0 database, a retrospective analysis of UTUC patients who underwent robotic/laparoscopic RNU+LND±NAC was performed. Patients were stratified by NAC and pathologic nodal status into pN0, ypN0, pN+, and ypN+ subgroups. Overall (OS), metastasis-free (MFS), and urothelial recurrence-free survivals (RFS) were compared using Kaplan-Meier curves and multivariable Cox regression modeling. RESULTS: The cohort included 883 patients (15% received NAC). 212 (24%) patients had (y)pN+ disease. Median follow-up was 19 months. Compared to pN+ patients, ypN+ patients had significantly worse 1- (64% vs. 72%), 3- (40% vs. 54%), and 5-year (20% vs. 31%) OS rates. Node-negative patients had similar OS, irrespective of NAC treatment (1-year: 94%; 3-year: 77%-82%). At 1 year, all ypN+ patients had metastases, while 13% of pN+ patients remained metastasis-free. Among ypN+ patients, 89% experienced nodal/regional or distant metastases as the site of initial recurrence, compared to 39% of pN+ patients. Initial nodal/regional or distant metastases occurred in 42% and 18% of ypN0 and pN0 patients, respectively. CONCLUSION: ypN+ patients have worse survival compared to pN+ patients. Recurrence patterns differ by nodal and NAC status, with ypN+ patients having a significantly higher incidence of nodal/regional or distant metastases as the initial site of recurrence.

These survival outcomes and recurrence patterns differences may have important surveillance and treatment implications.

Urology
Tinsley SA, **Stephens A**, **Morrison C**, **Richard C**, **Hares K**, **Lutchka J**, **Rogers C**, and **Abdollah F**. Utilization and Cancer Control Outcomes of Active Surveillance Amongst Black and White Men with Intermediate Risk Prostate Cancer in a Population-Based Analysis. *J Racial Ethn Health Disparities* 2025; Epub ahead of print. PMID: 40048083. Full Text

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INTRODUCTION: To assess the utilization and prostate cancer (PCa)-specific mortality (PCSM) between non-Hispanic Black (NHB) and non-Hispanic White (NHW) on active surveillance (AS) with intermediate risk PCa (iPCa). METHODS: The Surveillance, Epidemiology, and End Results database was queried between 2010-2016. The rate of AS was calculated per year between NHB and NHW using univariable logistic analysis (UVA) and multivariable logistic analysis (MVA). Next, inverse probability of treatment weighting was performed on those that underwent watchful waiting (WW) and competing-risks cumulative incidence function (CIF) and MVA were used to assess the impact of race on other-cause mortality (OCM) and PCSM. Statistical significance defined as $p < 0.05$, but some observations were deemed non-statistically significant per our Benjamini-Hochberg procedures, RESULTS: 50,315 patients had iPCa, and 3,310 underwent AS/WW. The rate of AS increased amongst NHB (+ 3.1%) and NHW (+ 5.7%) from 2010 - 2016. UVA did not show an association with race, but MVA showed a negative association, based on our Benjamini-Hochberg correction, between NHB and AS [OR 0.68 (95% CI: 5.4-0.87; $p = 0.002$)]. On CIF, NHB and NHW had non-significant differences in OCM in the weighted cohort ($p = 0.03$), due to the Benjamini-Hochberg correction, and that was confirmed with MVA with a HR of 1.23 (95% CI: 1.02-1.49; $p = 0.03$). However, the CIF on PCSM showed NHB had a higher risk of PCSM ($p < 0.0001$), and that was confirmed with MVA with a HR of 3.01 (95% CI: 2.00-4.53; $p < 0.001$). CONCLUSION: The utilization of AS for iPCa increased amongst NHB and NHW patients. Unfortunately, NHB race was associated with increased risk of PCSM from one year to the next compared to NHW patients.

Urology
Viganò S, **Finati M**, **Stephens A**, **Bertini A**, **Finocchiaro A**, Lughezzani G, Buffi N, Salonia A, Briganti A, Montorsi F, Rossanese M, Di Trapani E, Ficarra V, Sood A, **Rogers C**, and **Abdollah F**. Socioeconomic Disparities in Prostate Cancer Treatment: The Impact of Area Deprivation Index on Initial Treatment Type for Localized PCa in a North-American Cohort. *Prostate* 2025; Epub ahead of print. PMID: 40066656. Full Text

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BACKGROUND: Socioeconomic status and geographical location contribute to disparities in localized prostate cancer (PCa) treatment. We examined the impact of area of deprivation index (ADI) on initial treatment type for localized PCa in a North-American cohort. METHODS: We performed a retrospective analysis of patients diagnosed with localized PCa, treated within Henry Ford Health (HFH), between 1995

and 2022, with available ADI-data. ADI was assigned based on residential census block group, ranked as a national deprivation percentile. Patients were categorized into three treatment-groups: radical prostatectomy (RP), radiation therapy (RT) and "other" treatment. Using multinomial logistic regression, we assessed ADI impact on treatment choice. After excluding patients without cT, ISUP-grade and/or PSA, we stratified by D'Amico risk-classification and repeated the regression analysis in each subgroup. RESULTS: Among 14,204 patients, 28.4% were NHB. Median (IQR) age at diagnosis was 65 (59-71) years. Median (IQR) ADI was 58 (36-83) for overall cohort and 51 (30-74), 66 (45-91), and 62 (39-88) for RP, RT, and "other" groups, respectively ($p < 0.0001$). Multivariable analysis showed ADI as an independent predictor of treatment choice ($p = 0.01$): for each 10-unit increase in ADI, patients were 3% more likely to receive RT and 10% less likely to receive RP. High ADI predicted a lower likelihood of receiving initial surgery across all risk-groups ($p < 0.001$). CONCLUSIONS: Patients in more advantaged areas were more likely to receive RP, while those in disadvantaged areas received more RT. Recognizing how neighborhood factors affect treatment choices is crucial for improving health equity and reducing disparities in PCa outcomes.

Urology
Wang Y, **Wilder S**, Til MV, Gammons M, Mirza M, Noyes SL, Jafri M, Seifman B, Ghani KR, Semerjian A, **Rogers CG**, and Lane BR. Durability of Active Surveillance for Localized Renal Masses: 3-year Outcomes in the Michigan Urological Surgery Improvement Collaborative. *Eur Urol Open Sci* 2025; 75:11-19. PMID: Not assigned. Full Text

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Background and objective: In Michigan, around 50% of patients with localized renal masses of ≤7 cm (cT1RMs) are managed without immediate intervention, contradicting previous reports indicating active surveillance (AS) rates of <10–20%. Questions remain regarding the durability of AS when applied so broadly. We evaluated the oncologic outcomes of patients at 1, 2, and 3 yr after the initiation of AS, including survival and delayed intervention rates, hypothesizing that these will be comparable to prior reports. Methods: Between May 2017 and September 2023, data regarding 2161 (52% of 4178) patients with cT1RMs who initiated AS at Michigan Urological Surgery Improvement Collaborative (MUSIC) practices were reviewed. Factors associated with staying on AS were analyzed. Overall survival and the cumulative incidence of treatment were assessed using the Kaplan-Meier method. Key findings and limitations: In total, 2161 patients from 21 practices initiated AS, including 51% with tumors of ≤2 cm, 26% with tumors of 2.1–3.0 cm, and 24% with tumors of 3.1–7.0 cm. At 36 mo, overall survival was 90%, with metastasis and death from kidney cancer in only one patient who refused intervention. The cumulative incidence rates of treatment were 6%, 11%, and 13% at 1, 2, and 3 yr, respectively, with 9.6% for ≤2 cm, 16% for 2.1–3.0 cm, and 18% for >3 cm tumors at 3 yr. Limitations include the study's retrospective review of prospectively enrolled data limiting conclusions beyond 3 yr of follow-up. Conclusions and clinical implications: MUSIC practices initiate AS for >50% of patients with 13% incidence of delayed intervention and <1% incidence of metastasis within 3 yr, indicating that AS is a safe and durable option for many patients with cT1RMs. Further investigations into imaging protocols and longer-term outcomes of AS are warranted. Patient summary: In Michigan, most patients diagnosed with localized renal masses of <4 cm and some with tumors up to 7 cm in size elect active surveillance (AS), with a 13% cumulative incidence of undergoing intervention within 3 yr of detection. At 3 yr after initiating AS, the cohort had 90% overall survival and >99% cancer-specific survival, indicating that AS is a safe and durable strategy.

Urology
Yoshida T, **Rogers CG**, **Raza J**, Matsuda T, and Kinoshita H. Reply to: "Photodynamic Diagnosis-Guided Ureteroscopic Laser Ablation of Upper Tract Urothelial Carcinoma: Some Concerns and Future Direction". *Ann Surg Oncol* 2025; Epub ahead of print. PMID: 40089618. Full Text

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Administration
Razdan P, **Gowda T**, **Alaamili A**, and **Katzman S**. RECURRENT BOSUTINIB-INDUCED PERICARDIAL EFFUSION IN CML. *J Am Coll Cardiol* 2025; 85(12):3980. Full Text

Background Chronic myeloid leukemia (CML) once had a poor prognosis, but the development of tyrosine kinase inhibitors (TKI) have enhanced outcomes and extended life expectancy. Since bosutinib's approval in 2012, its cardiac adverse reactions have been described and are quite rare. Case A 72 year-old female with a history of CML presented due to shortness of breath over the past 2 months. An echocardiogram showed a large pericardial effusion without tamponade. Bosutinib was discontinued due to suspicion that it triggered the effusion. Pericardiocentesis was performed with resolution of symptoms, no infection/malignant cells were found. 2 weeks later, repeat imaging showed another large pericardial effusion without tamponade. CT surgery placed a pericardial window and imaging showed reduction of fluid. Decision-making Bosutinib is a TKI shown to increase risk of effusions, most commonly pericardial/pleural with a 13.3% incidence. In 2018, an expert panel published guidelines on managing adverse reactions, but knowledge on such severe cases requiring pericardiocentesis was limited. Little evidence exists on managing extreme reactions, recurrence duration, and essential cardiac assessments before starting bosutinib. Conclusion Awareness of bosutinib's cardiac risks needs to be raised. Questions remain, such as should these patients should switch to alternate agents or lower the dosage of bosutinib. More research is needed to understand severe reactions and future options going forward. [Formula presented]

Allergy and Immunology
Finkel K, **Lin CH**, **Sitarik A**, **Kim H**, **Eapen A**, **Baptist A**, **Levin A**, **Cassidy-Bushrow A**, **Johnson C**, and **Zoratti E**. Associations between genetic ancestry and serum Immunoglobulin E trajectory, allergen-specific IgE sensitization, and asthma at 10 years among Black children in the WHEALS birth cohort. *J Allergy Clin Immunol* 2025; 155(2):AB269-AB269. Full Text

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Allergy and Immunology
Schutt M, Gadd S, Senter J, Barrera L, Cho S, Pongracic J, Liu AD, Gruchalla R, Kercsmar C, Hershey GK, **Zoratti E**, **Johnson C**, Teach S, Kattan M, Bacharier L, O'Connor G, Gern J, Visness C, Coleman A, Gergen P, Becker P, Jackson D, Altman M, and Kumar R. PAI-1 genotype and regulation of airway PAI-1 in vivo: relationships with patterns of airway gene expression during illness. *J Allergy Clin Immunol* 2025; 155(2):AB279-AB279. Full Text

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Anesthesiology
Rabbani B, **Lee JC**, **Parikh S**, **Sanders J**, **Zweig B**, **Wang DD**, and **Mitchell J**. TRANSESOPHAGEAL ECHOCARDIOGRAPHY SIMULATOR TRAINING FOR VISUALIZATION OF THE PULMONARY VEINS: A RANDOMIZED CONTROLLED STUDY. *J Am Coll Cardiol* 2025; 85(12):2528. Full Text

Background We sought to determine if transesophageal (TEE) simulation training would improve fellow preparation, clinical performance, and learning environment at an urban teaching hospital. To do so, we focused on the challenging process of visualizing all pulmonary veins. Methods Fellows in cardiology or anesthesiology were randomized to simulator training. All completed a pre and post-test survey. The intervention group received a comprehensive 1.5 hour TEE simulation session. All then performed a clinically indicated TEE exam and were rated on clarity of pulmonary vein images and ability to image each structure independently. Results Control and intervention groups were evenly matched in demographics and experience. Survey results demonstrate a significant difference in comfort level with the theory, interpretation, and technical performance of a complete TEE exam, and effectiveness of attendings. However, there was no difference in overall satisfaction with TEE training and comfort level obtaining pulmonary veins. Additionally, assessment data did not show a difference between the clarity of images or the ability to achieve the pulmonary veins independently. [Formula presented] Conclusion Simulation training did not improve real-world trainee performance in imaging all pulmonary veins compared to standard TEE training. But simulation training is a means to improve overall understanding of interpretation and performance of TEE, and teaching effectiveness of attendings.

Cardiology/Cardiovascular Research

Abdelhai OS, **Mahfouz R**, **Maligireddy A**, **Rangavajla G**, **Andrews TQ**, **Jabri A**, **Memon M**, **McBride P**, **Villablanca PA**, **Jamil D**, and **Aggarwal V**. THE IMPACT OF ATRIAL FIBRILLATION ON IN-HOSPITAL OUTCOMES IN PATIENTS UNDERGOINGLIVER TRANSPLANTATION USING NIS 2016-2021. *J Am Coll Cardiol* 2025; 85(12):94. Full Text

Background The influence of atrial fibrillation (AF) on outcomes in patients undergoing liver transplantation has not been extensively investigated in the literature. This study aims to assess the prevalence of pre-transplant AF and its association with postoperative outcomes in patients undergoing liver transplantation. Methods Data from the National Inpatient Sample (2016-2021) identified liver transplant patients and their AF status. T-tests and chisquare tests compared the data. Outcomes included mortality risk, in-hospital results, and risk factors. Univariate and multivariate logistic regressions calculated odds ratios for comorbidities. Results The study identified 45,460 liver transplant patients, 3,905 of whom had AF. AF patients had a longer LOS (28.6 vs. 19.9 days, $p = 0.001$) and higher hospital charges ($768,558 vs. $624,364, $p < 0.001$). The mortality rate was also greater in AF patients (5.89% vs. 2.72%, $p < 0.001$), and this finding was confirmed by multivariate analysis, which showed an odds ratio of 1.54 ($p < 0.001$) after adjusting for age, gender, race, and comorbidities. Conclusion Our study demonstrated that liver transplant patients with a history of AF in a national cohort experienced higher mortality and morbidity rates. This finding underscores the importance for physicians to prioritize optimizing AF management in this patient group, which could help reduce complications, shorten hospital stays, and lower overall mortality. [Formula presented]

Cardiology/Cardiovascular Research

Abdelhai OS, **Mohammed M**, **Frisoli TM**, **Lee JC**, **O'Neill WW**, **Zweig B**, **O'Neill BP**, **Dawdy J**, **Gonzalez PE**, and **Villablanca PA**. SAFETY AND EFFICACY OF PARAVALVULAR LEAK CLOSURE IN POST TAVR PATIENTS: A SINGLECENTER EXPERIENCE. *J Am Coll Cardiol* 2025; 85(12):924. Full Text

Background Paravalvular leak (PVL) is a notable complication following transcatheter aortic valve replacement (TAVR) and is associated with adverse impacts on both short- and long-term survival. This study aims to assess the safety and efficacy of PVL closure in a singlecenter experience. Methods We retrospectively analyzed all patients who underwent PVL closure post TAVR at Henry Ford Hospital between 2012 and 2022. Data collected included patient demographics, types and number of devices used, severity of residual PVL post-closure, and overall success rates. Severity of PVL was categorized as severe, moderate, and mild. Results Fifty patients (median age: 80 for females [n=32], 75 for males [n=18]) underwent attempted PVL closure. Comorbidities included hypertension, diabetes, hyperlipidemia, and heart failure. The AVP II plug Amplatzer was the most used device (72%, n=36), followed by Amplatzer Muscular VSD occluders (28%, n=14). On average, two devices were used per procedure. Post-intervention, all patients had minimal or no residual leak, with significant improvement in PVL

severity (Figure 1). Conclusion This single-center experience demonstrates that percutaneous PVL closure after TAVR is a safe and effective procedure, as illustrated by the significant reduction in paravalvular leak severity (Figure 1). The use of Amplatzer devices, particularly the AVP II plug, resulted in a high technical success rate with minimal residual PVL. [Formula presented]

Cardiology/Cardiovascular Research
Abdelhai OS, **Villablanca PA**, **Rangavajla G**, **Frisoli TM**, **O'Neill BP**, **Lee JC**, **Zweig B**, **Fram G**, and **Nguyen F**. RIGHT VENTRICULAR FUNCTION AS ASSESSED BY TRICUSPID ANNULAR PLANE SYSTOLIC EXCURSION IN PATIENTS UNDERGOING TRANSCATHETER TRICUSPID VALVE REPLACEMENT WITH EVOQUE VALVE. *J Am Coll Cardiol* 2025; 85(12):933. Full Text

Background Transcatheter tricuspid valve replacement (TTVR) with the Evoque valve represents a new commercially available nonsurgical therapy for severe tricuspid regurgitation (TR) in the US. Limited data has been published on the impact of this intervention on right ventricular function. Methods We performed a retrospective review of patients that underwent commercial TTVR with Evoque valve at our institution between February and July 2024 (n=40), assessing tricuspid annular plane systolic excursion (TAPSE) as reported by interpreting physician on transthoracic echocardiogram before the procedure, 1-day post-procedure and 30-days post-procedure. Results The median TAPSE reported pre-procedure was 15.3 mm (IQR 14-19) with reductions seen at 1 day [13.8 mm (IQR 11-16, p=0.03)] and 30 days [12.1 mm (IQR 10-16; p=0.01)]. Despite two deaths and five heart failure (HF) readmissions in this cohort at the 30day follow-up, no statistical correlation was found between TAPSE reduction and mortality or HF readmissions (p=0.62, CI=0.24-2.4). Conclusion The use of TAPSE to assess right ventricular function post TTVR with Evoque has yet to be validated, and further investigation on how to best assess right ventricular function post TTVR is needed. We investigated a cohort of patients in whom TAPSE has been reported and noted a post-procedural reduction in median TAPSE at 30 days that was not associated with instances of hospitalization or mortality. [Formula presented]

Cardiology/Cardiovascular Research
Alkehef Y, **Kheyrbek M**, **Alsheikh O**, **Khan A**, **Zein RK**, and **Azoury F**. THE SILENT CRISIS: A CASE OF LEFT INTERNAL MAMMARY ARTERY GRAFT RUPTURE FOLLOWING CABG. *J Am Coll Cardiol* 2025; 85(12):2919. Full Text

Background Left Internal Mammary Artery (LIMA) graft rupture is a rare but fatal complication of coronary artery bypass graft (CABG). It may have subtle presentation such as dyspnea and syncope but can rapidly progress to hemorrhagic shock. Case 77-year-old male with history of coronary artery disease status post CABG two months prior presented with syncope. He was noted to be hypotensive and tachycardic. Computed Tomography (CT) of the chest showed sternal hematoma and left pleural effusion. Echocardiogram was normal. A chest tube was placed which drained 250 cc bloody fluid. Patient continued to be in shock requiring blood transfusions and vasopressors. Decision-making Our priority was to identify the source of bleeding in the chest. Video-assisted thoracoscopic surgery was non-revealing. He improved following the procedure only to get worse the next day. Repeat chest x-ray showed recurrence of left pleural effusion. CT angiogram of the chest was done (fig 1), and this time showed extravasation of contrast from the LIMA into the pleural space. He was taken emergently to the cath lab. LIMA angiogram (fig 2) showed mid-vessel extravasation. A covered stent was placed. Post angiogram showed no further extravasation and we were able to wean off vasopressors. He was stable for discharge days later. Conclusion Thorough clinical exam and multimodality imaging are essential to identify CABG complications. Emergent management with surgery or catheter interventions might be necessary. [Formula presented]

Cardiology/Cardiovascular Research
Almajed MR, **Zimmerman A**, **Obeidat L**, **Fadel R**, **Grafton G**, **Cowger JA**, and **AlDarzi W**. A FATAL INTERSECTION: ANTIPHOSPHOLIPID ANTIBODY SYNDROME AND CARDIOGENIC SHOCK. *J Am Coll Cardiol* 2025; 85(12):4348. Full Text

Background Cardiac involvement in antiphospholipid syndrome (APS) manifests as valvular heart disease, ventricular dysfunction, and thrombosis. Mechanical support (MCS) and advanced heart failure

(HF) therapies may be necessary in patients who do not respond to conventional management. Case A 32-year-old woman with a history of APS and systemic lupus erythematosus presented with shortness of breath and was admitted for cardiogenic shock. One month prior, she underwent cesarean section delivery at 26-weeks of gestation for hemolysis, elevated liver enzymes, and low platelet count (HELLP) syndrome. Echocardiogram revealed biventricular dysfunction. Invasive coronary angiography was negative for coronary artery ischemia or dissection. She was medically managed for decompensated HF but developed worsening shock despite vasopressor and inotropic support. Hemodynamic assessment revealed biventricular dysfunction (RA pressure 18 mmHg, wedge pressure 30 mmHg), with a reduced cardiac output of 3.54 L/min. Due to worsening hemodynamics, a peripherally cannulated transcaval left atrial veno-arterial extracorporeal membrane oxygenation (ECMO) was placed. Further evaluation for HF etiologies was unremarkable with a bland endomyocardial biopsy. Despite therapeutic systemic anticoagulation, her course was complicated by extensive thrombosis involving the arterial and venous catheters, and ECMO inflow cannula at the IVC extending into the left atrium. Decision-making Our patient developed refractory cardiogenic shock and extensive arterial and venous thrombosis concerning for catastrophic APS. She was treated with plasmapheresis, systemic steroids, and therapeutic anticoagulation with a modified higher intensity protocol. She underwent orthotropic heart transplantation ten days after hospitalization. Biopsy of the explanted heart revealed myocardium with extensive transmural necrosis and granulation tissue. Conclusion APS associated cardiomyopathy confers a poor prognosis and early MCS evaluation should be considered. Management requires a multidisciplinary approach that could include hematologic interventions and advanced HF therapies.

Cardiology/Cardiovascular Research
Andrews TQ, **McBride P**, **Abdelhai OS**, **Toiv A**, **Zimmerman A**, and **Cowger JA**. ADRENERGIC MYOCARDITIS DUE TO PHEOCHROMOCYTOMA. *J Am Coll Cardiol* 2025; 85(12):2880. Full Text

Background Chronic adrenergic stimulation has adverse effects on cardiomyocytes including hypertrophy, apoptosis, and contraction band necrosis resulting in cardiac dysfunction. Case A 33-year-old male with no medical history presented with subacute palpitations, flushing, and dyspnea found to have LVEF of 10%, LVH, and apical thrombus with right parietal lobe infarct on CT. RHC showed bivencticular volume overload with low cardiac index and AKI. Blood pressures were unusually elevated. Cardiac MRI showed subendocardial LGE deposition consistent with myocarditis. Further imaging revealed a 4.3 x 3.9 cm left adrenal mass. Laboratory tests showed elevated total metanephrines and catecholamines raising concern for pheochromocytoma. He was transitioned from nitroprusside to doxazosin for alpha-blockade along with GDMT. He underwent adrenalectomy with pathology showing pheochromocytoma followed by normalization of cardiac function. Decision-making The patient's history of flushing and unusual hypertension in setting of low cardiac output prompted laboratory assessment with abdominal imaging which effectively confirmed the diagnosis. The removal of the adrenal tumor led to myocardial cure. Conclusion Adrenergic myocarditis is a rare condition associated with pheochromocytoma and can present with acute hemodynamic compromise. Clinical history is crucial for diagnosing and managing this uncommon disorder. Effective treatment requires a multidisciplinary approach. [Formula presented]

Cardiology/Cardiovascular Research
Andrews TQ, **McBride P**, **Abdelhai OS**, **Toiv A**, **Zimmerman A**, and **Cowger JA**. CARDIOGENIC SHOCK SECONDARY TO HUMAN IMMUNODEFICIENCY VIRUS INDUCED MYOCARDITIS. *J Am Coll Cardiol* 2025; 85(12):3210. Full Text

Background HIV associated cardiomyopathy is a stage IV defining HIV illness conferring increased mortality among infected individuals. Favorable outcomes rely on an interdisciplinary care approach. Case A 28-year-old male with no medical history or high risk social features presented to outside hospital with dyspnea and found in cariogenic shock (CGS) with positive HIV PCR. He escalated to intermediate hospital for Impella CP then to HFH where Impella was upgraded to 5.5. HIV viral load was 3.8M copies with low CD4. HAART was started with emtricitabine/tenofovir and Dolutegravir. At week two, LVEF improved to 33% with hemodynamic stabilization. The Impella was removed and the patient tolerated GDMT. Repeat HIV viral load of 172 copies. He was transitioned to bictegravir/emtrcitabine/tenofovir and discharged. At four weeks post-discharge, he was NYHA I-II on four-pillar GDMT. Decision-making Even in 2024, HIV should be considered in the differential diagnosis of acute myocarditis as risks for HIV may

not be readily shared. Prompt consideration of HIV, initiation of HAART, and aggressive stabilization through MCS was essential in managing the underlying process. Conclusion This case highlights a potentially reversible cardiomyopathy with a complex interplay of acute HIV myocarditis and CGS. The patient's significant improvement, evidenced by reduced HIV viral load and successful weaning from MCS, underscores the effectiveness of a multidisciplinary approach. [Formula presented]

Cardiology/Cardiovascular Research
Chou A, **Vishwanath R**, **Dawdy J**, and **Ananthasubramaniam K**. COVID19 MYOCARDITIS: A MULTI-MODALITY IMAGING APPROACH TO DIAGNOSIS. *J Am Coll Cardiol* 2025; 85(12):3550. Full Text

Background COVID19 is primarily a respiratory illness, but with multisystem organ involvement. The incidence of COVID19 myocarditis in the USA is estimated to be < 1%. Patients present with a range of symptoms from chest pain to fulminant cardiogenic shock. Case A 24 year old male with no past medical history presented to the ER after multiple syncopal episodes and 3 days of respiratory symptoms. Labs were notable for HS troponins < 4 and he was positive for COVID19. He improved with IV fluids and was discharged. Three days later, he re-presented to the ER with 12 hours of substernal chest pain. Labs showed elevated HS troponins, CRP and ESR. He was started on a heparin drip and admitted to the hospital Decision-making An echocardiogram showed normal ejection fraction with no wall motion abnormalities, but abnormal strain with a value of -15.2% concerning for possible early myocardial dysfunction. Given high suspicion for myocarditis, heparin drip was stopped and a cardiac MRI was ordered. Cardiac MRI showed increased T2-weighted signal and mid myocardial to subepicardial late gadolinium enhancement consistent with acute myocarditis. Conclusion Myocarditis is a rare complication of COVID19 infection that has been associated with a mortality rate as high as 15%. It is more common in young males. Given non-specific presenting symptoms, a multi-modality imaging approach is important to establish a diagnosis. While TTE is an important first line diagnostic tool, cardiac MRI can help provide a definitive diagnosis. [Formula presented]

Cardiology/Cardiovascular Research
Ethakota J, **Doddi H**, **Kumar D**, **Salib N**, and **Memon MA**. FROM INCIDENTAL CARDIAC MASS TO METASTATIC NEUROENDOCRINE TUMOR: A DIAGNOSTIC JOURNEY. *J Am Coll Cardiol* 2025; 85(12):3982. Full Text

Background Cardiac metastasis of neuroendocrine tumors (NET) is rare with incidence less than 5%. They are mostly asymptomatic and detected incidentally. Case A 73-year-old man with past medical history of Coronary artery disease, hypertension, COPD underwent a CT chest for lung cancer screening, it showed a small isodense mass in the right ventricle in relation to interventricular septum near cardiac apex . Further workup included a transthoracic echocardiogram showing a normal ventricular function, EF of 65% and normal valves. Heart catherization showed a severe right and circumflex disease with moderate LAD disease. Cardiac MRI showed an enhancing lesion at the right ventricular apex attached to the RV and septum. PET scan showed mildly hypermetabolic cardiac apical region mass measuring about 2.1 x 1.5 cm. He underwent a CABG with right ventricular mass excision at the Cleveland Clinic. Pathology showed the tumor cells to be diffusely and strongly positive with synaptophysin and no reactivity with ACTH. Movat stain showed pseudocapsule around the tumor and focal moderate interstitial fibrosis of the myocardium. The mass was deemed to be a NET. Followed by a Ga-68 dotatate scan showed masslike thickening in the terminal ileum. Metastatic lesions in the left hepatic lobe and mesentery were seen as well. CT chest/abdomen/pelvis showed 2.5 x 2 cm mass in the ileocolic mesentery in proximity to the ileocolonic junction containing coarse calcifications. He was diagnosed with stage IV neuroendocrine cancer. Lab work showed a chromogranin A level of 160 ng/ml (reference range 0 - 160 ng/mL) and 5HIAA level of 13.5 mg (reference range < 10 mg/24h). Eventhough the patient was asymptomatic he was started on octreotide injections monthly in the setting of visceral and cardiac metastasis. A repeat echocardiogram showed EF in the range of 65 - 70% and normal pattern of LV diastolic filling. Decision-making The echocardiography, Cardiac MRI, dotatate scan, and PET/CT guided the diagnosis and management. Mass resection and immunostaining confirmed diagnosis. Conclusion As the cardiac NET are mostly asymptomatic, multimodal imaging plays an important role in early detection and management is patient-specific.

Cardiology/Cardiovascular Research

Fadel R, **Alrayes H**, **Jabri A**, **Giustino G**, **Gonzalez PE**, **O'Neill BP**, **Lee JC**, **Nemeh H**, **Frisoli TM**, **Basir MB**, **O'Neill WW**, and **Villablanca PA**. LEFT ATRIAL VENO-ARTERIAL EXTRACORPOREAL MEMBRANE OXYGENATION (LAVA-ECMO) AS A BRIDGE TO SURGICAL OR PERCUTANEOUS CLOSURE OF POST-MYOCARDIAL INFARCTION VENTRICULOSEPTAL DEFECTS (MI-VSD): A CASE SERIES. *J Am Coll Cardiol* 2025; 85(12):1377. Full Text

Background Post-myocardial infarct (MI) ventricular septal defect (VSD) is a rare complication with a high mortality rate. The use of venoarterial extracorporeal membrane oxygenation (VA-ECMO) as a bridge to surgical or percutaneous repair has been published, but is limited to small case series primarily utilizing surgical ECMO, with the main drawback of potentially increasing afterload and left ventricle pressure, further worsening VSD shunting. Left-atrial VA-ECMO (LAVA-ECMO) can potentially absolve this concern, utilizing bi-atrial drainage through a trans-septal fenestrated cannula. Methods Consecutive cases were reviewed from 2018-2023 at a quaternary care center in Metropolitan Detroit. Results 5 patients were included, all with VSD secondary to MI, and managed with LAVA-ECMO as a bridge to repair. Average age was 62 ± 4.2 years, and left ventricular ejection fraction of 46.6 ± 13.8%. Hemodynamic monitoring demonstrated improvement in right atrial, right ventricular, pulmonary, left atrial, and left ventricular pressures post cannulation. Average time to repair was 7.4 ± 3.9 days. All 5 patients survived to repair, with 4 undergoing surgical and 1 undergoing percutaneous closure. Conclusion This case series highlights LAVA-ECMO as a bridge to MI-VSD repair in patients with cardiogenic shock. Bi-atrial drainage with LV unloading makes LAVA-ECMO a desirable cannulation strategy in patients with large VSD, and provides cardiopulmonary support pending definitive treatment. [Formula presented]

Cardiology/Cardiovascular Research

Fadel R, **Lai L**, **Zweig B**, **Alrayes H**, **Fram G**, **Gonzalez PE**, **Lee JC**, **Frisoli TM**, **Villablanca PA**, and **O'Neill BP**. TRANSCATHETER CLOSURE OF LEFT VENTRICULAR OUTFLOW TRACT-TO-LEFT ATRIUM FISTULA AS A COMPLICATION OF BASILICA TAVR (BIOPROSTHETIC OR NATIVE AORTIC SCALLOP INTENTIONAL LACERATION TO PREVENT IATROGENIC CORONARY ARTERY OBSTRUCTION DURING TRANSCATHETER AORTIC VALVE REPLACMENT). *J Am Coll Cardiol* 2025; 85(12):2976. Full Text

Background Left ventricular outflow tract (LVOT) perforation is not a widely recognized complication of BASILICA TAVR (Bioprosthetic Aortic Scallop Intentional Laceration to prevent Iatrogenic Coronary Artery obstruction during Transcatheter Aortic Valve Replacement). Case An 85-year-old female patient presented for valve-in-valve TAVR with BASILICA of a severely stenosed 23 mm bioprosthetic surgical valve. Under transesophageal echocardiogram (TEE) guidance, the left coronary cusp leaflet was lacerated, followed by surgical valve fracture using a 24 mm balloon valvuloplasty catheter. A 23 mm TAVR was subsequently deployed successfully with only trivial aortic regurgitation. The patient developed significant hypotension requiring vasopressor support. A significant LVOT-left atrium fistula was promptly identified on TEE, with severe mitral regurgitation, and a new pericardial effusion (figure 1). Decision-making An emergent pericardiocentesis was performed due to tamponade, with improvement in hemodynamics. Next, the decision was made to perform a transseptal puncture to facilitate closure of the fistula using a 10 mm VSD occluder device (figure 1). The decision was made to access the perforation through transseptal puncture due to its anterior location and freshly deployed TAVR valve. Conclusion Recognizing LVOT and mitral annular perforation as a complication of BASILICA TAVR is critical to prompt diagnosis and management. VSD occluder devices may be used in this setting. [Formula presented]

Cardiology/Cardiovascular Research

Fadel R, **Memon M**, **Swanson B**, and **Jamil D**. A RARE POST-INFARCT LEFT VENTRICULAR SEPTAL PSEUDOANEURYSM WITH RUPTURE INTO THE RIGHT VENTRICLE: A DIAGNOSTIC CHALLENGE MIMICKING VENTRICULAR SEPTAL DEFECT. *J Am Coll Cardiol* 2025; 85(12):3150. Full Text

Background Left ventricular pseudoaneurysms are rare, potentially fatal complications of STEMI, posing diagnostic challenges when in atypical locations with perforation. Case A 62-year-old man with type 2

diabetes and hypertension presented four days post-chest pain, diagnosed with inferior STEMI. Coronary angiogram showed triple vessel disease, including 40% left main disease, not amendable to revascularization. He developed cardiogenic shock requiring left atrial veno-arterial extracorporeal membrane oxygenation (LAVA-ECMO), with initial TTE suggesting VSD. Subsequent TEE identified a large pseudoaneurysm perforating into the right ventricle (figure 1). He underwent successful pseudoaneurysm exclusion and coronary bypass, discharging in stable condition. Decision-making This case underscores the importance of precise VSD and pseudoaneurysm detection via multimodality imaging, including TTE and TEE. The rare pseudoaneurysm's atypical location and perforation mimicked a VSD, highlighting mechanical circulatory support's role in stabilizing post-STEMI complications before definitive surgery. Conclusion A contained left ventricular pseudoaneurysm perforating into the right ventricle post-STEMI is rare, with accurate diagnosis critical for guiding surgical intervention. [Formula presented]

Cardiology/Cardiovascular Research

Fang JX, **Villablanca-Spinetto P**, **Frisoli TM**, **Lee JC**, **Gonzalez PE**, **Lai L**, **Giustino G**, **Alrayes H**, **Wang DD**, **O'Neill WW**, and **O'Neill BP**. COMPARATIVE EFFECTIVENESS OF BALLOON AORTIC VALVULOPLASTY WITH NON-COMPLIANT AND COMPLIANT BALLOONS IN THE ERA OF TRANSCATHETER AORTIC VALVE REPLACEMENT (TAVR) AND RADIAL ACCESS. *J Am Coll Cardiol* 2025; 85(12):852. Full Text

Background Balloon aortic valvuloplasty (BAV) is increasingly used in the TAVR era, and radial access is now feasible. We investigate the comparative effectiveness of compliant and non-compliant balloons for BAV Methods 253 Patients undergoing BAV at a tertiary center in USA from 2021-2024 were evaluated. Changes in peak gradient and aortic insufficiency, adoption of radial access, and number of balloon inflation; periprocedural VARC-III vascular and bleeding events, and nonaccess events including heart block, stroke, hypotension, severe AI and periprocedural death; and 30-day composite of death, heart failure hospitalization, stroke, and discharge failure was assessed. Chi-square test, Wilcoxon ranksum test, and Kaplan Meier estimates with logrank test were used for dichotomous variables, non-parametric continuous variables, and time-to-event, respectively Results Compliant and non-compliant balloons were used in 58.1 and 41.9% of cases, respectively. There was no significant difference in drop in gradient, increase in AI, number of balloon inflation. (A-B). Radial access use was more common with compliant balloons, 53.6% vs 27.2%($p<0.001$) (B). Periprocedural and 30-day event rates were similar (all $p>0.05$) with numerically more non-access events with noncompliant balloons (C-D) Conclusion In the contemporary era, BAV with noncompliant and compliant balloons have similar hemodynamic and clinical outcomes and a higher adoption rate of radial access with compliant balloons [Formula presented]

Cardiology/Cardiovascular Research

Fram G, **Dawdy J**, **Alrayes H**, **Lai L**, **Chou A**, **Zweig B**, **Parikh S**, **Gonzalez PE**, **Villablanca PA**, **Frisoli TM**, **O'Neill BP**, and **Lee JC**. UTILITY OF INTRACARDIAC ECHOCARDIOGRAPHY IN EARLY COMMERCIAL TRANSCATHETER TRICUSPID VALVE REPLACEMENT. *J Am Coll Cardiol* 2025; 85(12):953. Full Text

Background Transcatheter tricuspid valve replacement (TTVR) with the Evoque Valve (Edwards, USA) is a recent commercially available treatment for patients with severe tricuspid regurgitation. Procedural success is highly dependent on intraprocedural imaging quality. Methods TTVR was performed on 57 patients at a large quaternary center between February and September 2024, with intraprocedural imaging primarily driven by transesophageal echocardiography (TEE). In select patients, concomitant TEE and 3-D intracardiac echocardiography (ICE) was used. A retrospective review of baseline characteristics and procedural outcomes was conducted. Results In 14 (24.5%) vs 43 (75.5%) of 57 patients, ICE + TEE vs. TEE alone were used to assist with intraprocedural imaging. Decisions about use of imaging modality were made at the operator's discretion, dependent on TEE imaging quality. ICE utilization increased over time, as seen in figure 1A. Patients had similar baseline characteristics, however patients for whom ICE was used had worse NYHA symptoms prior to procedure (NYHA IV, 21% vs. NYHA IV, 5%, $p=0.03$), as seen in figure 1B. There was a signal towards higher procedural success in patients for whom ICE and TEE was used, as compared to TEE alone ($n=14$, 100% vs. $n=34$, 79%, $p=0.095$). [Formula presented] Conclusion ICE facilitates procedural success in TTVR patients,

particularly assisting with visualization of leaflets interaction with the anchors of the TTVR. ICE with TEE to guide TTVR was increasingly used over time.

Cardiology/Cardiovascular Research
Gonzalez PE, **Abdelhai OS**, **O'Neill BP**, **Villablanca PA**, **Halboni A**, **Frisoli TM**, **Fram G**, **Lee JC**, and **O'Neill WW**. RACIAL AND SEX DIFFERENCES IN THE TREATMENT ALLOCATIONS AND OUTCOMES AMONG PATIENTS WITH SEVERE MITRAL VALVE DISEASE AND CHALLENGING ANATOMY. *J Am Coll Cardiol* 2025; 85(12):2256. Full Text

Background Patients with mixed mitral valve disease or mitral stenosis and small predicted neo-left ventricular outflow tract (LVOT) are difficult to treat with percutaneous therapies given risk of LVOT obstruction and often are not offered intervention. This study investigates racial and sex differences in treatment and outcomes. Methods We included 104 patients referred to the Henry Ford Hospital (Detroit, MI) between 2018 and 2024 with severe mitral stenosis (MS group) or severe mixed valve disease. These patients were mostly, high or prohibitive risk for surgery and were being considered for possible transcatheter mitral valve replacement. All these had a predicted neo-LVOT <150 mm2. Results The MS group consisted of 93 patients (89%) and the MV group of 11(11%). The cohort consisted of 92 females (88%) and 85 white patients (82%).The all-cause mortality was 30%, with cardiovascular (CV) death at 21% for the entire cohort. All-cause mortality among females was 28% vs 38% in males (p = 0.33), and CV death among females was 20% vs 33% in males (p = 0.27). The 1-year allcause mortality for females was 20% vs 38% in males (p = 0.083), and 1-year CV death was 15% for females vs 33% in males (p = 0.12). All-cause mortality among white patients was 28% vs 37% in non-whites (p = 0.46), and CV death for whites was 18% vs 37% in nonwhites (p = 0.064). The 1-year all-cause mortality was in both white and non-white patients was 21%(p = 0.99), and the 1-year CV death for whites was 15% vs 21% in non-whites (p = 0.54).Intervention rates also varied by sex and race, with 43% of females undergoing treatment compared to 67% of males. Both white (46%) and non-white (47%) patients demonstrated similar rates of undergoing. The all-cause mortality of those patients that did not undergo intervention (medical therapy only) were: females 27% vs males 25%, and white patients 23% vs non-white 40%. Conclusion This study underscores that most of the patients presenting to this tertiary heart valve center were female and mostly white. It is also notable that female patients were treated less often, and non-white patients had a higher rate of all-cause mortality when not treated percutaneously.

Cardiology/Cardiovascular Research
Kattula M, **Al-suraimi A**, **Fadel R**, **Patel V**, **Basir MB**, and **Rabbani B**. THE EFFECT OF AN ONLINE LEARNING MODULE ON TRAINEE UNDERSTANDING AND TROUBLESHOOTING OF MECHANICAL CIRCULATORY SUPPORT DEVICES IN THE CICU. *J Am Coll Cardiol* 2025; 85(12):2524. Full Text

Background We identified a need to standardize mechanical circulatory support (MCS) device training for learners in an urban teaching hospital. We hypothesized that an enduring educational resource in the form of an asynchronous online module reviewing principles, daily care, and complications would improve understanding and ability to troubleshoot. Methods We developed a module, using Articulate Rise 360, addressing intraaortic balloon pumps (IABP), Impella, extracorporeal membrane oxygenation (ECMO), and left ventricular assist devices (LVAD). Content was derived from textbooks, guidelines, articles, and hospital policies. A control cohort of residents and cardiology fellows in the cardiac intensive care unit (CICU) were surveyed at the beginning and end of their month-long rotation. The module was then made available to the intervention cohort, which was subsequently surveyed. Results An independent samples t-test comparing post-rotation scores demonstrated a significant improvement in learners' perceptions about their ability to troubleshoot complications, time spent on formal education, and thoroughness of attending staff education. It did not, however, significantly improve learners' views of their basic understanding compared to standard training except for ECMO. Conclusion Our asynchronous online module improved CICU learners' perceptions of their ability to troubleshoot MCS devices and the time and quality of instruction provided to them. [Formula presented]

Cardiology/Cardiovascular Research

Lanfear DE, Lowry J, Amendola L, **Trepanier A**, **Aurora L**, **Ferrari H**, **Cabral W**, Kesari A, Rajkumar R, Chawla A, Coffey A, Hostin D, Huertas-Vazquez A, Perry D, Longoni M, and Taft R. CLINICAL GENOME SEQUENCING IN ROUTINE CARDIOLOGY: INITIAL FINDINGS OF THE CARDIOSEQ STUDY. *J Am Coll Cardiol* 2025; 85(12):1364. Full Text

Background Cardiovascular disease (CVD) is multifactorial and includes monogenic and polygenic contributors to onset and severity. Clinical genetic testing in practice seldom meets guideline recommendations, in part due to test limitations, disease heterogeneity and uncertainty about the utility of positive findings. The CardioSeq study was designed to evaluate the diagnostic yield and clinical impact of comprehensive clinical genome sequencing (cGS) spanning hundreds of genes and genetic disorders, risk factors and potential care modifiers in patients presenting with CVD. Methods A prospective, open-label, single-center clinical trial was conducted at Henry Ford Health. Inclusion required a diagnosis of at least one among: cardiomyopathy or heart failure, aortopathy, arrhythmia, coronary or peripheral artery disease, and/or dyslipidemia. The cGS test included 215 CVD-associated genes, 4 common genetic variants associated with increased CVD risk, 35 optional non-CVD ACMG secondary findings genes, pharmacogenomic variants and a coronary artery disease (CAD) PRS. Results Of the 1,000 participants who received cGS testing, 501 were assigned male sex at birth (median age 69, IQR 61-75) and 499 were assigned female (median age 70, IQR 62-76). The most common self-reported races were white (57.9%) and African American (39.2%). Cardiomyopathy or heart failure accounted for 33.5% of the entire cohort. A total of 74 participants received a monogenic finding, roughly half of which were due to variants in three genes: TTR (n = 16, 21.6%), TTN (n = 14, 18.9%), and LDLR (n = 8, 10.8%). The TTR p.Val142Ile variant accounted for 20.3% of positive cases. Unadjusted diagnostic yield was highest in African American cases (11.5%). Risk allele findings were reported in 10.1% of study participants, secondary findings in 1.4%, and pharmacogenomic findings in <99%. An elevated CAD PRS was reported in 4.6% of participants. Conclusion A single comprehensive cGS test can provide useful diagnostic and genetic risk data across a broad range of CVD phenotypes and genetic ancestries. The investigation of the impact of cGS findings on clinical management is ongoing and will be reported at CardioSeq study completion.

Cardiology/Cardiovascular Research

Madanat L, Jabri A, Ayyad M, Al-Abdouh A, Mhanna M, Alhuneafat L, **Frisoli TM**, Shaban L, Hanson I, Abbas AE, **Alqarqaz M**, and **Villablanca PA**. NATIONAL TRENDS AND IN-HOSPITAL OUTCOMES OF TRANSCATHETER AND SURGICAL TRICUSPID VALVE PROCEDURES. *J Am Coll Cardiol* 2025; 85(12):831. Full Text

Background Advancements in transcatheter tricuspid valve interventions (TTVI) have surged exponentially in recent years. Methods We queried the national Inpatient sample (NIS) database and included data between Jan 1, 2011 and Dec 31, 2020. The primary objective was to characterize the trends in utilization of TTVI, surgical tricuspid valve repair (STVr) and replacement (STVR). The secondary objective of the study was to analyze the in-hospital outcomes associated with each type of intervention. A propensity score was calculated for all hospitalizations and unmatched hospitalizations were excluded from the outcome analysis. Results A total of 98,202 TV interventions were identified. Of these, 1,830 (1.9%) constituted TTVI, 76,747 (78.2%) STVr and 19,625 (19.9%) STVR. Over the study period, the total number of TV interventions exhibited an exponential increase with STVR's proportion relative to all interventions declining by 2020 (Figure 1A). STVR accounted for the highest proportion of TV procedure-related deaths overall, followed by STVr, and lastly, TTVI (Figure 1B). STVr and STVR were associated with increased inpatient mortality (7% vs 2.4%, 11.6% vs 2.3%, respectively), circulatory shock (24.0% vs 11.8%, 25.7% vs 13.6%) and respiratory failure (10.8% vs 1.5%, 12.4% vs 1.9%, p<0.001) when compared to TTVI (p <0.001). Conclusion TTVI are increasing in practice. Compared to surgical TV interventions, TTVI have improved in hospital mortality, circulatory shock and respiratory failure. [Formula presented]

Cardiology/Cardiovascular Research

Mazhar MA, **McGwire J**, **Alsheikh ON**, and **Zein RK**. EFFECT OF TEACHING HOSPITAL STATUS ON HEART FAILURE OUTCOMES: ANALYSIS OF THE NATIONAL INPATIENT SAMPLE 2021. *J Am Coll Cardiol* 2025; 85(12):1572. Full Text

Background Heart failure is a growing concern in the U.S., affecting nearly 6.5 million Americans aged 20 and older, with over 960,000 new cases diagnosed annually. It contributes to 8.5% of heart disease-related deaths. Previous research has explored the impact of teaching hospital (TH) status on outcomes across various diseases. This study aimed to determine whether TH status influenced outcomes for heart failure patients. Methods Data were drawn from the 2021 National Inpatient Sample, including 6,666,752 admissions. After filtering for heart failure (ICD10 I50), 16,519 patients remained. Exclusions included 3,444 rural nonteaching hospital (NTH) admissions. The final cohort included 3,402 urban NTH and 13,117 urban TH admissions. Chi-square and logistic regression analyzed mortality, cardiogenic shock, ICU admission, AKI, vasopressor use, and blood transfusion, with TH status as the independent variable. Results The study analyzed 16,519 patients with a mortality rate of 3.81%. Mortality was higher in THs (4.05%) than NTHs (2.88%) (p 0.002). Cardiogenic shock occurred in 7.77%, more in THs (9.13%) than NTHs (2.50%) (p 0.001). ICU admission was higher in THs (3.35%) than NTHs (1.52%) (p 0.001). AKI incidence was 29.01%, higher in THs (30.80%) than NTHs (22.10%) (p 0.001). Vasopressor use occurred in 2.81% of patients overall, more in THs (3.26%) than NTHs (1.06%) (p 0.001). Blood transfusions were higher in THs (2.59%) than NTHs (1.73%) (p 0.004). Conclusion Significant differences exist in outcomes between THs and NTHs for heart failure patients, with THs showing more severe presentations, evidenced by higher mortality, cardiogenic shock, ICU admission, AKI, vasopressor use, and transfusions.

Cardiology/Cardiovascular Research

McBride P, **Andrews TQ**, **Abdelhai OS**, **Zimmerman A**, and **Cowger JA**. METASTATIC CARDIAC CALCIFICATION OF UNCLEAR ETIOLOGY - SARCOIDOSIS OR MASQUERADER? *J Am Coll Cardiol* 2025; 85(12):4130. Full Text

Background Myocardial calcification typically occurs in the setting of previous myocardial injury, although abnormal calcium homeostasis and some systemic diseases can lead to calcium deposition. Understanding disease patterns is important to guide management in undifferentiated patients. Case 40-year-old male with a history significant for ESRD on HD secondary to IgA nephropathy was found to have nonischemic cardiomyopathy with reduced ejection fraction, refractory VT, and complete heart block. CT chest showed mediastinal adenopathy and opacities. Multiple bronchoscopies were negative for malignancy/granulomas. Cardiac MRI demonstrated abnormal signal on delayed gadolinium enhancement images involving the basal to mid left ventricle. PET CT showed moderate intensity signal involving basal/mid anterior, lateral, septal, and inferior walls in the setting of normal perfusion concerning for sarcoidosis. Endomyocardial biopsy showed normal myocardium and was negative for amyloid. He was managed for sarcoidosis due to multiorgan involvement consistent with the disease. He was treated with Prednisone but unfortunately had recurrent admission for ventricular tachycardia. He was recommended to pursue comfort care. Decision-making It is believed that he had myocardial calciphylaxis leading to inflammation of the myocardium as the active areas on PET correlated with the areas of calcium deposition on CT and MRI. Other etiologies for such a presentation include sarcoidosis or amyloidosis however he had an extensive workup that showed no other signs of sarcoid or amyloid (1). He was managed empirically for cardiac sarcoidosis with a trial of steroids and was started on a phosphate binder to help with calcium balance. He continues to have issues with arrythmias and is being managed medically as he is not a candidate for more advanced therapies. Conclusion While this patient was managed empirically for cardiac sarcoidosis, his disease continued to be uncontrolled on traditional immunosuppression. A second opinion at another academic center was also unrevealing. Understanding the spectrum of disease that can occur with sarcoidosis is important to guide decisions based on therapy.

Cardiology/Cardiovascular Research

Nguyen F, **Fadel R**, **Cowger JA**, **Nemeh H**, and **Basir MB**. AORTIC VALVE THROMBUS ASSOCIATED WITH LEFT ATRIAL VENOARTERIAL EXTRACORPOREAL MEMBRANE OXYGENATION (LAVA-ECMO) WHILE ON BIVALIRUDIN. *J Am Coll Cardiol* 2025; 85(12):3322. Full Text

Background LAVA-ECMO is an ECMO configuration that uses a single trans-septal cannula to provide biventricular unloading. Despite its advantages, the risk of thrombosis remains. Case A 32-year-old male with a history of nonischemic cardiomyopathy and recurrent venous thromboses on apixiban was admitted with decompensated heart failure. Right heart catheterization showed elevated filling pressures and very reduced cardiac output. He is started on diuretics and afterload reducing agents. On hospital day #4, he develops worsening cardiogenic shock with severe lactic acidosis and acute hypoxic respiratory failure requiring intubation. He is taken urgently for LAVA-ECMO. Decision-making Given the patient's thrombosis history, body habitus, and difficulties maintaining heparin at therapeutic range, heparin was switched to bivalirudin after cannulation. After 3 days, his mental status declines. A transesophageal echocardiogram was performed revealing severe smoke around the aortic valve and root, suspicious for thrombus. A CT head was performed showing an acute infarct in the right frontal lobe. Bivalirudin is switched back to heparin. Discussions of durable support are expedited, and patient is taken for LVAD. He is subsequently extubated and demonstrated intact neurologic function. Conclusion In this patient with thromboembolic history, bivalirudin may not have provided adequate anticoagulation while on ECMO. Improving protocols for anticoagulation for ECMO may help reduce this risk. [Formula presented]

Cardiology/Cardiovascular Research

Nguyen F, **Gandolfo C**, **Rangavajla G**, **Giustino G**, **Fang JX**, **Alrayes H**, **Lai L**, **Fram G**, **Ilg KJ**, **Greenberg J**, **Dawdy J**, **Gonzalez PE**, **Villablanca PA**, **Lee JC**, **Zweig B**, **O'Neill WW**, **Frisoli TM**, and **O'Neill BP**. IN-HOSPITAL AND 30-DAY PACEMAKER LEAD OUTCOMES IN PATIENTS UNDERGOING TRANSCATHETER TRICUSPID VALVE REPLACEMENT. *J Am Coll Cardiol* 2025; 85(12):829. Full Text

Background There has been increasing use of transcatheter tricuspid valve replacement (TTVR) to treat severe tricuspid regurgitation (TR). Many patients with severe TR have permanent pacemaker (PPM) or implantable cardiac defibrillator (ICD) leads. The impact of TTVR on jailed lead parameters out to 30 days is unknown. Methods Patients with PPM/ICDs undergoing TTVR with the commercial EVOQUE valve at Henry Ford Hospital from FebruarySeptember 2024 were included. Device interrogations were performed prior to TTVR, 24 hours after, and at 30 days. Lead-related outcomes including impedance, thresholds, dislodgements, and need for extraction were evaluated. Results 16 patients with PPM/ICDs underwent EVOQUE for severe TR, of which 11 had 30-day follow-up. Mean age was 82.1 years old. Mean NYHA Class was 2.8 ± 0.5. 14 patients had PPMs, 2 had ICDs. 15 patients had right atrial and right ventricular (RV) leads (94%), 1 had a His lead (6%), 7 had coronary sinus leads (44%). Average change in lead impedance at 24 hours compared to baseline was -6.72% ± 7.88%. In patients with 30-day follow-up, average change in lead impedance at 30-days was -3.16% ± 6.46%. Average change in RV thresholds at 30-days was 11.38% ± 25.56%. There were no lead dislodgements or need for lead extraction. Mild TR or better was achieved in 14 patients (88%). Conclusion There was a small change in PPM/ICD lead parameters out to 30 days after EVOQUE placement in this small cohort. Future studies with longer follow-up are needed. [Formula presented]

Cardiology/Cardiovascular Research

Obeidat L, **Zimmerman A**, **Almajed MR**, **Modi S**, **Al-Darzi W**, and **Ananthasubramaniam K**. NEVER ENDING SAGA OF TAKOTSUBO CARDIOMYOPATHY RECURRENCES. *J Am Coll Cardiol* 2025; 85(12):3146. Full Text

Background Takotsubo cardiomyopathy (TC) is an acute, transient left ventricular (LV) dysfunction triggered by emotional or physical stress. While most recover quickly, recurrence occurs in 2%-4%. Here, we describe multiple recurrences of TC with different echocardiographic patterns. Case A 67-year-old woman with a history of hypertension (HTN) and non-obstructive CAD, first presented with uncontrolled HTN, dyspnea, nausea, and flushing. Workup showed elevated troponin levels, normal EKG, and an echocardiogram showing reduced EF of 2025% with apical akinesis. Coronary angiography confirmed no significant CAD, and a left ventriculogram revealed Takotsubo pattern with apical akinesis and basal hyperkinesis. On follow-up, her symptoms completely resolved, and a repeat echocardiogram normalized. She presented three years later with similar symptoms. Echocardiogram showed an EF of 51%, new severe MR, with basal septal and inferior wall hypokinesis with apical hyperkinesis, pattern consistent

with reverse TC. She responded well to medical therapy, with resolution of the wall motion abnormalities. Since then, she has experienced three additional episodes, with evidence of recurrence of both typical and reverse Takotsubo patterns. Extensive workup has been negative for secondary causes of HTN. She remains asymptomatic between episodes with no clear triggers for her recurrent presentations. Decision-making TC is a reversible stress-induced cardiomyopathy characterized by LV dysfunction involving apical or periapical walls. A variant, reverse TC, is less common, accounting for fewer than 20% of cases and involves basal and inferior wall hypokinesis with apical hyperkinesis. Potential causes include catecholamine surge, microvascular dysfunction, or coronary spasm. Management focuses on supportive care, GDMT, and monitoring for complications such as shock and ventricular thrombi. Conclusion Our patient experienced five episodes of TC over a six-year period, which is an unusually high recurrence rate. Contrary to prior literature of benign outcomes, our case reiterates that a subset of TC patients suffer from ongoing morbidity and should be followed closely long term.

Cardiology/Cardiovascular Research

Obeidat L, **Zimmerman A**, **Almajed MR**, **Sabra M**, **Nguyen F**, **Michaels AT**, and **Al-Darzi W**. RIDING THE VT STORM : COMPLEX CARE FOR A POMPE DISEASE PATIENT WITH VA-ECMO AND ENZYME REPLACEMENT THERAPY. *J Am Coll Cardiol* 2025; 85(12):3015. Full Text

Background Pompe disease, also known as glycogen storage disease type II, leads to glycogen buildup in various tissues, including the heart. This can cause hypertrophic cardiomyopathy and conduction abnormalities, increasing the risk of arrhythmias such as ventricular tachycardia (VT). Case We present a case of a 33-year-old female patient with prior genetic testing revealing one pathogenic variant and one Variant of Uncertain Significance (VUS) in the GAA gene, associated with autosomal recessive Pompe disease. She was admitted with VT storm. EKG revealed polymorphic VT with prolonged QT interval, and echocardiogram showed a mildly reduced left ventricular ejection fraction (LVEF) but was otherwise normal. Initial antiarrhythmic therapy with lidocaine and nadolol, along with temporary pacing and multiple cardioversions, failed to resolve VT, necessitating veno-arterial extracorporeal membrane oxygenation (VA ECMO) cannulation. Right and left heart catheterizations demonstrated normal hemodynamics and no evidence of CAD. Neurology recommended enzyme replacement therapy (ERT) for treatment. She was started on Nexviazyme (avalglucosidase alfa) and received a total of three doses. Her condition eventually improved, allowing for VA ECMO decannulation. She underwent stellate ganglion nerve block and received an implantable cardioverter-defibrillator (ICD) for secondary prevention. She was discharged on mexiletine and amiodarone. Due to her muscle weakness and frailty, cardiac transplantation was not considered a viable long-term option. Decision-making Glycogen accumulation in cardiac tissue can lead to multiple conduction abnormalities, which predispose patients to VT and sudden death. Alglucosidase alfa has been shown to improve cardiac function, although it does not eliminate the risk of arrhythmias. Conclusion In Pompe disease, cardiac findings can differ in terms of severity, structures involved, age of onset, and rate at which the condition progresses. In our case, VT was the first manifestation of the disease and occurred during adulthood. Regular cardiac evaluations, including 24-hour Holter monitoring, are recommended to detect and manage arrhythmias.

Cardiology/Cardiovascular Research

Qadeer YK, Krittanawong C, Wang Z, Ahuja T, Alam M, and Jneid H. BIVALIRUDIN VERSUS HEPARIN IN PATIENTS UNDERGOING PERCUTANEOUS CORONARY INTERVENTION IN ACUTE CORONARY SYNDROMES. *J Am Coll Cardiol* 2025; 85(12):949. Full Text

Background Data on outcomes between unfractionated heparin and bivalirudin anticoagulation during percutaneous coronary intervention (PCI) in acute coronary syndromes (ACS) remains inconclusive. We aimed to systematically analyze PCI outcomes comparing unfractionated heparin and bivalirudin. Methods We systematically searched Ovid MEDLINE, Ovid Embase, Ovid Cochrane Database of Systematic Reviews, Scopus, and Web of Science from database inception in 1966 through January 2024 for studies evaluating PCI outcomes comparing unfractionated heparin and bivalirudin. Two investigators independently reviewed data. Conflicts were resolved through consensus. Random-effects metaanalyses were used. Results Ten prospective trials were identified that enrolled 42,253 individuals who presented with an acute coronary syndrome. Our analysis found that heparin when compared to bivalirudin was associated with an increased risk of trial-based definition of major bleeding (RR 1.68, 95%

CI 1.29-2.20), non-access site complications (RR 4.6, 95% CI 1.75-12.09), TIMI major bleeding (RR 1.70, 95% CI 1.202.41), major bleeding risks (RR 1.87, 95% CI 1.49-2.36), cardiovascular disease death (RR 1.26, 95% CI 1.02-1.57), and thrombocytopenia (RR 1.67, 95% CI 1.07-2.62). There were no statistically significant differences between heparin and bivalirudin for all-cause mortality, MACE (RR 1.05, 95% CI .94-1.17), stroke, reinfarction, target vessel revascularization, acute or stent thrombosis (RR .81, 95% CI .42- 1.56). Conclusion Our data demonstrates bivalirudin reduces major bleeding when used for anticoagulation during PCI in patients with acute coronary syndromes and is not associated with an increased risk of stent thrombosis or major adverse cardiac events.

Cardiology/Cardiovascular Research
Qureshi MA, Bakht D, Rehman AU, Amjad Z, Rehman OU, Bokhari SFH, **Tareen H**, Haseeb S, **Ahmed O**, Khan LA, Munir S, and **Othman H**. EFFICACY AND SAFETY OF PROTAMINE IN REDUCING BLEEDING AND VASCULAR COMPLICATIONS AFTER TAVR: A META-ANALYSIS. *J Am Coll Cardiol* 2025; 85(12):1071. Full Text

Background Transcatheter aortic valve replacement (TAVR) often causes postoperative bleeding and vascular complications due to intraoperative heparin. Protamine sulfate reverses heparin but its routine clinical use in TAVR remains debated. This meta-analysis aims to evaluate protamine's efficacy and safety in reducing bleeding and vascular complications compared to standard practices Methods PubMed, Embase, Cochrane and clinicaltrials.gov were searched. Primary outcomes were 30-day mortality, major bleeding, lifethreatening bleeding, and vascular complications. Secondary outcomes were minor bleeding, myocardial infarction, stroke, acute kidney injury, and hospital stay. Odds ratios (OR) and mean differences (MD) were calculated through a random-effects model using RevMan 5.4 Results 6 studies with a total of 4,123 patients were included in the quantitative synthesis. Protamine reduced minor (OR=0.63, p=0.01), major (OR=0.46, p<0.001), and life-threatening bleeding (OR=0.35, p<0.001), minor (OR=0.82, p=0.03) and major vascular complications (OR=0.45, p<0.001), and shortened hospital stay (MD=-1.95 days, p=0.02). Protamine did not significantly affect 30-day mortality, risk of pacemaker implantation, myocardial infarction, stroke, acute kidney injury, or postoperative transfusion requirement Conclusion Protamine reduces bleeding and vascular complications in TAVR without raising mortality or thromboembolic risks. More trials are needed to support routine use [Formula presented]

Cardiology/Cardiovascular Research
Rabbani B, **Lee JC**, **Parikh S**, **Sanders J**, **Zweig B**, **Wang DD**, and **Mitchell J**. TRANSESOPHAGEAL ECHOCARDIOGRAPHY SIMULATOR TRAINING FOR VISUALIZATION OF THE PULMONARY VEINS: A RANDOMIZED CONTROLLED STUDY. *J Am Coll Cardiol* 2025; 85(12):2528. Full Text

Background We sought to determine if transesophageal (TEE) simulation training would improve fellow preparation, clinical performance, and learning environment at an urban teaching hospital. To do so, we focused on the challenging process of visualizing all pulmonary veins. Methods Fellows in cardiology or anesthesiology were randomized to simulator training. All completed a pre and post-test survey. The intervention group received a comprehensive 1.5 hour TEE simulation session. All then performed a clinically indicated TEE exam and were rated on clarity of pulmonary vein images and ability to image each structure independently. Results Control and intervention groups were evenly matched in demographics and experience. Survey results demonstrate a significant difference in comfort level with the theory, interpretation, and technical performance of a complete TEE exam, and effectiveness of attendings. However, there was no difference in overall satisfaction with TEE training and comfort level obtaining pulmonary veins. Additionally, assessment data did not show a difference between the clarity of images or the ability to achieve the pulmonary veins independently. [Formula presented] Conclusion Simulation training did not improve real-world trainee performance in imaging all pulmonary veins compared to standard TEE training. But simulation training is a means to improve overall understanding of interpretation and performance of TEE, and teaching effectiveness of attendings.

Cardiology/Cardiovascular Research

Rangavajla G, **Patel R**, **Abdelhai OS**, **Nguyen F**, **Gupta K**, **Fang JX**, **Giustino G**, **Raad M**, **Villablanca PA**, **Gonzalez PE**, **O'Neill BP**, and **Frisoli TM**. INCIDENCE OF CONDUCTION SYSTEM DISTURBANCES AFTER EVOQUE TRICUSPID VALVE IMPLANTATION. *J Am Coll Cardiol* 2025; 85(12):1126. Full Text

Background EVOQUE transcatheter tricuspid valve replacement (EVOQUE) is a new treatment for severe tricuspid regurgitation. The initial TRISCEND study suggested a high risk of post-EVOQUE conduction system disturbance (CSD) with 13.3% of non-paced patients requiring new pacemakers. The incidence of real-world CSD with EVOQUE is less clear. Methods Patients undergoing commercial EVOQUE at Henry Ford Hospital (HFH) in Detroit, MI were monitored both in-hospital and outpatient for new CSD. Baseline characteristics and outcomes were compared to published results from TRISCEND using Z tests. Results Of 34 HFH patients undergoing successful EVOQUE, 22 had no prior pacemaker and were included for outcomes analyses. Baseline differences between HFH and TRISCEND patients are noted (Table 1). Over a median follow up of 92 days (IQR 55-148), only 1 patient required a post-implant pacemaker (Table 2) which was implanted 5 days after EVOQUE for high-grade AV block. Three of 5 developing new right bundle branch block had resolution within 30 days; no patient developed left bundle branch block or sinus pauses <5 seconds. Conclusion Real-world EVOQUE patients may have significantly lower rates of post-EVOQUE pacemaker implantation and CSD compared to published results. Registry data is needed to determine the veracity of this finding in larger samples. [Formula presented]

Cardiology/Cardiovascular Research

Ronchetto E, **Zimmerman A**, and **Obeidat L**. THE RHYTHM OF SURVIVAL: OVERCOMING ARRHYTHMIC CHAOS IN EMERY- DREIFUSS MUSCULAR DYSTROPHY. *J Am Coll Cardiol* 2025; 85(12):3030. Full Text

Background Emery-Dreifuss muscular dystrophy (EDMD) is a rare, X-linked disorder with a range of neuromuscular and cardiac phenotypes. Interestingly, cardiac disease can be the first and only manifestation of EDMD in some patients. Case At age 38, a previously healthy and very active male developed extreme fatigue. Following extensive evaluation, he underwent pacemaker placement for symptomatic junctional bradycardia. Device interrogations noted atrial fibrillation. His course was complicated by a stroke, thought to be cardioembolic, at age 38 and again at age 49, while on anticoagulation. His device was updated to a biventricular ICD following an echocardiogram showing an EF of 30% with severe biatrial enlargement at age 47. He underwent whole gene sequencing, which revealed a nonsense variant of the EMD gene (c.441C>A), not previously known to be pathologic. At age 50, he had his first ICD shock for ventricular tachycardia (VT), which progressed despite antiarrhythmics. Device interrogation also noted innumerable antitachycardia pacing episodes. Transplant evaluation was initiated due to recurrent and high burden of VT and ventricular fibrillation, and he ultimately underwent orthotopic heart transplant (OHT). Decision-making The EMD gene encodes the emerin nuclear envelope protein, important for gene regulation and intercalated disc function in cardiomyocytes. EMD gene mutations result in the X-linked recessive disorder, EDMD. The term “cardiac emerinopathy” describes patients with EDMD who lack neuromuscular symptoms typically seen in muscular dystrophies. Cardiac manifestations of EDMD classically present with conduction abnormalities, including progressive atrial arrhythmias leading to atrial standstill, increasing risk for cardioembolic stroke and pulmonary embolism. Cardiomyopathy is another notable manifestation. And lastly, males with EMD gene variants are high risk for malignant ventricular arrhythmias. Conclusion This case presents extensive cardiac manifestations of EDMD, ultimately requiring OHT, with delayed recognition of etiology. A lower threshold for genetic testing should be had in young patients without obvious causes for cardiomyopathy.

Cardiology/Cardiovascular Research

Sabbah HN, **Gupta RC**, **Zhang KF**, and **Lanfear DE**. Abnormalities Of Mitochondria! Function In Renal Epithelial Cells Of Dogs With Chronic Heart Failure And Dogs With Cardiorenal Syndrome. *J Card Fail* 2025; 31(1):2. Full Text

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Cardiology/Cardiovascular Research

Sabra M, **La Starza B**, **Vishwanath R**, **Ebinger MW**, **Ilg KJ**, **Michaels AT**, **Maskoun W**, and **Gorgis S**. A SHOCKING RESCUE: NOVEL USE OF ENZYME REPLACEMENT THERAPY FOR VENTRICULAR TACHYCARDIA IN LATE-ONSET POMPE DISEASE. *J Am Coll Cardiol* 2025; 85(12):2886. Full Text

Background Pompe disease is an autosomal recessive disorder caused by a deficiency of the enzyme acid alpha-glucosidase (GAA). Late-onset Pompe disease (LOPD),the adult form, causes glycogen buildup in skeletal, cardiac, and smooth muscles, leading to cardiac issues such as hypertrophy and rhythm disturbances. Case A 33-year-old woman with untreated childhood-onset Pompe disease presented after out-of-hospital cardiac arrest. After return of spontaneous circulation, the electrocardiogram(ECG) showed sinus bradycardia and significant QT interval prolongation (QTc=599 ms), with echocardiogram revealing an LVEF of 35%. The patient subsequently experienced a polymorphic ventricular tachycardia(PMVT) storm, requiring multiple defibrillations. She was started on a lidocaine infusion and underwent temporary pacemaker implantation for overdrive pacing. Despite this, she continued to have multiple episodes of sustained PMVT requiring cardioversion/defibrillation. The patient was cannulated for Venoarterial Extracorporeal Membrane Oxygenation(VA-ECMO) for hemodynamic support.Despite VA-ECMO support, she continued to have PMVT during weaning attempts. Enzyme replacement therapy (ERT) with avalglucosidase alfa was initiated seven days after presentation. Following two ERT infusions, she was successfully weaned off VA-ECMO and decannulated. However, she continued to have non-sustained VT with weaning sedation.The patient subsequently underwent a stellate ganglion block, followed by the placement of a dual-chamber implantable cardioverter defibrillator. She was discharged to a rehabilitation facility with plans of biweekly enzyme infusions. Three months later, the patient continues to receive infusions with no ICD shocks noted. Decision-making Pompe disease causes progressive cardiomyopathy and conduction abnormalities,often showing prolonged QTc on ECG,which raises the risk of PMVT with ectopy.While ERT is typically used in infantile Pompe to reduce hypertrophy and arrhythmias,our case presents a novel use in late-onset Pompe disease. Conclusion Our case presents a unique application of ERT in late-onset Pompe disease for VT suppression.

Cardiology/Cardiovascular Research

Sabra M, **Nguyen F**, and **Ananthasubramaniam K**. DIFFUSE INFILTRATIVE METASTATIC NEUROENDOCRINE TUMOR PRESENTING WITH DYNAMIC OUTFLOW OBSTRUCTION: ROLE OF MULTIMODALITY IMAGING. *J Am Coll Cardiol* 2025; 85(12):4599. Full Text

Background Neuroendocrine tumors (NET) are rare, slow-growing tumors with an incidence of 2.25 per 100,000, and cardiac metastasis is an exceptionally rare complication. Case 66-year-old male with metastatic somatostatin receptor positive NET presented to cardiology clinic for evaluation prior to starting radionuclide therapy. He underwent a transthoracic echocardiogram (TTE) that showed severe asymmetric septal hypertrophy (2.5 cm) and dynamic LVOT obstruction (Fig. E,F). Additionally, increased backscatter and focal echogenic areas and masses were noted (Fig. A,B). Subsequently, he underwent a whole body FDG PET scan that showed patchy increased uptake in the left ventricle and right ventricle suspicious for cardiac metastasis (Fig. C,D). The patient was referred for radionuclide therapy. Decision-making Cardiac metastasis is rare, typically seen in advanced, widespread tumors. NET with cardiac metastasis are usually asymptomatic from a cardiac perspective, although some cases present with heart failure. Left ventricle metastasis occurs in 53% of cases. While TTE can be challenging to detect metastasis, our case highlights the crucial role of multimodality imaging (TTE and SPECT) in identifying obstructive physiology and cardiac metastasis. Conclusion Multimodality imaging using TTE and FDG PET is a valuable tool for the surveillance and detection of cardiac metastases in NET. [Formula presented]

Cardiology/Cardiovascular Research

Shahrori ZM, Jabri A, Srivats S, Maligireddy A, Zghouzi M, and **Aggarwal V**. INCIDENCE AND PREDICTORS OF NEW ONSET SEVERE MENTAL HEALTH ILLNESS AMONGST INPATIENTS READMITTED AFTER A RECENT PULMONARY EMBOLISM: A NATIONAL READMISSION DATABASE ANALYSIS. *J Am Coll Cardiol* 2025; 85(12):2172. Full Text

Background Pulmonary embolism (PE) is associated with significant in-hospital mortality and long-term complications, including persistent dyspnea, exercise limitations, and mental stress, collectively known as post-PE syndrome (PPES). While chronic thromboembolic pulmonary hypertension (CTEPH) is well recognized in PPES patients, the psychological effects, particularly severe mental health illness (SMHI), remain underexplored. This study investigates the incidence and predictors of SMHI among patients readmitted after acute PE. Methods A retrospective cohort study was conducted using data from the Nationwide Readmissions Database (NRD) from 2016 to 2020. The NRD, which tracks hospital readmissions across 28 states, was used to identify patients aged 18 or older diagnosed with PE. To focus on new-onset mental health disorders, patients with a documented history of anxiety, depression, or schizophrenia/psychosis were excluded. Readmissions occurring 90+ days post-PE were analyzed for new-onset SMHI. Demographics, comorbidities, and socioeconomic factors were examined as predictors. Results Among readmitted PE patients, women accounted for 61.5% of new-onset anxiety cases (P<0.0001) and 59.2% of new-onset depression cases (P<0.0001). Medicare recipients made up 57.4% of new-onset anxiety (P<0.0001) and 57.4% of new-onset depression (P<0.0001). No significant gender difference was seen for schizophrenia or psychosis. Lower household income was significantly associated with new-onset schizophrenia, with 42.3% of cases (P<0.0001) in the lowest income quartile; this effect was not seen for anxiety or depression. Non-metropolitan areas reported the lowest incidence of all conditions, indicating potential urban-rural disparities. Conclusion The associations with gender, socioeconomic status, and insurance highlight the need for targeted mental health interventions, especially for women, Medicare recipients, and low-income patients. Urban-rural disparities suggest that geographical factors may affect access to care, supporting region-specific approaches. Early identification of at-risk patients could improve outcomes and reduce healthcare burdens.

Cardiology/Cardiovascular Research
Shaik A, **Khan A**, Elshaer A, **Adi MB**, Hariri M, Yousif M, **Sayar S**, and Yousaf H. VENTRICULAR ELECTRICAL STORM FOLLOWING LEADLESS PACEMAKER IMPLANTATION. *J Am Coll Cardiol* 2025; 85(12):4096. Full Text

Background Leadless pacemakers (LP) are alternative to transvenous pacemakers for bradyarrhythmia, offering favorable safety profile. We report a rare yet significant complication of ventricular electrical storm after LP insertion. Case A 65-year-old male with hypertrophic obstructive cardiomyopathy and sick sinus syndrome presented after his subcutaneous implanted cardioverter-defibrillator (ICD) was discharged which was thought to be from pause-dependent ventricular fibrillation (VF) and was treated by LP. Two days later, the patient had recurrent refractory monomorphic ventricular tachycardia (MVT) requiring defibrillation. Subsequent left heart catheterization led to stenting of left anterior descending artery. His discharge was uneventful but returned a week later with chest pain and multiple ICD shocks along with EKG showing persistent MVT despite antiarrhythmics. An EP study revealed scar tissue in LV, which was ablated but the VT storm persisted post-ablation. A repeat EP study was performed, leading to the removal of the leadless pacemaker and implantation of a biventricular ICD, which resolved the VT storm. Decision-making Persistent MVT after LP insertion raised concern for ischemia, prompting cardiac catheterization and stenting. When VT storm persisted, EP study was done which identified a potential site for ablation in the LV. The patient's MVT persisted even after ablation and medical management. A repeat EP study identified the LP implantation site as the origin of the MVT. LP was removed leading to the resolution of arrhythmia. Conclusion Persistent MVT post LP implantation highlights temporal relationship as arrhythmias ceased after LP removal illustrating a significant complication. The proposed mechanisms of MVT post LP implantation include myocardial irritation and proarrhythmic effects of LP components. Our case aims to educate physicians for the need of further research into the safety profile of LP.

Cardiology/Cardiovascular Research
Shaik A, **Khan A**, Elshaer A, Hariri M, **Adi MB**, and Yousif M. EMBOLIZATION OF LEADLESS PACEMAKER INTO THE PULMONARY ARTERY. *J Am Coll Cardiol* 2025; 85(12):3999. Full Text

Background Leadless pacemakers (LPs) are increasingly utilized in patients for ventricular pacing due to their low complication rates. However, embolization of device remains a concern, especially when it

migrates to pulmonary artery (PA). Case A 74-year-old female with recent AV nodal ablation and LP placement for atrial fibrillation was sent for bradycardia from the clinic during a routine follow-up. Upon arrival, she was asymptomatic with a heart rate in the 40s, otherwise vitally stable. EKG revealed a complete heart block while chest x-ray confirmed LP dislodgement in the left middle PA (a). Percutaneous retrieval was performed successfully after several tries using a snare (b). An alternate LP was implanted without complication, and patient was discharged uneventfully. [Formula presented] Decision-making Due to LP embolization into PA in the setting of recent nodal ablation, decision was made to retrieve and implant a new device. The retrieval was complex as the docking button of device was not accessible initially. Repeated attempts were made using snares culminating in a successful extraction. Reimplantation of new device was uneventful and patient was subsequently discharged without complications. Conclusion Retrieval of LP in PA presents with challenges and novelty as only a handful of such cases are documented in literature. When determining the appropriate treatment approach, the likelihood of device re-dislodgement should be carefully considered versus risk of a pulmonary artery tear during retrieval.

Cardiology/Cardiovascular Research

Thacker H, **Banthiya S**, and **Saba S**. THE ENDOCARDITIS ENIGMA: SPOTLIGHT ON AN UNUSUAL MICROBE. *J Am Coll Cardiol* 2025; 85(12):4467. Full Text

Background Group B Streptococcus (GBS) infections in non-pregnant adults have been increased in recent decades. Most invasive GBS disease occurs at mean age of 60 & has high mortality. We present a case of idiopathic GBS infection in a healthy adult. Case A 55-year old male without any cardiac history presented to the emergency department with generalized fatigue. On arrival he was febrile, but not tachycardic or dyspneic. Physical examination was significant for a grade 2/6 systolic murmur in the right 2nd intercostal space. Blood cultures obtained resulted positive for Streptococcus Agalactiae, a GBS. Empiric antimicrobial treatment was initiated. On obtaining further history, he was recently treated in the hospital for lower extremity cellulitis and a Trans-Thoracic Echocardiogram (TTE) during the admission performed showed normal ejection fraction, moderate Aortic Regurgitation (AR) but no vegetations on valves. Further investigating AR, having positive Duke Criteria, a Trans-Esophageal Echocardiogram (TEE) was performed. TEE unveiled a sessile mass attached to the ventricular side of the left coronary cusp of the aortic valve, measuring 15mm with prolapse of the leaflet, severe aortic regurgitation. These findings were most consistent with a large vegetation. A diagnostic angiogram revealed healthy coronary vasculature. Eventually, the patient underwent a successful surgical aortic valve replacement with a 29mm stented porcine bioprosthetic aortic valve. Decision-making Aortic Valve Endocarditis secondary to GBS is uncommonly reported in literature. Immunocompetent patients are not at high risk for invasive GBS. Clinical acumen and vigilance for endocarditis backed by examination and echocardiographic skills is needed. Thus, timely diagnosis & prevention of complications is important. Conclusion The incidence of invasive GBS amongst adults has greatly increased and usually elderly patients are affected, converse to our case reported. GBS bacteremia & endocarditis carry a very high mortality rate. Healthy patients with invasive GBS should undergo a comprehensive workup for potential underlying illness. Combined medical-surgical therapy confers better outcomes.

Cardiology/Cardiovascular Research

Toiv A, **Andrews TQ**, **Goleniak R**, **Karmally R**, and **Rudraiah L**. POCUS GUIDED CONSERVATIVE MANAGEMENT OF SEPTAL HEMATOMA: A RARE COMPLICATION OF HIS BUNDLE PACING. *J Am Coll Cardiol* 2025; 85(12):3244. Full Text

Background The introduction of His bundle pacing has shown significant electrophysiologic benefits but also comes with its own set of procedural complications. Point-of-care ultrasound (POCUS) is valuable in identifying these structural complications. Case A 75-year-old male with no cardiac history presented for sick sinus syndrome. He underwent successful placement of a permanent dual chamber pacemaker with a para-Hisian lead. One-hour post-procedure, he developed substernal chest pressure with ST elevation in lead III, a new RBBB, and troponin elevation (>20,000 ng/L). A POCUS showed concern for ventricular septal hematoma. Emergent cardiac catheterization ruled out coronary occlusion but revealed contrast extravasation from the left coronary artery into the ventricular septal wall. A follow-up TTE confirmed a 7.74 cm x 3.75 cm anechoic space within the ventricular septum protruding into the right ventricle and

causing obstruction. Decision-making The ultrasound findings guided acute management leading to the decision to avoid anti-thrombotic therapy which would have increased the risk of hematoma expansion and progressive right ventricular obstruction. Conclusion This case highlights the role of POCUS and echocardiography in acute chest pain after intervention and provides rapid and effective means to identify structural complications. Additionally, interventricular septal hematoma following His bundle pacer placement is a rare complication that has not yet been described. [Formula presented]

Cardiology/Cardiovascular Research
Vishwanath R, **Clark N**, and **Ananthasubramaniam K**. ACUTE CHEST PAIN PERFUSION IMAGING: UNDERUTILIZED BUT ALIVE AND WELL. *J Am Coll Cardiol* 2025; 85(12):3335. Full Text

Background In patients with chest pain, differentiating ischemic versus non ischemic etiologies can be challenging. Acute chest pain imaging with perfusion tracers which help identify critical ischemia leading to timely intervention. Case A 36-year-old female patient with history of hyperlipidemia, and morbid obesity BMI 46 presented with chest pressure, constant and present for 5 days without relief. Worse with exertion and inspiration. Hs-cTn I 30 ng/L. ECG did not show any evidence of ischemia. Decision-making We proceeded with acute chest pain perfusion nuclear imaging. Patient was injected with 25.2 millicurie of Tc 99m sestamibi and rest imaging obtained during symptoms. This showed a distal septal perfusion defect raising concern for acute ischemia in the LAD distribution. Coronary angiogram revealed 99% occlusion of the mid-LAD, and 71% mid-RCA disease. She then went PCI with a DES to the mid-LAD and staged PCI to the RCA. Conclusion Prolonged chest pain without definitive evidence of ischemia can be tricky to evaluate. SPECT chest pain imaging is done to evaluate if symptoms are to ischemia. Normal scan has a negative predictive value of 99.3% to exclude ischemic etiology of chest pain. The only class 1A recommendation for SPECT cardiac imaging is rest only imaging in patients with chest pain and non-ischemic ECG and equivocal troponin elevations as illustrated by this case. The use of rest only SPECT chest pain perfusion imaging serves as a valuable adjunct to assess for acute myocardial ischemia. [Formula presented]

Cardiology/Cardiovascular Research
Walji M, **Cieslak R**, **Abuzahrieh O**, **Phillips C**, and **Arnautovic J**. PREPARED FOR THE WORST, HOPE FOR THE BEST: COLLABORATIVE MEDICINE AGAINST A MASSIVE PULMONARY EMBOLISM IN A YOUNG WOMAN. *J Am Coll Cardiol* 2025; 85(12):3815. Full Text

Background Approximately 900,000 Americans experience pulmonary embolisms (PEs) each year, with 5-10% of those classified as high-risk or massive PE. The mortality risk for an untreated massive PE is alarmingly high, ranging from 30-60% within hours of onset. Even with prompt treatment, it remains one of the leading causes of cardiovascular death. Treatment requires a multifaceted, coordinated team approach that considers the patient's clinical condition, risk factors, and contraindications (CIs). Case A 24-year-old woman with a past medical history of obesity, oral contraceptive therapy, and back pain presented to a communityhospital with tachycardia, lightheadedness, and shortness of breath after a recent epidural spinal injection (ESI). She was diagnosed with a massive saddle PE and quickly became hemodynamically unstable with hypoxia and hypotension. A STAT echocardiogram demonstrated a severely dilated right ventricle (RV) with evidence of strain and a small, hyperdynamic left ventricle. Decision-making Neurosurgery was consulted due to the relative CI for thrombolysis after an ESI and determined the patient to be at an acceptable risk to proceed with thrombectomy and anticoagulation. She was urgently transported to the catheterization lab. A cardiothoracic surgeon (CTS) was present during the case with cardiopulmonary bypass prepped along with a pharmacist with thrombolysis if needed. Patient underwent a successful transfemoral embolectomy and was closely monitored. She was later initiated on oral anticoagulation. At her two-month follow-up, she was doing well with her echocardiogram demonstrating an exceptional, complete recovery of her RV. Conclusion This case emphasizes the importance of collaborative multidisciplinary care in a rural-hospital setting, especially in high-risk cases. Obtaining Neurosurgery clearance in an urgent manner helped expedite treatment. Having CTS and their team on standby, as well as a pharmacist with thrombolysis, allowed for alternative treatment options that could be seamlessly initiated. Coordinating care to this degree is uncommon, but vital in optimizing the utilization of all available resources when dealing with a massive PE.

Center for Individualized and Genomic Medicine Research

Lanfear DE, Lowry J, Amendola L, **Trepanier A**, **Aurora L**, **Ferrari H**, **Cabral W**, Kesari A, Rajkumar R, Chawla A, Coffey A, Hostin D, Huertas-Vazquez A, Perry D, Longoni M, and Taft R. CLINICAL GENOME SEQUENCING IN ROUTINE CARDIOLOGY: INITIAL FINDINGS OF THE CARDIOSEQ STUDY. *J Am Coll Cardiol* 2025; 85(12):1364. Full Text

Background Cardiovascular disease (CVD) is multifactorial and includes monogenic and polygenic contributors to onset and severity. Clinical genetic testing in practice seldom meets guideline recommendations, in part due to test limitations, disease heterogeneity and uncertainty about the utility of positive findings. The CardioSeq study was designed to evaluate the diagnostic yield and clinical impact of comprehensive clinical genome sequencing (cGS) spanning hundreds of genes and genetic disorders, risk factors and potential care modifiers in patients presenting with CVD. Methods A prospective, open-label, single-center clinical trial was conducted at Henry Ford Health. Inclusion required a diagnosis of at least one among: cardiomyopathy or heart failure, aortopathy, arrhythmia, coronary or peripheral artery disease, and/or dyslipidemia. The cGS test included 215 CVD-associated genes, 4 common genetic variants associated with increased CVD risk, 35 optional non-CVD ACMG secondary findings genes, pharmacogenomic variants and a coronary artery disease (CAD) PRS. Results Of the 1,000 participants who received cGS testing, 501 were assigned male sex at birth (median age 69, IQR 61-75) and 499 were assigned female (median age 70, IQR 62-76). The most common self-reported races were white (57.9%) and African American (39.2%). Cardiomyopathy or heart failure accounted for 33.5% of the entire cohort. A total of 74 participants received a monogenic finding, roughly half of which were due to variants in three genes: TTR (n = 16, 21.6%), TTN (n = 14, 18.9%), and LDLR (n = 8, 10.8%). The TTR p.Val142Ile variant accounted for 20.3% of positive cases. Unadjusted diagnostic yield was highest in African American cases (11.5%). Risk allele findings were reported in 10.1% of study participants, secondary findings in 1.4%, and pharmacogenomic findings in <99%. An elevated CAD PRS was reported in 4.6% of participants. Conclusion A single comprehensive cGS test can provide useful diagnostic and genetic risk data across a broad range of CVD phenotypes and genetic ancestries. The investigation of the impact of cGS findings on clinical management is ongoing and will be reported at CardioSeq study completion.

Dermatology

Paller A, **Gold LS**, Weidinger S, Staumont-Sallé D, Nakajima S, Simpson E, de Bruin-Weller M, Demil N, Davey S, Rahawi K, and Bernigaud C. 110: Amlitelimab (an anti-OX40 ligand antibody) vs placebo in patients with moderate-to-severe atopic dermatitis: Study design of phase 3 OCEANA clinical trials COAST1/2, SHORE, AQUA, and ESTUARY. *J Invest Dermatol* 2025; 145(3):e27. Full Text

Abstract: Amlitelimab, a fully human nondepleting anti-OX40 ligand (OX40L) monoclonal antibody, has demonstrated safety and efficacy in patients with atopic dermatitis (AD) in phase 2a and 2b trials. The phase 2b STREAM-AD trial showed improvements in AD signs, symptoms, and biomarkers over 24 weeks of amlitelimab treatment in adults with AD. Most clinical responders maintained improvements after a 28-week treatment withdrawal, indicating potential for extended dosing. The OCEANA phase 3 randomized, double-blind, placebo-controlled trials (COAST1, COAST2, SHORE, AQUA, and ESTUARY) assess two subcutaneous amlitelimab dosing regimens (every 4 or 12 weeks) in adults and adolescents. Key inclusion criteria for COAST1/2, SHORE, and AQUA include patients (≥12y; ≥25kg) with AD ≥1y and inadequate response to topical and/or systemic therapies. SHORE and AQUA evaluate amlitelimab in patients on background topical corticosteroids/calcineurin inhibitors, with AQUA restricted to patients with inadequate prior response to AD biologics or oral Janus kinase inhibitors. Doses for patients <40kg are halved compared to patients ≥40kg. Primary endpoints include proportion of participants with validated Investigator Global Assessment-AD 0/1 and reduction from baseline of ≥2 points. Primary endpoints are evaluated at Week 24 (COAST1/2, SHORE) or 36 (AQUA). Patients completing COAST1/2 or SHORE can enter ESTUARY, a blinded extension study; patients completing AQUA can enter RIVER-AD, a phase 2/3 open-label study. ESTUARY and RIVER-AD will evaluate long-term safety and efficacy, including maintenance of effect with treatment withdrawal. Enrollment began Q4 2023. Results will explore different dosing regimens, including extended dosing, and evaluate response durability on- and off-treatment in adults and adolescents. Layperson Summary: Amlitelimab is an antibody therapy that

targets an important protein in the immune system called OX40 Ligand (OX40L) and is being evaluated for treatment of moderate-to-severe atopic dermatitis (AD). By blocking OX40L, amlitelimab helps normalize the immune system by reducing inflammatory signals in the body. Phase 2 trials have shown that patients with moderate-to-severe AD receiving amlitelimab every 4 weeks had improvements in AD signs and symptoms. These improvements were maintained through 28 weeks following discontinuation of amlitelimab, indicating the possibility of extended-interval dosing, which helps to ease patient burden. Ongoing phase 3 trials are evaluating the efficacy and safety of amlitelimab treatment every 4 or 12 weeks in adolescent (≥12 years old) and adult patients, both alone (COAST1/2 trials) and in combination with topical medications (SHORE, AQUA). Patients completing these trials can enter ESTUARY or RIVER-AD, which are longer studies that will assess long-term safety and efficacy.

Emergency Medicine

Munroe E, Bernstein S, **Cahill M**, Esteitie R, **Kaatz S**, Horowitz J, McLaughlin E, Posa P, Swaminathan L, Younas M, Flanders S, and Prescott H. CHARACTERIZING ICU STRUCTURE AND HANDOFF PRACTICES IN MICHIGAN HOSPITALS. *Crit Care Med* 2025; 53(1). Full Text

E. Munroe, University of Michigan, Ann Arbor, MI, United States

INTRODUCTION: Intensive Care Unit (ICU) to floor transfer can be a high-risk time for patients, particularly in hospitals with closed ICUs where the primary team changes when a patient is transferred out of the ICU. We sought to characterize ICU structure and hand-off practices at Michigan hospitals. METHODS: We surveyed hospitals in the Michigan Hospital Medicine Safety Consortium (HMS) Sepsis Initiative, a collaborative quality initiative sponsored by Blue Cross Blue Shield of Michigan. HMS includes 69 hospitals with diverse characteristics. Surveys were completed in spring 2024 by each hospital's HMS representative. The survey included a question about ICU structure: closed (dedicated ICU team) vs open (same team manages patients both in and out of the ICU). A Chi-squared test was used to compare ICU structure by hospital urbanicity (using Rural-Urban Continuum Codes). Hospitals with closed ICUs were asked about use of standardized hand-off tools, including tool type and inclusion of informational elements important for effective transitions of care per the literature. RESULTS: 69/69 (100%) hospitals completed the survey; 37 (53.6%) had closed ICUs, 22 (31.9%) had open ICUs, and 10 (14.5%) reported other ICU structures, most often a combination of open/closed ICUs depending on the unit (e.g., specialty vs medical). Urban hospitals were more likely than rural hospitals to have closed ICUs (94.6% vs 5.4%, p=0.003). Among the 37 hospitals with closed ICUs, 34 (91.9%) had standardized tools to facilitate transfer, most often progress note templates (21, 56.8%), communication guides (20, 54.1%), and transfer note templates (17, 45.9%). Only 9 (24.3%) had hand-off tools that included all 7 key transfer elements: information about urinary catheters (27, 81.8%), temporary central venous access (26, 78.8%), goals of care (24, 72.7%), antibiotic course (23, 69.7%), volume status (20, 60.6%), new controlled medications (18, 54.5%), and ICU delirium (15, 45.5%). CONCLUSIONS: Over half of Michigan hospitals have closed ICUs. While most have standardized hand-off tools to facilitate inter-team communication, these tools are often missing key information. Understanding ICU structure and transfer processes is important to target initiatives to transitions of care for patients with sepsis admitted to the ICU.

Hematology-Oncology

Hwang C, **Symanowski J**, **Shore N**, **Russell D**, **Kral P**, **Elsouda D**, **El-Chaar N**, and **Karsh L**. CHARACTERISTICS, TREATMENT PATTERNS, AND OUTCOMES OF AFRICAN AMERICAN VERSUS CAUCASIAN PATIENTS WITH METASTATIC CASTRATION-RESISTANT PROSTATE CANCER: POST HOC ANALYSIS OF TRUMPET REGISTRY. *Urol Oncol* 2025; 43(3):7. Full Text

Introduction: Racial disparities exist in the treatment of prostate cancer in the US, and robust data for African American (AA) vs Caucasian (CAU) patients with metastatic castration-resistant prostate cancer (mCRPC) are scarce. This study explored characteristics, treatment patterns, and outcomes of AA vs CAU patients with mCRPC in the real-world setting. Methods: TRUMPET, a prospective, observational, multicenter study, enrolled 1028 patients who initiated CRPC treatment at 147 urology and oncology sites in the US (2015[sbnd]2019). The post hoc analysis included patients with mCRPC who identified as AA or CAU. Patients were enrolled within 90 days of the decision to treat or treatment initiation. Characteristics and treatment patterns were analyzed descriptively; radiographic progression-free survival (rPFS),

prostate-specific antigen PFS (PSA-PFS), overall survival (OS), and time to skeletal-related events (SREs) were analyzed using Kaplan–Meier methods and adjusted Cox proportional hazards models. An exploratory sub-analysis compared outcomes by race in patients initially treated with androgen receptor pathway inhibitors (ARPIs). Results: In total, 133 AA vs 661 CAU patients with M1 CRPC at baseline were included: median age, 69.0 vs 74.0 years; hypertension, 72% vs 66%; diabetes, 32% vs 23%; osteoporosis, 5% vs 12%; other cancers, 6% vs 24%; PSA at diagnosis, 48.8 vs 13.9 ng/mL; N1 tumors, 17% vs 11%; M1 tumors, 29% vs 23%. Primary treatment before CRPC diagnosis (AA vs CAU patients): surveillance, 12% vs 19%; radical prostatectomy, 18% vs 36%; radiation, 48% vs 41%. Initial mCRPC treatment: chemotherapy, 12% vs 6%; ARPI, 62% vs 57%; immunotherapy, 29% vs 41%. After treatment initiation, a trend toward improved clinical outcomes was seen in AA vs CAU patients (Table). In the exploratory analysis, AA patients initiating ARPIs showed a trend toward improved OS vs CAU patients (adjusted median time to death [95% CI]: 41.86 [33.25, not estimable] vs 32.30 [28.62, 40.08] months; adjusted HR [95% CI]: 0.71 [0.45–1.14]). Conclusions: AA patients were younger, had higher rates of some comorbidities and more severe disease, and were more likely to receive ARPIs or chemotherapy. Despite our initial hypothesis predicting differences favoring CAU patients, we observed generally similar treatment patterns and a trend toward better outcomes in AA patients. Further research is needed to better understand the outcomes of AA patients with mCRPC.

Hematology-Oncology

Nadal E, Rittmeyer A, De Marinis F, Lee DH, **Gadgeel S**, Vilariño N, Bria E, Arulananda S, Cronenberg EH, Antic V, Bennett E, Hu Y, Madden-Raja K, Williams P, Prizant H, and Popat S. 7MO: A phase II trial of tobemstomig (tobe) + platinum-based chemotherapy (chemo) vs pembrolizumab (pembro) + chemo in patients (pts) with untreated locally advanced or metastatic non-small cell lung cancer (NSCLC). *J Thorac Oncol* 2025; 20(3):S11-S12. Full Text

Background: Tobemstomig (tobe) is a novel bispecific antibody targeting programmed death-1 (PD-1) and lymphocyte-activation gene 3 (LAG-3). BO44178 (NCT05775289) is a randomised, double-blind, phase II study evaluating tobe + chemo vs pembro + chemo in pts with NSCLC who are ineligible for surgery or definitive chemoradiotherapy. Methods: Eligible pts with previously untreated, locally advanced unresectable or metastatic NSCLC were randomised 1:1 to receive either induction tobe + chemo (carboplatin + paclitaxel/pemetrexed) or pembro + chemo for four 21-day cycles, followed by maintenance tobe or pembro with/without pemetrexed every 3 weeks until disease progression, toxicity or loss of clinical benefit. Pts were stratified by PD-ligand 1 expression, histology and smoking status. Primary endpoints: confirmed objective response rate (ORR); progression-free survival (PFS). Secondary endpoints included overall survival (OS), duration of response (DoR) and safety. Results At data cutoff (20 June 2024), 181 pts were randomised to receive tobe + chemo (n = 90) or pembro + chemo (n = 91). Median duration of follow-up was 6 months. Baseline characteristics were similar across treatment arms; median age was 66 years. There was no improvement in confirmed ORR with tobe + chemo (41.1%) vs pembro + chemo (46.2%) and no PFS difference was observed between treatment arms (HR 0.99; 95% CI 0.63, 1.56; Table). OS data were immature at this analysis. Efficacy results were consistent across subgroups. The rates of grade 3/4 adverse events (AEs), serious AEs and immune-mediated AEs were higher with tobe + chemo vs pembro + chemo; however, the rate of treatment withdrawal due to AEs was similar between arms. [Formula presented] Conclusions: At this interim analysis, no ORR or PFS benefit was observed in pts with untreated locally advanced or metastatic NSCLC receiving tobe + chemo over pembro + chemo. OS data remain immature. Clinical trial identification NCT05775289.

Hematology-Oncology

Ozcan K, **Theisen B**, **Khan G**, **Chang Q**, and **Ahsan B**. 1613 Adenosquamous Carcinoma of the Pancreas: A Clinicopathologic Analysis of 33 Cases. *Lab Invest* 2025; 105(3). Full Text

Background: Adenosquamous carcinoma (ASC) of the pancreas is a rare subtype of cancer. Clinicopathologic and molecular data on this entity remains limited. Here we identify and describe clinical and molecular features on a population of ASC. Design: We identified 33 cases of ASC and performed a detailed analysis of clinicopathologic features and molecular results. ASC cases were compared with a cohort of 70 consecutive conventional pancreatic ductal adenocarcinoma (PDAC) cases. Next Generation Sequencing assay (NGS) was performed on a subset of ASC. Results: Clinicopathologic features of

pancreatic ASC and PDAC are summarized in Table. There were slightly more male patients than female patients diagnosed with ASC. Compared to PDAC, ASC patients were older (median: 74, range 54-81, p<.0005), with larger tumor size (median: 4.3 cm, range 1-8.2, p<.00001), higher T stage (T3 or T4: 63% vs 23%, p<.001), and higher clinical stage (Stage III or IV: 60% vs 28.6%, p<.0003). However, ASC did not show higher rate of nodal metastases when compared with PDAC (60.9% vs 54.4%). ASC of the pancreas was more frequently located in the body/tail (51.6% vs 18.6%, p<.01). Radiologic findings of all available patients showed hypodense lesions, with 21% significant for central necrosis. Squamous differentiation was detected on fine needle aspiration for 12 patients and reported as "(adeno)carcinoma with squamous differentiation". In all cases, CK 5/6, p40 or p63 were used to highlight the squamous component. Squamous cell carcinoma was the predominant component in one case. NGS data were available for 13 cases. Most commonly encountered mutations included KRAS (69.2%), TP53 (53.9%), CDKN2A (30.8%), SMAD4 (23.1%), KMT (23.1%) and PIK3CA (15.4%). On follow up, ASC had significantly worse prognosis when compared to PDAC. 27 patients died of disease with a median survival of 6 months (range: 0-39). Only 6 patients were alive with disease with a median follow up of 15.5 months (range: 1--28 months)(Figure 1). Clinicopathologic features of adenosquamous carcinomas of the pancreas and pancreatic ductal adenocarcinomas [Formula presented] [Formula presented] Conclusions: Adenosquamous carcinoma of the pancreas is an aggressive malignancy with an even worse prognosis than PDAC. It presents as a larger mass, in older patients with higher T and clinical stages and has a higher propensity for body/tail. Although an arbitrary 30% cut-off is typically used to diagnose ASC, it is also known that presence of any squamous component is associated with a worse prognosis which aligns with our findings that ASC group diagnosed on FNA having similar behavior with the rest of ASC cohort.

Hematology-Oncology

Qadir H, **Inamdar K**, **Ghosh S**, **Shen Y**, **Gomez-Gelvez J**, **Kuriakose P**, and **Liu W**. 1279 Re-Classification of Acute Myeloid Leukemia Based on Latest World Health Organization & International Consensus Classifications and Its Clinical Impact in a Population-Based Comparative Study. *Lab Invest* 2025; 105(3). Full Text

Background: Significant changes in acute myeloid leukemia (AML) classification were made in the latest World Health Organization and International Consensus 2022 classifications (WHO22 and ICC22), underpinning the biology of diseases. Whether the classification is in line with clinical outcomes has yet to be fully elucidated. Design: From a pathology database,116 consecutive AML cases with complete data from 1/1/2020 to 12/31/2022 were reclassified based on WHO22 and ICC22. The clinical impact, with a focus on AML-MRC (renamed as AML-MR), was assessed, correlating with ELN2022 genetic risk stratification, post-induction therapy responses and overall survivals. Results: Of 116 AML patients (median age 67, M/F=1:1), 46 (39.7%) were with recurrent genetic abnormalities (RGA), 44 AML-MRC (37.9%), and 26 AML-NOS (22.4%) by WHO2016, most changes in the latter two categories. AML-NOS narrowed down to include 21 patients by WHO22, 17 by ICC22. 54 patients (46.6%) were reclassified as AML-MR by WHO22, including 10 previously classified as AML-NOS (rAML-MR). Most (53.7%, n=29) had both cytogenetic and molecular abnormalities, while 15 had only molecular, 7 had only cytogenetic changes, and 3 neither. Complex karyotype (43.3%, n=26) and ASXL1 mutation (30.2%, n=13) were the most common. Under ICC22, 39 patients (33.6%, also including 10 rAML-MR) were reclassified as AML-MR, 19 patients (16.3%) as AML-TP53, in comparison to WHO22 showing similar genetic composition (data not included). Under WHO22, rAML-MR (n=10) showed significantly higher rate of non-response to treatment than that of AML-NOS (66.6% vs 0%, p=0.0015) while no difference than that of remainder AML-MR (60.0%, p=0.68), with all (100%) concordantly classified in the adverse risk group by ELN2022 (vs 28.6% AML-NOS [p<0.0001] and vs 90.9% remainder AML-MR [p>0.9999]). Of note, while overall survival (OS) was significantly different by WHO22 among AML-NOS, rAML-MR and remainder AML-MR (42 vs undefined vs 704 days, p=0.001), no significance reached between AML-NOS and rAML-MR (p=0.16). Results from ICC22 were similar in addition to that AML-TP53 showed the shortest OS than those with rAML-MR, remainder AML-MR and AML-NOS subgroups (42 vs undefined vs 133 vs 488 days, p=0.0005). Conclusions: While rAML-MR showed significantly worse treatment response and associated with adverse risk by ELN2022, OS was not significantly different from that of AML-NOS. Additional studies are warranted.

Internal Medicine

Abdelhai OS, **Mahfouz R**, **Maligireddy A**, **Rangavajla G**, **Andrews TQ**, **Jabri A**, **Memon M**, **McBride P**, **Villablanca PA**, **Jamil D**, and **Aggarwal V**. THE IMPACT OF ATRIAL FIBRILLATION ON IN-HOSPITAL OUTCOMES IN PATIENTS UNDERGOINGLIVER TRANSPLANTATION USING NIS 2016-2021. *J Am Coll Cardiol* 2025; 85(12):94. Full Text

Background The influence of atrial fibrillation (AF) on outcomes in patients undergoing liver transplantation has not been extensively investigated in the literature. This study aims to assess the prevalence of pre-transplant AF and its association with postoperative outcomes in patients undergoing liver transplantation. Methods Data from the National Inpatient Sample (2016-2021) identified liver transplant patients and their AF status. T-tests and chisquare tests compared the data. Outcomes included mortality risk, in-hospital results, and risk factors. Univariate and multivariate logistic regressions calculated odds ratios for comorbidities. Results The study identified 45,460 liver transplant patients, 3,905 of whom had AF. AF patients had a longer LOS (28.6 vs. 19.9 days, $p = 0.001$) and higher hospital charges ($768,558 vs. $624,364, $p < 0.001$). The mortality rate was also greater in AF patients (5.89% vs. 2.72%, $p < 0.001$), and this finding was confirmed by multivariate analysis, which showed an odds ratio of 1.54 ($p < 0.001$) after adjusting for age, gender, race, and comorbidities. Conclusion Our study demonstrated that liver transplant patients with a history of AF in a national cohort experienced higher mortality and morbidity rates. This finding underscores the importance for physicians to prioritize optimizing AF management in this patient group, which could help reduce complications, shorten hospital stays, and lower overall mortality. [Formula presented]

Internal Medicine

Abdelhai OS, **Mohammed M**, **Frisoli TM**, **Lee JC**, **O'Neill WW**, **Zweig B**, **O'Neill BP**, **Dawdy J**, **Gonzalez PE**, and **Villablanca PA**. SAFETY AND EFFICACY OF PARAVALVULAR LEAK CLOSURE IN POST TAVR PATIENTS: A SINGLECENTER EXPERIENCE. *J Am Coll Cardiol* 2025; 85(12):924. Full Text

Background Paravalvular leak (PVL) is a notable complication following transcatheter aortic valve replacement (TAVR) and is associated with adverse impacts on both short- and long-term survival. This study aims to assess the safety and efficacy of PVL closure in a singlecenter experience. Methods We retrospectively analyzed all patients who underwent PVL closure post TAVR at Henry Ford Hospital between 2012 and 2022. Data collected included patient demographics, types and number of devices used, severity of residual PVL post-closure, and overall success rates. Severity of PVL was categorized as severe, moderate, and mild. Results Fifty patients (median age: 80 for females [n=32], 75 for males [n=18]) underwent attempted PVL closure. Comorbidities included hypertension, diabetes, hyperlipidemia, and heart failure. The AVP II plug Amplatzer was the most used device (72%, n=36), followed by Amplatzer Muscular VSD occluders (28%, n=14). On average, two devices were used per procedure. Post-intervention, all patients had minimal or no residual leak, with significant improvement in PVL severity (Figure 1). Conclusion This single-center experience demonstrates that percutaneous PVL closure after TAVR is a safe and effective procedure, as illustrated by the significant reduction in paravalvular leak severity (Figure 1). The use of Amplatzer devices, particularly the AVP II plug, resulted in a high technical success rate with minimal residual PVL. [Formula presented]

Internal Medicine

Abdelhai OS, **Villablanca PA**, **Rangavajla G**, **Frisoli TM**, **O'Neill BP**, **Lee JC**, **Zweig B**, **Fram G**, and **Nguyen F**. RIGHT VENTRICULAR FUNCTION AS ASSESSED BY TRICUSPID ANNULAR PLANE SYSTOLIC EXCURSION IN PATIENTS UNDERGOING TRANSCATHETER TRICUSPID VALVE REPLACEMENT WITH EVOQUE VALVE. *J Am Coll Cardiol* 2025; 85(12):933. Full Text

Background Transcatheter tricuspid valve replacement (TTVR) with the Evoque valve represents a new commercially available nonsurgical therapy for severe tricuspid regurgitation (TR) in the US. Limited data has been published on the impact of this intervention on right ventricular function. Methods We performed a retrospective review of patients that underwent commercial TTVR with Evoque valve at our institution between February and July 2024 (n=40), assessing tricuspid annular plane systolic excursion (TAPSE) as

reported by interpreting physician on transthoracic echocardiogram before the procedure, 1-day post-procedure and 30-days post-procedure. Results The median TAPSE reported pre-procedure was 15.3 mm (IQR 14-19) with reductions seen at 1 day [13.8 mm (IQR 11-16, p=0.03)] and 30 days [12.1 mm (IQR 10-16; p=0.01)]. Despite two deaths and five heart failure (HF) readmissions in this cohort at the 30day follow-up, no statistical correlation was found between TAPSE reduction and mortality or HF readmissions (p=0.62, CI=0.24-2.4). Conclusion The use of TAPSE to assess right ventricular function post TTVR with Evoque has yet to be validated, and further investigation on how to best assess right ventricular function post TTVR is needed. We investigated a cohort of patients in whom TAPSE has been reported and noted a post-procedural reduction in median TAPSE at 30 days that was not associated with instances of hospitalization or mortality. [Formula presented]

Internal Medicine

Alkehef Y, **Kheyrbek M**, **Alsheikh O**, **Khan A**, **Zein RK**, and **Azoury F**. THE SILENT CRISIS: A CASE OF LEFT INTERNAL MAMMARY ARTERY GRAFT RUPTURE FOLLOWING CABG. *J Am Coll Cardiol* 2025; 85(12):2919. Full Text

Background Left Internal Mammary Artery (LIMA) graft rupture is a rare but fatal complication of coronary artery bypass graft (CABG). It may have subtle presentation such as dyspnea and syncope but can rapidly progress to hemorrhagic shock. Case 77-year-old male with history of coronary artery disease status post CABG two months prior presented with syncope. He was noted to be hypotensive and tachycardic. Computed Tomography (CT) of the chest showed sternal hematoma and left pleural effusion. Echocardiogram was normal. A chest tube was placed which drained 250 cc bloody fluid. Patient continued to be in shock requiring blood transfusions and vasopressors. Decision-making Our priority was to identify the source of bleeding in the chest. Video-assisted thoracoscopic surgery was non-revealing. He improved following the procedure only to get worse the next day. Repeat chest x-ray showed recurrence of left pleural effusion. CT angiogram of the chest was done (fig 1), and this time showed extravasation of contrast from the LIMA into the pleural space. He was taken emergently to the cath lab. LIMA angiogram (fig 2) showed mid-vessel extravasation. A covered stent was placed. Post angiogram showed no further extravasation and we were able to wean off vasopressors. He was stable for discharge days later. Conclusion Thorough clinical exam and multimodality imaging are essential to identify CABG complications. Emergent management with surgery or catheter interventions might be necessary. [Formula presented]

Internal Medicine

Almajed MR, **Zimmerman A**, **Obeidat L**, **Fadel R**, **Grafton G**, **Cowger JA**, and **AlDarzi W**. A FATAL INTERSECTION: ANTIPHOSPHOLIPID ANTIBODY SYNDROME AND CARDIOGENIC SHOCK. *J Am Coll Cardiol* 2025; 85(12):4348. Full Text

Background Cardiac involvement in antiphospholipid syndrome (APS) manifests as valvular heart disease, ventricular dysfunction, and thrombosis. Mechanical support (MCS) and advanced heart failure (HF) therapies may be necessary in patients who do not respond to conventional management. Case A 32-year-old woman with a history of APS and systemic lupus erythematosus presented with shortness of breath and was admitted for cardiogenic shock. One month prior, she underwent cesarean section delivery at 26-weeks of gestation for hemolysis, elevated liver enzymes, and low platelet count (HELLP) syndrome. Echocardiogram revealed biventricular dysfunction. Invasive coronary angiography was negative for coronary artery ischemia or dissection. She was medically managed for decompensated HF but developed worsening shock despite vasopressor and inotropic support. Hemodynamic assessment revealed biventricular dysfunction (RA pressure 18 mmHg, wedge pressure 30 mmHg), with a reduced cardiac output of 3.54 L/min. Due to worsening hemodynamics, a peripherally cannulated transcaval left atrial veno-arterial extracorporeal membrane oxygenation (ECMO) was placed. Further evaluation for HF etiologies was unremarkable with a bland endomyocardial biopsy. Despite therapeutic systemic anticoagulation, her course was complicated by extensive thrombosis involving the arterial and venous catheters, and ECMO inflow cannula at the IVC extending into the left atrium. Decision-making Our patient developed refractory cardiogenic shock and extensive arterial and venous thrombosis concerning for catastrophic APS. She was treated with plasmapheresis, systemic steroids, and therapeutic anticoagulation with a modified higher intensity protocol. She underwent orthotropic heart transplantation

ten days after hospitalization. Biopsy of the explanted heart revealed myocardium with extensive transmural necrosis and granulation tissue. Conclusion APS associated cardiomyopathy confers a poor prognosis and early MCS evaluation should be considered. Management requires a multidisciplinary approach that could include hematologic interventions and advanced HF therapies.

Internal Medicine
Andrews TQ, **McBride P**, **Abdelhai OS**, **Toiv A**, **Zimmerman A**, and **Cowger JA**. ADRENERGIC MYOCARDITIS DUE TO PHEOCHROMOCYTOMA. *J Am Coll Cardiol* 2025; 85(12):2880. Full Text

Background Chronic adrenergic stimulation has adverse effects on cardiomyocytes including hypertrophy, apoptosis, and contraction band necrosis resulting in cardiac dysfunction. Case A 33-year-old male with no medical history presented with subacute palpitations, flushing, and dyspnea found to have LVEF of 10%, LVH, and apical thrombus with right parietal lobe infarct on CT. RHC showed bivencticular volume overload with low cardiac index and AKI. Blood pressures were unusually elevated. Cardiac MRI showed subendocardial LGE deposition consistent with myocarditis. Further imaging revealed a 4.3 x 3.9 cm left adrenal mass. Laboratory tests showed elevated total metanephrines and catecholamines raising concern for pheochromocytoma. He was transitioned from nitroprusside to doxazosin for alpha-blockade along with GDMT. He underwent adrenalectomy with pathology showing pheochromocytoma followed by normalization of cardiac function. Decision-making The patient's history of flushing and unusual hypertension in setting of low cardiac output prompted laboratory assessment with abdominal imaging which effectively confirmed the diagnosis. The removal of the adrenal tumor led to myocardial cure. Conclusion Adrenergic myocarditis is a rare condition associated with pheochromocytoma and can present with acute hemodynamic compromise. Clinical history is crucial for diagnosing and managing this uncommon disorder. Effective treatment requires a multidisciplinary approach. [Formula presented]

Internal Medicine
Andrews TQ, **McBride P**, **Abdelhai OS**, **Toiv A**, **Zimmerman A**, and **Cowger JA**. CARDIOGENIC SHOCK SECONDARY TO HUMAN IMMUNODEFICIENCY VIRUS INDUCED MYOCARDITIS. *J Am Coll Cardiol* 2025; 85(12):3210. Full Text

Background HIV associated cardiomyopathy is a stage IV defining HIV illness conferring increased mortality among infected individuals. Favorable outcomes rely on an interdisciplinary care approach. Case A 28-year-old male with no medical history or high risk social features presented to outside hospital with dyspnea and found in cariogenic shock (CGS) with positive HIV PCR. He escalated to intermediate hospital for Impella CP then to HFH where Impella was upgraded to 5.5. HIV viral load was 3.8M copies with low CD4. HAART was started with emtricitabine/tenofovir and Dolutegravir. At week two, LVEF improved to 33% with hemodynamic stabilization. The Impella was removed and the patient tolerated GDMT. Repeat HIV viral load of 172 copies. He was transitioned to bictegravir/emtrcitabine/tenofovir and discharged. At four weeks post-discharge, he was NYHA I-II on four-pillar GDMT. Decision-making Even in 2024, HIV should be considered in the differential diagnosis of acute myocarditis as risks for HIV may not be readily shared. Prompt consideration of HIV, initiation of HAART, and aggressive stabilization through MCS was essential in managing the underlying process. Conclusion This case highlights a potentially reversible cardiomyopathy with a complex interplay of acute HIV myocarditis and CGS. The patient's significant improvement, evidenced by reduced HIV viral load and successful weaning from MCS, underscores the effectiveness of a multidisciplinary approach. [Formula presented]

Internal Medicine
Ethakota J, **Doddi H**, **Kumar D**, **Salib N**, and **Memon MA**. FROM INCIDENTAL CARDIAC MASS TO METASTATIC NEUROENDOCRINE TUMOR: A DIAGNOSTIC JOURNEY. *J Am Coll Cardiol* 2025; 85(12):3982. Full Text

Background Cardiac metastasis of neuroendocrine tumors (NET) is rare with incidence less than 5%. They are mostly asymptomatic and detected incidentally. Case A 73-year-old man with past medical history of Coronary artery disease, hypertension, COPD underwent a CT chest for lung cancer screening, it showed a small isodense mass in the right ventricle in relation to interventricular septum near cardiac apex . Further workup included a transthoracic echocardiogram showing a normal ventricular function, EF

of 65% and normal valves. Heart catherization showed a severe right and circumflex disease with moderate LAD disease. Cardiac MRI showed an enhancing lesion at the right ventricular apex attached to the RV and septum. PET scan showed mildly hypermetabolic cardiac apical region mass measuring about 2.1 x 1.5 cm. He underwent a CABG with right ventricular mass excision at the Cleveland Clinic. Pathology showed the tumor cells to be diffusely and strongly positive with synaptophysin and no reactivity with ACTH. Movat stain showed pseudocapsule around the tumor and focal moderate interstitial fibrosis of the myocardium. The mass was deemed to be a NET. Followed by a Ga-68 dotatate scan showed masslike thickening in the terminal ileum. Metastatic lesions in the left hepatic lobe and mesentery were seen as well. CT chest/abdomen/pelvis showed 2.5 x 2 cm mass in the ileocolic mesentery in proximity to the ileocolonic junction containing coarse calcifications. He was diagnosed with stage IV neuroendocrine cancer. Lab work showed a chromogranin A level of 160 ng/ml (reference range 0 - 160 ng/mL) and 5HIAA level of 13.5 mg (reference range < 10 mg/24h). Eventhough the patient was asymptomatic he was started on octreotide injections monthly in the setting of visceral and cardiac metastasis. A repeat echocardiogram showed EF in the range of 65 - 70% and normal pattern of LV diastolic filling. Decision-making The echocardiography, Cardiac MRI, dotatate scan, and PET/CT guided the diagnosis and management. Mass resection and immunostaining confirmed diagnosis. Conclusion As the cardiac NET are mostly asymptomatic, multimodal imaging plays an important role in early detection and management is patient-specific.

Internal Medicine
Fadel R, **Memon M**, **Swanson B**, and **Jamil D**. A RARE POST-INFARCT LEFT VENTRICULAR SEPTAL PSEUDOANEURYSM WITH RUPTURE INTO THE RIGHT VENTRICLE: A DIAGNOSTIC CHALLENGE MIMICKING VENTRICULAR SEPTAL DEFECT. *J Am Coll Cardiol* 2025; 85(12):3150. Full Text

Background Left ventricular pseudoaneurysms are rare, potentially fatal complications of STEMI, posing diagnostic challenges when in atypical locations with perforation. Case A 62-year-old man with type 2 diabetes and hypertension presented four days post-chest pain, diagnosed with inferior STEMI. Coronary angiogram showed triple vessel disease, including 40% left main disease, not amendable to revascularization. He developed cardiogenic shock requiring left atrial veno-arterial extracorporeal membrane oxygenation (LAVA-ECMO), with initial TTE suggesting VSD. Subsequent TEE identified a large pseudoaneurysm perforating into the right ventricle (figure 1). He underwent successful pseudoaneurysm exclusion and coronary bypass, discharging in stable condition. Decision-making This case underscores the importance of precise VSD and pseudoaneurysm detection via multimodality imaging, including TTE and TEE. The rare pseudoaneurysm’s atypical location and perforation mimicked a VSD, highlighting mechanical circulatory support’s role in stabilizing post-STEMI complications before definitive surgery. Conclusion A contained left ventricular pseudoaneurysm perforating into the right ventricle post-STEMI is rare, with accurate diagnosis critical for guiding surgical intervention. [Formula presented]

Internal Medicine
Gonzalez PE, **Abdelhai OS**, **O'Neill BP**, **Villablanca PA**, **Halboni A**, **Frisoli TM**, **Fram G**, **Lee JC**, and **O'Neill WW**. RACIAL AND SEX DIFFERENCES IN THE TREATMENT ALLOCATIONS AND OUTCOMES AMONG PATIENTS WITH SEVERE MITRAL VALVE DISEASE AND CHALLENGING ANATOMY. *J Am Coll Cardiol* 2025; 85(12):2256. Full Text

Background Patients with mixed mitral valve disease or mitral stenosis and small predicted neo-left ventricular outflow tract (LVOT) are difficult to treat with percutaneous therapies given risk of LVOT obstruction and often are not offered intervention. This study investigates racial and sex differences in treatment and outcomes. Methods We included 104 patients referred to the Henry Ford Hospital (Detroit, MI) between 2018 and 2024 with severe mitral stenosis (MS group) or severe mixed valve disease. These patients were mostly, high or prohibitive risk for surgery and were being considered for possible transcatheter mitral valve replacement. All these had a predicted neo-LVOT <150 mm2. Results The MS group consisted of 93 patients (89%) and the MV group of 11(11%). The cohort consisted of 92 females (88%) and 85 white patients (82%).The all-cause mortality was 30%, with cardiovascular (CV) death at 21% for the entire cohort. All-cause mortality among females was 28% vs 38% in males (p = 0.33), and

CV death among females was 20% vs 33% in males (p = 0.27). The 1-year allcause mortality for females was 20% vs 38% in males (p = 0.083), and 1-year CV death was 15% for females vs 33% in males (p = 0.12). All-cause mortality among white patients was 28% vs 37% in non-whites (p = 0.46), and CV death for whites was 18% vs 37% in nonwhites (p = 0.064). The 1-year all-cause mortality was in both white and non-white patients was 21%(p = 0.99), and the 1-year CV death for whites was 15% vs 21% in non-whites (p = 0.54).Intervention rates also varied by sex and race, with 43% of females undergoing treatment compared to 67% of males. Both white (46%) and non-white (47%) patients demonstrated similar rates of undergoing. The all-cause mortality of those patients that did not undergo intervention (medical therapy only) were: females 27% vs males 25%, and white patients 23% vs non-white 40%. Conclusion This study underscores that most of the patients presenting to this tertiary heart valve center were female and mostly white. It is also notable that female patients were treated less often, and non-white patients had a higher rate of all-cause mortality when not treated percutaneously.

Internal Medicine

Helaly M, **Elfaham A**, **Jamil D**, and **Helaly Z**. THE TRIPLE M - NEUROMUSCULAR TRIAD WITH IMMUNE CHECKPOINT INHIBITORS - MYOCARDITIS, MYOSITIS, AND MYASTHENIA GRAVIS-LIKE SYNDROME WITH NIVOLUMAB-RELATLIMAB. *J Am Coll Cardiol* 2025; 85(12):3791. Full Text

Background Immune checkpoint inhibitors (ICIs) have shown significant effectiveness against advanced malignancies, including malignant melanoma, but they can lead to life-threatening immune-related adverse events (iRAEs), particularly when used in combination therapies. In May 2024, Relatlimab in combination with Nivolumab was approved for unresectable or metastatic melanoma in patients aged 12 and older. Approximately 60 cases of myocarditis, myositis, and myasthenia gravis-like syndrome associated with various ICIs have been reported, however no cases were reported with Relatlimab or its combination with Nivolumab. Case A 74-year-old male with a history of scalp melanoma on Nivolumab and Relatlimab for three weeks, presented to the emergency department with mid-lower back pain, dizziness, double vision, and right eye droop. Exam findings included right eye complete ptosis and left eye incomplete ptosis with 4/5 hip strength. Initial tests indicated elevated troponin levels and CPK. EKG showing new left bundle branch block. He was managed for concern for NSTEMI. He went for left heart catheterization which revealed non-obstructive coronary artery disease and there symptoms and troponins attriubuted to myocarditis. Neurological evaluation suggested autoimmune myasthenia gravis and myositis due to immunotherapy. Decision-making Following a multidisciplinary meeting, the ICI was stopped, patient was immediately started on high-dose steroids and given IVIG for persistent symptoms with improvement. At three month follow up, there was significant improvement in symptoms and troponin and CPK levels almost back to normal. Conclusion Given the potential severity of myocarditis, myositis, and myasthenia gravis-like syndrome, immediate corticosteroid treatment is recommended upon suspicion, without awaiting a confirmed diagnosis.

Internal Medicine

Kattula M, **Al-suraimi A**, **Fadel R**, **Patel V**, **Basir MB**, and **Rabbani B**. THE EFFECT OF AN ONLINE LEARNING MODULE ON TRAINEE UNDERSTANDING AND TROUBLESHOOTING OF MECHANICAL CIRCULATORY SUPPORT DEVICES IN THE CICU. *J Am Coll Cardiol* 2025; 85(12):2524. Full Text

Background We identified a need to standardize mechanical circulatory support (MCS) device training for learners in an urban teaching hospital. We hypothesized that an enduring educational resource in the form of an asynchronous online module reviewing principles, daily care, and complications would improve understanding and ability to troubleshoot. Methods We developed a module, using Articulate Rise 360, addressing intraaortic balloon pumps (IABP), Impella, extracorporeal membrane oxygenation (ECMO), and left ventricular assist devices (LVAD). Content was derived from textbooks, guidelines, articles, and hospital policies. A control cohort of residents and cardiology fellows in the cardiac intensive care unit (CICU) were surveyed at the beginning and end of their month-long rotation. The module was then made available to the intervention cohort, which was subsequently surveyed. Results An independent samples t-test comparing post-rotation scores demonstrated a significant improvement in learners' perceptions about their ability to troubleshoot complications, time spent on formal education, and thoroughness of attending staff education. It did not, however, significantly improve learners' views of their basic understanding compared to standard training except for ECMO. Conclusion Our asynchronous online

module improved CICU learners' perceptions of their ability to troubleshoot MCS devices and the time and quality of instruction provided to them. [Formula presented]

Internal Medicine
Mazhar MA, **McGwire J**, **Alsheikh ON**, and **Zein RK**. EFFECT OF TEACHING HOSPITAL STATUS ON HEART FAILURE OUTCOMES: ANALYSIS OF THE NATIONAL INPATIENT SAMPLE 2021. *J Am Coll Cardiol* 2025; 85(12):1572. Full Text

Background Heart failure is a growing concern in the U.S., affecting nearly 6.5 million Americans aged 20 and older, with over 960,000 new cases diagnosed annually. It contributes to 8.5% of heart disease-related deaths. Previous research has explored the impact of teaching hospital (TH) status on outcomes across various diseases. This study aimed to determine whether TH status influenced outcomes for heart failure patients. Methods Data were drawn from the 2021 National Inpatient Sample, including 6,666,752 admissions. After filtering for heart failure (ICD10 I50), 16,519 patients remained. Exclusions included 3,444 rural nonteaching hospital (NTH) admissions. The final cohort included 3,402 urban NTH and 13,117 urban TH admissions. Chi-square and logistic regression analyzed mortality, cardiogenic shock, ICU admission, AKI, vasopressor use, and blood transfusion, with TH status as the independent variable. Results The study analyzed 16,519 patients with a mortality rate of 3.81%. Mortality was higher in THs (4.05%) than NTHs (2.88%) (p 0.002). Cardiogenic shock occurred in 7.77%, more in THs (9.13%) than NTHs (2.50%) (p 0.001). ICU admission was higher in THs (3.35%) than NTHs (1.52%) (p 0.001). AKI incidence was 29.01%, higher in THs (30.80%) than NTHs (22.10%) (p 0.001). Vasopressor use occurred in 2.81% of patients overall, more in THs (3.26%) than NTHs (1.06%) (p 0.001). Blood transfusions were higher in THs (2.59%) than NTHs (1.73%) (p 0.004). Conclusion Significant differences exist in outcomes between THs and NTHs for heart failure patients, with THs showing more severe presentations, evidenced by higher mortality, cardiogenic shock, ICU admission, AKI, vasopressor use, and transfusions.

Internal Medicine
McBride P, **Andrews TQ**, **Abdelhai OS**, **Zimmerman A**, and **Cowger JA**. METASTATIC CARDIAC CALCIFICATION OF UNCLEAR ETIOLOGY - SARCOIDOSIS OR MASQUERADER? *J Am Coll Cardiol* 2025; 85(12):4130. Full Text

Background Myocardial calcification typically occurs in the setting of previous myocardial injury, although abnormal calcium homeostasis and some systemic diseases can lead to calcium deposition. Understanding disease patterns is important to guide management in undifferentiated patients. Case 40-year-old male with a history significant for ESRD on HD secondary to IgA nephropathy was found to have nonischemic cardiomyopathy with reduced ejection fraction, refractory VT, and complete heart block. CT chest showed mediastinal adenopathy and opacities. Multiple bronchoscopies were negative for malignancy/granulomas. Cardiac MRI demonstrated abnormal signal on delayed gadolinium enhancement images involving the basal to mid left ventricle. PET CT showed moderate intensity signal involving basal/mid anterior, lateral, septal, and inferior walls in the setting of normal perfusion concerning for sarcoidosis. Endomyocardial biopsy showed normal myocardium and was negative for amyloid. He was managed for sarcoidosis due to multiorgan involvement consistent with the disease. He was treated with Prednisone but unfortunately had recurrent admission for ventricular tachycardia. He was recommended to pursue comfort care. Decision-making It is believed that he had myocardial calciphylaxis leading to inflammation of the myocardium as the active areas on PET correlated with the areas of calcium deposition on CT and MRI. Other etiologies for such a presentation include sarcoidosis or amyloidosis however he had an extensive workup that showed no other signs of sarcoid or amyloid (1). He was managed empirically for cardiac sarcoidosis with a trial of steroids and was started on a phosphate binder to help with calcium balance. He continues to have issues with arrythmias and is being managed medically as he is not a candidate for more advanced therapies. Conclusion While this patient was managed empirically for cardiac sarcoidosis, his disease continued to be uncontrolled on traditional immunosuppression. A second opinion at another academic center was also unrevealing. Understanding the spectrum of disease that can occur with sarcoidosis is important to guide decisions based on therapy.

Internal Medicine

Obeidat L, **Zimmerman A**, **Almajed MR**, **Modi S**, **Al-Darzi W**, and **Ananthasubramaniam K**. NEVER ENDING SAGA OF TAKOTSUBO CARDIOMYOPATHY RECURRENCES. *J Am Coll Cardiol* 2025; 85(12):3146. Full Text

Background Takotsubo cardiomyopathy (TC) is an acute, transient left ventricular (LV) dysfunction triggered by emotional or physical stress. While most recover quickly, recurrence occurs in 2%-4%. Here, we describe multiple recurrences of TC with different echocardiographic patterns. Case A 67-year-old woman with a history of hypertension (HTN) and non-obstructive CAD, first presented with uncontrolled HTN, dyspnea, nausea, and flushing. Workup showed elevated troponin levels, normal EKG, and an echocardiogram showing reduced EF of 2025% with apical akinesis. Coronary angiography confirmed no significant CAD, and a left ventriculogram revealed Takotsubo pattern with apical akinesis and basal hyperkinesis. On follow-up, her symptoms completely resolved, and a repeat echocardiogram normalized. She presented three years later with similar symptoms. Echocardiogram showed an EF of 51%, new severe MR, with basal septal and inferior wall hypokinesis with apical hyperkinesis, pattern consistent with reverse TC. She responded well to medical therapy, with resolution of the wall motion abnormalities. Since then, she has experienced three additional episodes, with evidence of recurrence of both typical and reverse Takotsubo patterns. Extensive workup has been negative for secondary causes of HTN. She remains asymptomatic between episodes with no clear triggers for her recurrent presentations. Decision-making TC is a reversible stress-induced cardiomyopathy characterized by LV dysfunction involving apical or periapical walls. A variant, reverse TC, is less common, accounting for fewer than 20% of cases and involves basal and inferior wall hypokinesis with apical hyperkinesis. Potential causes include catecholamine surge, microvascular dysfunction, or coronary spasm. Management focuses on supportive care, GDMT, and monitoring for complications such as shock and ventricular thrombi. Conclusion Our patient experienced five episodes of TC over a six-year period, which is an unusually high recurrence rate. Contrary to prior literature of benign outcomes, our case reiterates that a subset of TC patients suffer from ongoing morbidity and should be followed closely long term.

Internal Medicine

Qureshi MA, Bakht D, Rehman AU, Amjad Z, Rehman OU, Bokhari SFH, **Tareen H**, Haseeb S, **Ahmed O**, Khan LA, Munir S, and **Othman H**. EFFICACY AND SAFETY OF PROTAMINE IN REDUCING BLEEDING AND VASCULAR COMPLICATIONS AFTER TAVR: A META-ANALYSIS. *J Am Coll Cardiol* 2025; 85(12):1071. Full Text

Background Transcatheter aortic valve replacement (TAVR) often causes postoperative bleeding and vascular complications due to intraoperative heparin. Protamine sulfate reverses heparin but its routine clinical use in TAVR remains debated. This meta-analysis aims to evaluate protamine’s efficacy and safety in reducing bleeding and vascular complications compared to standard practices Methods PubMed, Embase, Cochrane and clinicaltrials.gov were searched. Primary outcomes were 30-day mortality, major bleeding, lifethreatening bleeding, and vascular complications. Secondary outcomes were minor bleeding, myocardial infarction, stroke, acute kidney injury, and hospital stay. Odds ratios (OR) and mean differences (MD) were calculated through a random-effects model using RevMan 5.4 Results 6 studies with a total of 4,123 patients were included in the quantitative synthesis. Protamine reduced minor (OR=0.63, p=0.01), major (OR=0.46, p<0.001), and life-threatening bleeding (OR=0.35, p<0.001), minor (OR=0.82, p=0.03) and major vascular complications (OR=0.45, p<0.001), and shortened hospital stay (MD=-1.95 days, p=0.02). Protamine did not significantly affect 30-day mortality, risk of pacemaker implantation, myocardial infarction, stroke, acute kidney injury, or postoperative transfusion requirement Conclusion Protamine reduces bleeding and vascular complications in TAVR without raising mortality or thromboembolic risks. More trials are needed to support routine use [Formula presented]

Internal Medicine

Rangavajla G, **Patel R**, **Abdelhai OS**, **Nguyen F**, **Gupta K**, **Fang JX**, **Giustino G**, **Raad M**, **Villablanca PA**, **Gonzalez PE**, **O'Neill BP**, and **Frisoli TM**. INCIDENCE OF CONDUCTION SYSTEM DISTURBANCES AFTER EVOQUE TRICUSPID VALVE IMPLANTATION. *J Am Coll Cardiol* 2025; 85(12):1126. Full Text

Background EVOQUE transcatheter tricuspid valve replacement (EVOQUE) is a new treatment for severe tricuspid regurgitation. The initial TRISCEND study suggested a high risk of post-EVOQUE conduction system disturbance (CSD) with 13.3% of non-paced patients requiring new pacemakers. The incidence of real-world CSD with EVOQUE is less clear. Methods Patients undergoing commercial EVOQUE at Henry Ford Hospital (HFH) in Detroit, MI were monitored both in-hospital and outpatient for new CSD. Baseline characteristics and outcomes were compared to published results from TRISCEND using Z tests. Results Of 34 HFH patients undergoing successful EVOQUE, 22 had no prior pacemaker and were included for outcomes analyses. Baseline differences between HFH and TRISCEND patients are noted (Table 1). Over a median follow up of 92 days (IQR 55-148), only 1 patient required a post-implant pacemaker (Table 2) which was implanted 5 days after EVOQUE for high-grade AV block. Three of 5 developing new right bundle branch block had resolution within 30 days; no patient developed left bundle branch block or sinus pauses <5 seconds. Conclusion Real-world EVOQUE patients may have significantly lower rates of post-EVOQUE pacemaker implantation and CSD compared to published results. Registry data is needed to determine the veracity of this finding in larger samples. [Formula presented]

Internal Medicine
Razdan P, **Gowda T**, **Alaamili A**, and **Katzman S**. RECURRENT BOSUTINIB-INDUCED PERICARDIAL EFFUSION IN CML. *J Am Coll Cardiol* 2025; 85(12):3980. Full Text

Background Chronic myeloid leukemia (CML) once had a poor prognosis, but the development of tyrosine kinase inhibitors (TKI) have enhanced outcomes and extended life expectancy. Since bosutinib's approval in 2012, its cardiac adverse reactions have been described and are quite rare. Case A 72 year-old female with a history of CML presented due to shortness of breath over the past 2 months. An echocardiogram showed a large pericardial effusion without tamponade. Bosutinib was discontinued due to suspicion that it triggered the effusion. Pericardiocentesis was performed with resolution of symptoms, no infection/malignant cells were found. 2 weeks later, repeat imaging showed another large pericardial effusion without tamponade. CT surgery placed a pericardial window and imaging showed reduction of fluid. Decision-making Bosutinib is a TKI shown to increase risk of effusions, most commonly pericardial/pleural with a 13.3% incidence. In 2018, an expert panel published guidelines on managing adverse reactions, but knowledge on such severe cases requiring pericardiocentesis was limited. Little evidence exists on managing extreme reactions, recurrence duration, and essential cardiac assessments before starting bosutinib. Conclusion Awareness of bosutinib's cardiac risks needs to be raised. Questions remain, such as should these patients should switch to alternate agents or lower the dosage of bosutinib. More research is needed to understand severe reactions and future options going forward. [Formula presented]

Internal Medicine
Ronchetto E, **Zimmerman A**, and **Obeidat L**. THE RHYTHM OF SURVIVAL: OVERCOMING ARRHYTHMIC CHAOS IN EMERY- DREIFUSS MUSCULAR DYSTROPHY. *J Am Coll Cardiol* 2025; 85(12):3030. Full Text

Background Emery-Dreifuss muscular dystrophy (EDMD) is a rare, X-linked disorder with a range of neuromuscular and cardiac phenotypes. Interestingly, cardiac disease can be the first and only manifestation of EDMD in some patients. Case At age 38, a previously healthy and very active male developed extreme fatigue. Following extensive evaluation, he underwent pacemaker placement for symptomatic junctional bradycardia. Device interrogations noted atrial fibrillation. His course was complicated by a stroke, thought to be cardioembolic, at age 38 and again at age 49, while on anticoagulation. His device was updated to a biventricular ICD following an echocardiogram showing an EF of 30% with severe biatrial enlargement at age 47. He underwent whole gene sequencing, which revealed a nonsense variant of the EMD gene (c.441C>A), not previously known to be pathologic. At age 50, he had his first ICD shock for ventricular tachycardia (VT), which progressed despite antiarrhythmics. Device interrogation also noted innumerable antitachycardia pacing episodes. Transplant evaluation was initiated due to recurrent and high burden of VT and ventricular fibrillation, and he ultimately underwent orthotopic heart transplant (OHT). Decision-making The EMD gene encodes the emerin nuclear envelope protein, important for gene regulation and intercalated disc function in cardiomyocytes. EMD gene mutations result in the X-linked recessive disorder, EDMD. The term "cardiac emerinopathy" describes

patients with EDMD who lack neuromuscular symptoms typically seen in muscular dystrophies. Cardiac manifestations of EDMD classically present with conduction abnormalities, including progressive atrial arrhythmias leading to atrial standstill, increasing risk for cardioembolic stroke and pulmonary embolism. Cardiomyopathy is another notable manifestation. And lastly, males with EMD gene variants are high risk for malignant ventricular arrhythmias. Conclusion This case presents extensive cardiac manifestations of EDMD, ultimately requiring OHT, with delayed recognition of etiology. A lower threshold for genetic testing should be had in young patients without obvious causes for cardiomyopathy.

Internal Medicine

Sater A, **Khan A**, **Palmer J**, and Rodriguez D. BACTERIAL ENDOCARDITIS MASQUERADING AS ANCA-ASSOCIATED VASCULITIS: A DIAGNOSTIC DILEMMA. *J Am Coll Cardiol* 2025; 85(12):4171. Full Text

Background The presentation and sequelae of bacterial endocarditis (BE) can vary, occasionally mimicking rheumatologic diseases. Antineutrophil cytoplasmic antibody (ANCA)-positive BE represents a distinct subgroup within this spectrum. According to one systematic review, ANCA positivity occurs in 18-43% of BE cases, predominantly c-ANCA (79%), followed by Perinuclear anti-neutrophil cytoplasmic antibodies p-ANCA (11%), and double positive (8%). Case A 58-year-old male with end-stage renal disease due to focal segmental glomerulosclerosis, recently started on hemodialysis, presented with a rash on his arms spreading to lower extremities. Laboratory results showed WBC 7.84 K/µL, hemoglobin 8.2 g/dL, ESR 14 mm/hr, CRP 38 mg/L. ANA negative, low C4, and c-ANCA titer (1:80). Transthoracic echocardiography revealed an ejection fraction of 70%, worsened aortic regurgitation, and multilobulated friable masses on the aortic valve (AV), confirmed by transesophageal echocardiography. Blood cultures grew Streptococcus sanguinis, susceptible to ceftriaxone. Skin biopsy exhibited leukocytoclastic vasculitis. He underwent bioprosthetic AV replacement and was discharged with a midline for a 6-week course of ceftriaxone. Decision-making ANCA vasculitis and BE share overlapping manifestations, posing diagnostic challenges. Misdiagnosis can lead to inappropriate treatment; immunosuppression for vasculitis may worsen BE, while delaying antibiotics can have severe consequences. In this case, high c-ANCA titers initially suggested vasculitis, but the presence of endocardial vegetations and positive blood cultures confirmed BE. This distinction was critical for guiding effective antibiotic therapy and surgical intervention. BE is a rare yet significant cause of ANCA positivity. The exact mechanism remains unclear, although proposed theories include cross-reactivity and homologies between microbial acid sequences and RNA proteins. Conclusion BE can manifest with cutaneous vasculitis. A meticulous medical history and high index of suspicion with relevant risk factors are essential for prompt diagnosis and appropriate treatment, thereby improving patient outcomes.

Internal Medicine

Shaik A, **Khan A**, Elshaer A, **Adi MB**, Hariri M, Yousif M, **Sayar S**, and Yousaf H. VENTRICULAR ELECTRICAL STORM FOLLOWING LEADLESS PACEMAKER IMPLANTATION. *J Am Coll Cardiol* 2025; 85(12):4096. Full Text

Background Leadless pacemakers (LP) are alternative to transvenous pacemakers for bradyarrhythmia, offering favorable safety profile. We report a rare yet significant complication of ventricular electrical storm after LP insertion. Case A 65-year-old male with hypertrophic obstructive cardiomyopathy and sick sinus syndrome presented after his subcutaneous implanted cardioverter-defibrillator (ICD) was discharged which was thought to be from pause-dependent ventricular fibrillation (VF) and was treated by LP. Two days later, the patient had recurrent refractory monomorphic ventricular tachycardia (MVT) requiring defibrillation. Subsequent left heart catheterization led to stenting of left anterior descending artery. His discharge was uneventful but returned a week later with chest pain and multiple ICD shocks along with EKG showing persistent MVT despite antiarrhythmics. An EP study revealed scar tissue in LV, which was ablated but the VT storm persisted post-ablation. A repeat EP study was performed, leading to the removal of the leadless pacemaker and implantation of a biventricular ICD, which resolved the VT storm. Decision-making Persistent MVT after LP insertion raised concern for ischemia, prompting cardiac catheterization and stenting. When VT storm persisted, EP study was done which identified a potential site for ablation in the LV. The patient's MVT persisted even after ablation and medical management. A repeat EP study identified the LP implantation site as the origin of the MVT. LP was removed leading to

the resolution of arrhythmia. Conclusion Persistent MVT post LP implantation highlights temporal relationship as arrhythmias ceased after LP removal illustrating a significant complication. The proposed mechanisms of MVT post LP implantation include myocardial irritation and proarrhythmic effects of LP components. Our case aims to educate physicians for the need of further research into the safety profile of LP.

Internal Medicine
Shaik A, **Khan A**, Elshaer A, Hariri M, **Adi MB**, and Yousif M. EMBOLIZATION OF LEADLESS PACEMAKER INTO THE PULMONARY ARTERY. *J Am Coll Cardiol* 2025; 85(12):3999. Full Text

Background Leadless pacemakers (LPs) are increasingly utilized in patients for ventricular pacing due to their low complication rates. However, embolization of device remains a concern, especially when it migrates to pulmonary artery (PA). Case A 74-year-old female with recent AV nodal ablation and LP placement for atrial fibrillation was sent for bradycardia from the clinic during a routine follow-up. Upon arrival, she was asymptomatic with a heart rate in the 40s, otherwise vitally stable. EKG revealed a complete heart block while chest x-ray confirmed LP dislodgement in the left middle PA (a). Percutaneous retrieval was performed successfully after several tries using a snare (b). An alternate LP was implanted without complication, and patient was discharged uneventfully. [Formula presented] Decision-making Due to LP embolization into PA in the setting of recent nodal ablation, decision was made to retrieve and implant a new device. The retrieval was complex as the docking button of device was not accessible initially. Repeated attempts were made using snares culminating in a successful extraction. Reimplantation of new device was uneventful and patient was subsequently discharged without complications. Conclusion Retrieval of LP in PA presents with challenges and novelty as only a handful of such cases are documented in literature. When determining the appropriate treatment approach, the likelihood of device re-dislodgement should be carefully considered versus risk of a pulmonary artery tear during retrieval.

Internal Medicine
Sheffeh MA, Baqal OJ, **Malik DA**, **Sheffeh J**, **Klein J**, **Oujamaa I**, Turkmani M, and Alraies MC. TRANSCATHETER PULMONARY VALVE REPLACEMENT OR REPAIR HAS BETTER IN-HOSPITAL OUTCOMES COMPARED TO SURGERY: A NATIONWIDE STUDY. *J Am Coll Cardiol* 2025; 85(12):957. Full Text

Background Reports of comparative outcomes of transcatheter pulmonary valve replacement (TPVR) or repair (TPVr) and surgical pulmonary valve replacement (SPVR) or repair (SPVr) are limited. We aimed to examine in-hospital outcomes of TPVR/TPVr and SPVR/SPVr Methods The National Inpatient Sample Database was utilized to identify TPVR/TPVr and SPVR/SPVr between 2018 and 2021. Patients younger than 18 years of age were excluded. The primary outcome was in-hospital mortality. Secondary outcomes included acute heart failure (AHF), cardiac arrest, ECMO, cardiogenic shock, mechanical ventilation (MV), vasopressor use, blood transfusion, bleeding and acute kidney injury (AKI). Multivariate logistic regression analyses were performed. Results There were 2205 (33%) TPVR/TPVr and 4575 (67%) SPVR/SPVr. Median age 35 (25-50) and 2825 (42%) were Female and 4730 (70%) were white. TPVR/TPVr was associated with significantly lower odds of ECMO, adjusted odds ratio [aOR]:0.17; 95% confidence interval [CI]:0.04-0.77; p=0.02), AKI aOR: 0.26; 0.17-0.41; <.0001, bleeding aOR: 0.07; 0.05-0.11; <.0001, blood transfusion aOR:0.09 (0.04-0.18); <.0001, vasopressor use aOR: 0.13; 0.06 -0.26; <.0001, MV aOR: 0.21; 0.09-0.45; <.0001, and cardiogenic shock aOR: 0.11 (0.05-0.23); <.0001 FIGURE Conclusion Transcatheter pulmonary valve replacement or repair is associated with favorable in-hospital outcomes compared to surgery. There was no difference in mortality between TPVR/TPVr and SPVR/SPVr. [Formula presented]

Internal Medicine
Sheffeh MA, **Sheffeh J**, **Klein J**, Baqal OJ, **Malik DA**, **Oujamaa I**, **Turkmani M**, and Alraies MC. HEART FAILURE IS ASSOCIATED WITH WORSE IN-HOSPITAL OUTCOMES IN PATIENTS UNDERGOING SURGICAL PULMONARY VALVE REPLACEMENT OR REPAIR: A NATIONWIDE STUDY. *J Am Coll Cardiol* 2025; 85(12):956. Full Text

Background There is limited data on the safety of surgical pulmonary valve replacement (SPVR) or repair (SPVr) in patients with heart failure (HF). We examined complications of SPVR/SPVr in patients with HF Methods Patients ≥ 18 yo underwent SPVR/SPVr between 2018-2021 were identified from the National Inpatient Sample Database. The cohort was further categorized into patients with and without heart failure. In-hospital outcomes include mortality, cardiac arrest, cardiogenic shock, mechanical ventilation (MV), Vasopressor use, Impella or intra-aortic balloon pump (IABP), ECMO, bleeding and acute kidney injury (AKI). We tested association using multivariate logistic regression analyses Results There were 4574 SPVR/SPVr, 1819 (39%) were female, median age was 35 years (26-52), 3254 (71%) were white and 1755(38%) had heart failure. HF was associated with an increased risk of mortality (adjusted odds ratio aOR 3.85 (95% CI 1.03-12.38); p-value 0.04), cardiac arrest (aOR 3.44 (1.03-11.4); 0.04, cardiogenic shock aOR 3.66 (2.34-5.74);<.0001, MV 1.75 (1.01-3.04); 0.04), vasopressor use (2.12 (1.37-3.28); 0.0007), Impella or IABP (4.52 (1.06-19.1); 0.04) and AKI (1.62 (1.11-2.36); 0.01) Figure Conclusion There is an increased risk of mortality and adverse cardiovascular events in patients with heart failure undergoing surgical pulmonary valve replacement or repair. Further research is needed to identify modifiable risk factors for better outcomes and optimize surgical timing and planning. [Formula presented]

Internal Medicine
Sheffeh MA, **Sheffeh J**, **Oujamaa I**, Baqal OJ, **Klein J**, **Malik DA**, **Turkmani M**, and Alraies MC. SAFETY OF ISOLATED TRANSCATHETER TRICUSPID VALVE REPLACEMENT OR REPAIR COMPARED TO SURGERY IN PATIENTS WITH CHRONIC KIDNEY DISEASE. *J Am Coll Cardiol* 2025; 85(12):955. Full Text

Background There is limited data on the safety of isolated transcatheter tricuspid valve replacement (TTVR) or repair (TTVr) compared to isolated surgical valve replacement (STVR) or repair (STVr) in patients with chronic kidney disease (CKD). We aimed to study complications of TTVR/TTVr in patients with CKD Methods We identified patients who underwent STVR/STVr and TTVR/TTVr between 2018-2021 using the National Inpatient Sample Database. Those <18 yo or had concomitant valvular procedures were excluded. In-hospital complications include mortality, acute kidney injury (AKI), bleeding, vasopressor use, cardiogenic shock, mechanical ventilation (MV), intra-aortic balloon pump (IABP) or Impella or permanent pacemaker (PPM) insertion. Multivariate logistic regression analyses were performed Results There were 555 (21%) patients who underwent TTVR/TTVr and 2115 (79%) who underwent STVR/STVr. Mean age 60 (±18) yr, and there were 1285 (48%) women, 1705 (64%) were White. TTVR/TTVr was associated with significantly lower odds of death aOR: 0.14; 95% CI (0.04-0.53);p=0.003, AKI aOR: 0.26 (0.15-0.44);<.0001, bleeding aOR: 0.09 (0.05-0.17);<.0001, vasopressor use aOR: 0.24; (0.110.54); 0.0006, MV aOR: 0.06 (0.01-0.21);<.0001, cardiogenic shock aOR: 0.12 (0.05-0.28); <.0001, Impella or IABP aOR: 0.06 (0.01-0.51); 0.009, PPM aOR: 0.21; (0.07-0.65); 0.006 FIGURE Conclusion TTVR/TTVr is safer in patients with CKD compared to surgerical interventions. Further prospective studies are needed [Formula presented]

Internal Medicine
Singh H, **Qureshi M**, Munir L, and Qureshi A. TUBERCULOSIS MORTALITY RATES IN THE UNITED STATES FROM 1999-2020: AN AREA OF CONCERN. *Crit Care Med* 2025; 53(1). Full Text

H. Singh, Henry Ford Health Jackson, United States

INTRODUCTION: Tuberculosis (TB) is a major source of global morbidity and mortality. In the United States, the incidence of new TB cases has been declining from 1999 to 2020, but TB-related mortality has been increasing steadily over the last many years. We extracted data on the ageadjusted mortality rate (AAMR) of TB from 1999 to 2020, used joinpoint regression analysis to identify the endpoint years contributing to this uptick of the AAMR, and compared race and gender differences. METHODS: We describe a retrospective population-based study where we obtained AAMR data from 1999 to 2020 with TB as the principal diagnosis through the previously validated International Classification of Diseases code. The data was extracted through the Multiple Causes of Death (MCOD) database available through the Centers for Disease Control and Prevention Wide-Ranging Online Data for Epidemiologic Research (CDC WONDER). We performed a joinpoint regression analysis of the overall AAMR of TB across

different genders and races. RESULTS: From 1999 to 2020, the AAMR of TB per 1,000,000 population declined from 0.68 to 0.23 in 2015 and rose steadily to 0.27 in 2020. Joinpoint analysis showed the average annual percent change of -4.31 (CI -5.23 to -3.39, p< 0.001) from 1999 to 2020. We recognized 2001 and 2015 as two statistically significant joinpoints in that range, creating three segments. The annual percent change (APC) was -12.24 (CI -19.31 to -4.56, p< 0.004) from 1999 to 2001, -5.55 (CI -6.05 to -5.04, p< 0.001) from 2001 to 2015, and became 2.72 (CI 0.23 to 5.23, p 0.03) from 2015 to 2020. The APC in Asian or Pacific Islanders in the segment from 2014 to 2020 was 0.49 (CI -4.03 to 5.23, p 0.82) and was -0.71 (CI -4.14 to 2.83, p 0.67) in black or African Americans. The white population did not have any statistically significant change in AAMR around the time of this positive skew. The AAMR in males was higher than in females in any given year. CONCLUSIONS: The slope of AAMR from TB, though declining from 1999 to 2015, has risen significantly till 2020. This could likely be attributed to the undiagnosed cases of latent TB causing its spread. This calls for strengthening public healthcare programs and collaboration with international partners to implement screening and appropriate treatment strategies.

Internal Medicine
Singh H, **Qureshi M**, Munir L, and Qureshi A. SEPSIS-RELATED MORTALITY RATES AND TRENDS BASED ON THE CAUSATIVE ORGANISM. *Crit Care Med* 2025; 53(1). Full Text

H. Singh, Henry Ford Health Jackson, United States

INTRODUCTION: Sepsis is the third leading cause of mortality in the United States and affects nearly 1.7 million adults every year. Previous studies have shown an increasing prevalence of sepsis but stable sepsis-related mortality rates. Until now, sepsis-related mortality rates and trends stratified by the inciting organism have not been evaluated. This study evaluates the epidemiology of sepsis from the most common types of bacteria. METHODS: We describe a retrospective populationbased study where we obtained age-adjusted mortality rate data with sepsis from Staphylococcus aureus (S. aureus), Streptococcus, and gram-negative bacteria as the principal diagnosis from 1999 to 2020. The data was extracted through the Multiple Causes of Death (MCOD) database available through the Centers for Disease Control and Prevention Wide-Ranging Online Data for Epidemiologic Research (CDC WONDER), and joinpoint regression analysis was performed. We selected decedents with sepsisrelated deaths, and the organism associated was identified using previously validated International Classification of Diseases codes. RESULTS: From 1999 to 2020, using the MCOD, the age-adjusted mortality rate per 1,000,000 population from sepsis from S. aureus declined from 18.56 to 6.6, Streptococcus from 8.26 to 3.53, and gram-negatives from 14.04 to 8.93. The average annual percentage change for S. aureus, Streptococcus, and gram-negative, was -5.37% (p< 0.001), -4.04% (p< 0.001), and -2.38% (p< 0.001), respectively. Across all the organism groups, males had a higher mortality rate than females. Black or African-American race had a higher mortality rate, followed by White and Asian descendants across all three groups. CONCLUSIONS: The rate of sepsis-related mortality rates has decreased considerably over the last two decades, in part from the Surviving Sepsis Campaign leading to better identification and treatment strategies. However, we note significant variation based on gender and racial groups, which should be considered in future studies.

Internal Medicine
Thacker H, **Banthiya S**, and **Saba S**. THE ENDOCARDITIS ENIGMA: SPOTLIGHT ON AN UNUSUAL MICROBE. *J Am Coll Cardiol* 2025; 85(12):4467. Full Text

Background Group B Streptococcus (GBS) infections in non-pregnant adults have been increased in recent decades. Most invasive GBS disease occurs at mean age of 60 & has high mortality. We present a case of idiopathic GBS infection in a healthy adult. Case A 55-year old male without any cardiac history presented to the emergency department with generalized fatigue. On arrival he was febrile, but not tachycardic or dyspneic. Physical examination was significant for a grade 2/6 systolic murmur in the right 2nd intercostal space. Blood cultures obtained resulted positive for Streptococcus Agalactiae, a GBS. Empiric antimicrobial treatment was initiated. On obtaining further history, he was recently treated in the hospital for lower extremity cellulitis and a Trans-Thoracic Echocardiogram (TTE) during the admission performed showed normal ejection fraction, moderate Aortic Regurgitation (AR) but no vegetations on

valves. Further investigating AR, having positive Duke Criteria, a Trans-Esophageal Echocardiogram (TEE) was performed. TEE unveiled a sessile mass attached to the ventricular side of the left coronary cusp of the aortic valve, measuring 15mm with prolapse of the leaflet, severe aortic regurgitation. These findings were most consistent with a large vegetation. A diagnostic angiogram revealed healthy coronary vasculature. Eventually, the patient underwent a successful surgical aortic valve replacement with a 29mm stented porcine bioprosthetic aortic valve. Decision-making Aortic Valve Endocarditis secondary to GBS is uncommonly reported in literature. Immunocompetent patients are not at high risk for invasive GBS. Clinical acumen and vigilance for endocarditis backed by examination and echocardiographic skills is needed. Thus, timely diagnosis & prevention of complications is important. Conclusion The incidence of invasive GBS amongst adults has greatly increased and usually elderly patients are affected, converse to our case reported. GBS bacteremia & endocarditis carry a very high mortality rate. Healthy patients with invasive GBS should undergo a comprehensive workup for potential underlying illness. Combined medical-surgical therapy confers better outcomes.

Internal Medicine

Toiv A, **Andrews TQ**, **Goleniak R**, **Karmally R**, and **Rudraiah L**. POCUS GUIDED CONSERVATIVE MANAGEMENT OF SEPTAL HEMATOMA: A RARE COMPLICATION OF HIS BUNDLE PACING. *J Am Coll Cardiol* 2025; 85(12):3244. Full Text

Background The introduction of His bundle pacing has shown significant electrophysiologic benefits but also comes with its own set of procedural complications. Point-of-care ultrasound (POCUS) is valuable in identifying these structural complications. Case A 75-year-old male with no cardiac history presented for sick sinus syndrome. He underwent successful placement of a permanent dual chamber pacemaker with a para-Hisian lead. One-hour post-procedure, he developed substernal chest pressure with ST elevation in lead III, a new RBBB, and troponin elevation (>20,000 ng/L). A POCUS showed concern for ventricular septal hematoma. Emergent cardiac catheterization ruled out coronary occlusion but revealed contrast extravasation from the left coronary artery into the ventricular septal wall. A follow-up TTE confirmed a 7.74 cm x 3.75 cm anechoic space within the ventricular septum protruding into the right ventricle and causing obstruction. Decision-making The ultrasound findings guided acute management leading to the decision to avoid anti-thrombotic therapy which would have increased the risk of hematoma expansion and progressive right ventricular obstruction. Conclusion This case highlights the role of POCUS and echocardiography in acute chest pain after intervention and provides rapid and effective means to identify structural complications. Additionally, interventricular septal hematoma following His bundle pacer placement is a rare complication that has not yet been described. [Formula presented]

Internal Medicine

Walji M, **Cieslak R**, **Abuzahrieh O**, **Phillips C**, and **Arnautovic J**. PREPARED FOR THE WORST, HOPE FOR THE BEST: COLLABORATIVE MEDICINE AGAINST A MASSIVE PULMONARY EMBOLISM IN A YOUNG WOMAN. *J Am Coll Cardiol* 2025; 85(12):3815. Full Text

Background Approximately 900,000 Americans experience pulmonary embolisms (PEs) each year, with 5-10% of those classified as high-risk or massive PE. The mortality risk for an untreated massive PE is alarmingly high, ranging from 30-60% within hours of onset. Even with prompt treatment, it remains one of the leading causes of cardiovascular death. Treatment requires a multifaceted, coordinated team approach that considers the patient's clinical condition, risk factors, and contraindications (CIs). Case A 24-year-old woman with a past medical history of obesity, oral contraceptive therapy, and back pain presented to a communityhospital with tachycardia, lightheadedness, and shortness of breath after a recent epidural spinal injection (ESI). She was diagnosed with a massive saddle PE and quickly became hemodynamically unstable with hypoxia and hypotension. A STAT echocardiogram demonstrated a severely dilated right ventricle (RV) with evidence of strain and a small, hyperdynamic left ventricle. Decision-making Neurosurgery was consulted due to the relative CI for thrombolysis after an ESI and determined the patient to be at an acceptable risk to proceed with thrombectomy and anticoagulation. She was urgently transported to the catheterization lab. A cardiothoracic surgeon (CTS) was present during the case with cardiopulmonary bypass prepped along with a pharmacist with thrombolysis if needed. Patient underwent a successful transfemoral embolectomy and was closely monitored. She was later initiated on oral anticoagulation. At her two-month follow-up, she was doing well with her

echocardiogram demonstrating an exceptional, complete recovery of her RV. Conclusion This case emphasizes the importance of collaborative multidisciplinary care in a rural-hospital setting, especially in high-risk cases. Obtaining Neurosurgery clearance in an urgent manner helped expedite treatment. Having CTS and their team on standby, as well as a pharmacist with thrombolysis, allowed for alternative treatment options that could be seamlessly initiated. Coordinating care to this degree is uncommon, but vital in optimizing the utilization of all available resources when dealing with a massive PE.

Nephrology
Abdelhai OS, **Mahfouz R**, **Maligireddy A**, **Rangavajla G**, **Andrews TQ**, **Jabri A**, **Memon M**, **McBride P**, **Villablanca PA**, **Jamil D**, and **Aggarwal V**. THE IMPACT OF ATRIAL FIBRILLATION ON IN-HOSPITAL OUTCOMES IN PATIENTS UNDERGOINGLIVER TRANSPLANTATION USING NIS 2016-2021. *J Am Coll Cardiol* 2025; 85(12):94. Full Text

Background The influence of atrial fibrillation (AF) on outcomes in patients undergoing liver transplantation has not been extensively investigated in the literature. This study aims to assess the prevalence of pre-transplant AF and its association with postoperative outcomes in patients undergoing liver transplantation. Methods Data from the National Inpatient Sample (2016-2021) identified liver transplant patients and their AF status. T-tests and chisquare tests compared the data. Outcomes included mortality risk, in-hospital results, and risk factors. Univariate and multivariate logistic regressions calculated odds ratios for comorbidities. Results The study identified 45,460 liver transplant patients, 3,905 of whom had AF. AF patients had a longer LOS (28.6 vs. 19.9 days, $p = 0.001$) and higher hospital charges ($768,558 vs. $624,364, $p < 0.001$). The mortality rate was also greater in AF patients (5.89% vs. 2.72%, $p < 0.001$), and this finding was confirmed by multivariate analysis, which showed an odds ratio of 1.54 ($p < 0.001$) after adjusting for age, gender, race, and comorbidities. Conclusion Our study demonstrated that liver transplant patients with a history of AF in a national cohort experienced higher mortality and morbidity rates. This finding underscores the importance for physicians to prioritize optimizing AF management in this patient group, which could help reduce complications, shorten hospital stays, and lower overall mortality. [Formula presented]

Nephrology
Toiv A, **Andrews TQ**, **Goleniak R**, **Karmally R**, and **Rudraiah L**. POCUS GUIDED CONSERVATIVE MANAGEMENT OF SEPTAL HEMATOMA: A RARE COMPLICATION OF HIS BUNDLE PACING. *J Am Coll Cardiol* 2025; 85(12):3244. Full Text

Background The introduction of His bundle pacing has shown significant electrophysiologic benefits but also comes with its own set of procedural complications. Point-of-care ultrasound (POCUS) is valuable in identifying these structural complications. Case A 75-year-old male with no cardiac history presented for sick sinus syndrome. He underwent successful placement of a permanent dual chamber pacemaker with a para-Hisian lead. One-hour post-procedure, he developed substernal chest pressure with ST elevation in lead III, a new RBBB, and troponin elevation (>20,000 ng/L). A POCUS showed concern for ventricular septal hematoma. Emergent cardiac catheterization ruled out coronary occlusion but revealed contrast extravasation from the left coronary artery into the ventricular septal wall. A follow-up TTE confirmed a 7.74 cm x 3.75 cm anechoic space within the ventricular septum protruding into the right ventricle and causing obstruction. Decision-making The ultrasound findings guided acute management leading to the decision to avoid anti-thrombotic therapy which would have increased the risk of hematoma expansion and progressive right ventricular obstruction. Conclusion This case highlights the role of POCUS and echocardiography in acute chest pain after intervention and provides rapid and effective means to identify structural complications. Additionally, interventricular septal hematoma following His bundle pacer placement is a rare complication that has not yet been described. [Formula presented]

Neurology
Helaly M, **Elfaham A**, **Jamil D**, and **Helaly Z**. THE TRIPLE M - NEUROMUSCULAR TRIAD WITH IMMUNE CHECKPOINT INHIBITORS - MYOCARDITIS, MYOSITIS, AND MYASTHENIA GRAVIS-LIKE SYNDROME WITH NIVOLUMAB-RELATLIMAB. *J Am Coll Cardiol* 2025; 85(12):3791. Full Text

Background Immune checkpoint inhibitors (ICIs) have shown significant effectiveness against advanced malignancies, including malignant melanoma, but they can lead to life-threatening immune-related adverse events (iRAEs), particularly when used in combination therapies. In May 2024, Relatlimab in combination with Nivolumab was approved for unresectable or metastatic melanoma in patients aged 12 and older. Approximately 60 cases of myocarditis, myositis, and myasthenia gravis-like syndrome associated with various ICIs have been reported, however no cases were reported with Relatlimab or its combination with Nivolumab. Case A 74-year-old male with a history of scalp melanoma on Nivolumab and Relatlimab for three weeks, presented to the emergency department with mid-lower back pain, dizziness, double vision, and right eye droop. Exam findings included right eye complete ptosis and left eye incomplete ptosis with 4/5 hip strength. Initial tests indicated elevated troponin levels and CPK. EKG showing new left bundle branch block. He was managed for concern for NSTEMI. He went for left heart catheterization which revealed non-obstructive coronary artery disease and there symptoms and troponins attriubuted to myocarditis. Neurological evaluation suggested autoimmune myasthenia gravis and myositis due to immunotherapy. Decision-making Following a multidisciplinary meeting, the ICI was stopped, patient was immediately started on high-dose steroids and given IVIG for persistent symptoms with improvement. At three month follow up, there was significant improvement in symptoms and troponin and CPK levels almost back to normal. Conclusion Given the potential severity of myocarditis, myositis, and myasthenia gravis-like syndrome, immediate corticosteroid treatment is recommended upon suspicion, without awaiting a confirmed diagnosis.

Pathology and Laboratory Medicine

Abbas O, Sun K, Alhamar M, **Dadhania V**, **Al-Obaidy K**, **Gupta N**, and **Hassan O**. 756 Is the Cumulative Linear Length (CLL) of Gleason Pattern 4 (GP4) in Prostate Biopsies of Grade Group II and III Prostate Cancer a Good Predictor of Radical Prostatectomy (RP) Findings and Outcomes. Our Institutional Experience. *Lab Invest* 2025; 105(3). Full Text

Background: In Prostate biopsies, Gleason Score (GS)/ Grade Group (GG) and tumor size have been used as markers to predict RP findings and clinical outcomes. In this study, we examined the significance of the CLL of GP4 in prostate biopsies of GG II and III prostate cancer to determine if it is a useful marker to predict RP findings and clinical outcomes. Design: The study was approved by our institutional review board (IRB). All consecutive prostate needle biopsies undertaken in 2016 with highest GS of 7 (GG II and III) and subsequent RP at our institution were included. All cases were signed out by specialized urologic pathologists. Detailed pathological findings were collected from our pathology archives. Clinical information was collected from medical records. The CLL of GP4 was calculated by multiplying the percentage of GP4 in each core by the length of the core involved and then adding these to get the CLL of GP4 in each case. Statistical analysis was performed using Mann-Whitney U test and Chi-squared test. Results: Overall, 95 patients were included in our study. Median age was 62. Of the 95 patients, 48/95 (50.5%) had extraprostatic extension (EPE) on RP, 12/95 (12.6%) had seminal vesicle invasion (SVI) on RP, 35/95 (36.8%) had positive resection margins and 11/94 (11.7%) had lymph node metastasis (LNM). On follow-up, 14/95 (14.7%) had disease recurrence (biochemical or local recurrence), while 3/95 (3.2%) distant metastasis. CLL of GP4 was significantly associated with EPE ($p = 0.029$). In addition, using a cutoff of ≥2 mm, GP4 CLL was significantly associated with EPE ($p = 0.037$). There were no significant association between GP4 CLL and SVI, positive resection margins, lymph node metastasis, distant metastasis and disease recurrence. [Formula presented] [Formula presented] Conclusions: Our results show that the CLL of GP4 in prostate biopsies of GG II and III is significantly associated with extraprostatic extension (EPE) on subsequent RP with a cutoff of 2 mm of GP4. These findings may be useful in stratifying patients with small tumor volume for conservative (CLL < 2 mm) versus definitive management (CLL ≥ 2 mm) options. Our overall findings may be used in deciding optimal management options for patients with small foci of GG II and III prostate cancer in needle biopsies.

Pathology and Laboratory Medicine

Agarwal P, **Diaz AL**, **Hassan O**, **Dadhania V**, Alhamar M, **Al-Obaidy K**, and **Gupta N**. 760 Histopathologic Characteristics of Prostatic Adenocarcinoma Showing Microscopic Bladder Neck Invasion on Radical Prostatectomy. *Lab Invest* 2025; 105(3). Full Text

Background: The current AJCC/TNM staging system for prostate cancer classifies microscopic bladder neck invasion (mBNI) or extension of prostatic adenocarcinoma (PCa) into surrounding soft tissue into one broad category/T stage of pT3a/extraprostatic extension (EPE). While the characteristics of tumors with soft tissue extension are well studied, it remains unclear whether tumors exhibit similar aggressive histopathologic features in cases of mBNI. Our study aims to highlight the tumor characteristics associated with mBNI in patients undergoing radical prostatectomy (RP). Design: We reviewed 2,080 cases of RP, from our hospital database from 2012-2016 to assess for presence of microscopic bladder neck invasion (mBNI). 77 patients (3.7%) were identified as having mBNI, with or without extraprostatic extension (EPE) elsewhere in the prostate. The data collected included patient age at the time of surgery, race, tumor location, percent of tumor volume (%TV), Grade Group (GG), margin status, seminal vesicle invasion (SVI) and lymph nodes metastasis (LNM). Results: Of the 77 cases with mBNI, 21 (27.3%) had mBNI without EPE, while 56 (72.7%) had additional EPE elsewhere. mBNI was significantly more common ($p<0.05$) in African American (AA) patients (57.1%) compared to Caucasians (38%) . Tumors in this group were predominantly located anteriorly (81%), compared to the more extensive anterior + posterior location (42%) observed in the mBNI + EPE group. The % TV was significantly lower ($p=0.0026$) in the mBNI group (19%) compared to the mBNI + EPE group (37%). Additionally, tumors in the mBNI group were generally of a lower grade (81% GG2) compared to those in the mBNI + EPE group, where the majority were GG3 or higher (60%). No evidence of SVI or LNM was observed in the mBNI group, whereas the mBNI + EPE group had a 41% incidence of SVI and 35.7% incidence of LNM. Statistical analysis was performed using Chi-square and two-tailed, unpaired t-test. The findings are summarized in the table below: [Formula presented] Conclusions: Tumors with mBNI, in the absence of EPE elsewhere, exhibit markedly different characteristics compared to those with mBNI+ EPE. These tumors are predominantly located anteriorly, with lower %TV and grade (mainly GG2), and lack other adverse features such as SVI or LNM. In contrast, the mBNI + EPE group shows more extensive/ anterior +posterior involvement, larger %TV, and a high incidence of SVI and LNM. We propose that mBNI without EPE be reclassified under a distinct pT stage subcategory, intermediate between organ confined (pT2) and EPE (pT3a).

Pathology and Laboratory Medicine

Agarwal P, **Hassan O**, **Dadhania V**, Alhamar M, **Gupta N**, and **Al-Obaidy K**. 759 Renal Cell Carcinoma with Inconclusive TFE3/TFEB Fluorescent in Situ Hybridization (FISH) Results: A Clinical and Pathological Study. *Lab Invest* 2025; 105(3). Full Text

Background: Renal cell carcinoma (RCC) presents with a wide spectrum of morphologic and immunohistochemical (IHC) findings that are used to characterize various subtypes. Molecular markers not only help identify the unique signatures of these entities but also serve as predictors of therapeutic response. The 2022 WHO classification introduced, for the first time, a subset of RCCs defined by molecular alterations, the accurate diagnosis of which is crucial for guiding therapy, prognostication, and follow-up. TFE3/TFEB-rearranged and amplified RCCs, prime examples of these subtypes, are diagnosed through molecular analysis, with Fluorescent In Situ Hybridization (FISH) being the gold standard. However, a subset of RCCs shows atypical morphological and/or IHC features, with inconclusive TFE3/TFEB FISH results, often in the form of aneuploidy. Thus, we sought to investigate the clinicopathological features of these tumors. Design: We retrospectively reviewed the clinicopathologic features of RCCs analyzed by FISH between 2021 and 2024. Results: Thirty-seven patients who underwent renal biopsy or nephrectomy were included (24 males, 13 females; mean age 62 years, range 30–86), seven of whom had end-stage kidney disease. Tumors were mostly left-sided (22; 60%) and unifocal (35; 95%), with a mean size of 5.6 cm (range 1.3–9.5 cm). Most tumors were WHO/ISUP grade 3 (19; 51%), followed by grade 4 (9; 24%), with pT3a (11; 30%) and pT1a (10; 27%) being the most common pathological stage categories. The presence of clear cells with abundant cytoplasm, clear cells with areas of cytoplasmic eosinophilia, and/or papillary structures by histology, along with positivity for TFE3 and/or melanocytic markers by IHC (Table 1), were the most common findings prompting FISH analysis. Of the 37 tumors submitted for FISH analysis, 6 had TFE3 rearrangement, 14 had chromosome 6 &/or X aneuploidy, and 17 were diploid. Aneuploidy tumors were eventually diagnosed as clear cell renal cell carcinoma (10; with complete membranous CA9 staining), unclassified (2 had oncocytic features and chr. 6 aneuploidy), ESC-RCC (1; with chr. 6 aneuploidy)and adult Wilms tumor (1). [Formula presented] Conclusions: In our findings, most tumors that showed chromosomal aneuploidy were

consistent with clear cell renal cell carcinoma, although they exhibited some immunohistochemical positivity for TFE3.This positivity must be interpreted with caution, especially in the absence of other features of TFE3/TFEB-rearranged renal cell carcinoma, to avoid unnecessary testing.

Pathology and Laboratory Medicine
Ahsan B, Din NU, Safdar F, **Ozcan K**, and Agaimy A. 27 Characterization of Low-Grade Fibromyxoid Sarcoma in Abdominopelvic and Retroperitoneal Locations: A Clinicopathologic Analysis of 11 Cases. *Lab Invest* 2025; 105(3). Full Text

Background: Low-grade fibromyxoid sarcoma (LGFMS) is an uncommon, slow-growing tumor that usually develops in the lower extremities. Its occurrence in the abdominal cavity, pelvis, and retroperitoneum is extremely rare. This study seeks to explore the clinicopathologic features and immunohistochemical and molecular profile of LGFMS in these unusual locations. Design: We analyzed 11 cases of LGFMS found in the abdominopelvic region and retroperitoneum. Clinical data were collected from electronic medical records. Immunohistochemical stains were carried out using antibodies against MUC4, smooth muscle actin (SMA), EMA, S100, CD34 and CD117. Additionally, FUS rearrangement was assessed in a subset of cases. Results: Age ranged from 5 – 75 years (median 40 years), with a female predominance (F:M 10:1). Out of 11 LGFMS cases from several sites: intra-abdominal/abdominal wall (3 cases), retroperitoneum (2 cases), pelvis (2 cases), small intestine mesentery (1 case), duodenum (1 case) transverse colon (1 case) and omentum (1 case). Tumor sizes ranged from 5 to 35 cm (median 10.5). Histologically, the tumors were characterized by spindle cells with mild to moderate atypia, arcade vessels with perivascular sclerosis and myxoid nodules alternating with hyalinized areas. The omental case shows hybrid morphologic features of LGFMS and sclerosing epithelioid fibrosarcoma. All cases tested positive for MUC4, and FUS gene rearrangement was identified in one of two cases examined. All cases were negative for EMA, SMA, S100, CD34 and CD117. Follow-up data were available in 8 patients. 1 patient died of disease. Remaining 7 patients are alive and free of disease (follow-up period 1 – 60 months, median 12 months). Conclusions: LGFMS occurring in these central areas shows clinicopathologic characteristics similar to those found in the extremities. Our study shows a striking female predominance compared to previous studies. Our results also differ from earlier studies in terms of tumor recurrence, as none of our patients experienced a recurrence. However, LGFMS is notorious to recur or metastasize after long periods (over 10 years) and some of our patients may still develop late recurrence/metastasis.

Pathology and Laboratory Medicine
Atto J, and **Allo G**. 310 Patterns of Cervical Cytology Testing in African American Women with Vulvar Dysplasia and Carcinoma. *Lab Invest* 2025; 105(3). Full Text

Background: Disparities in cervical cytology application and vulvar cancer exist. Vulvar cancers reportedly present at a younger age and advanced stage in African American (AA) women in comparison with Caucasians. The rates of cervical cytology utilization and the presence of a prior or a subsequent cervical abnormality in AA patients with vulvar dysplasias have not been studied. Design: This is retrospective analysis of the rates and results of cervical cytology and high-risk human papilloma virus (hr-HPV) testing data in AA women diagnosed with vulvar invasive squamous cell carcinoma (SqCC), vulvar high-grade squamous intraepithelial lesion (HSIL), and differentiated intraepithelial neoplasia (dVIN), diagnosed between November 2013 and September 2024. Descriptive analyses are used. Results: A total of 67 AA patients with SqCC (14, 21%), HSIL (51, 76%) and dVIN (2, 3%) were identified with median age of 57(27-87) years at time of first diagnosis. A prior cervical cytology was done in 53 (79%) patients (10, 67% in SqCC and 41, 80% in HSIL; 2, 100% in dVIN) at a median of 386(7-6092) days prior to the vulvar diagnosis, being normal in 40(60%) and HSIL in 3(5%) of patients. A prior hr-HPV testing was done in 21 (31%) patients (3, 14% in SqCC and 18, 35% in HSIL) being positive in 10 (21%) patients (2 in SqCC; 8 in HSIL). After the first diagnosis of the vulvar disease, cervical cytology was performed in 36(54%) patients (4 in SqCC; 30 in HSIL; 2 in dVIN), the earliest being at a median of 35 (0-1656) days post vulvar diagnosis, being normal in 25(69%) and ASC-H in 3(8%). Follow-up cervical HPV was done in 31(46%) of patients, being positive in 15 patients. [Formula presented] Conclusions: In this limited study of AA patients with vulvar dysplasia/carcinoma, cervical cytology rates are lower than the reported rates for AA or white women, and revealed a significant pathology in only a minority of patients. Similarly, follow-up

cervical cytology and HPV testing was performed at a lower rate, highlighting potential disparity in cancer screening among AA patients.

Pathology and Laboratory Medicine

Binte Tahir N, Venkataraman G, Rojek A, Symes E, Kaur A, Tjota M, Fitzpatrick C, Arber D, Wang P, Lager A, Perry A, Bell R, Chang H, Zhou Q, Menon M, Patel J, Patel A, Tariq H, Zhang J, Sojitra P, Nawas M, Patel A, DuVall A, Patil E, Badar T, Velmurugan S, Hasan F, and **Ghosh S**. 1295 Prognostic Impact of Chromosome 7 Losses in High-Grade TP53 Mutated Myeloid Neoplasms. *Lab Invest* 2025; 105(3). Full Text

Background: TP53 mutation (TP53MUT) and chromosome 7 loss (-7/7q) are both independently considered as adverse prognostic factors in high-grade (HG) myeloid neoplasms (MN). Whether the co-occurrence of -7/7q further worsens the poor prognosis of TP53MUT is unclear. To answer this, we evaluated the differential impact of -7/7q in HG TP53MUT MN. Design: We identified 322 patients with TP53MUT MN carrying ≥1 TP53MUT at a VAF ≥3% diagnosed between 2014-2024 across 10 centers with blasts ≥10% at diagnosis. Baseline clinical, pathological, cytogenetic and somatic information was extracted while stratifying patients by -7/7q status. The primary endpoint was to compare 24-month overall survival (OS24). Additional end-points included complete response to first-line (CR1) therapy per ELN 2022 guidelines (Table 1 footnote). Descriptive and outcome analyses were conducted in Stata 18 using flexible parametric (FP) and non-parametric survival methods. Results: The median age at diagnosis was 68.4 years. There was no difference in baseline characteristics stratified by -7/7q status (see Table 1). Patients with -7/7q were marginally more likely to harbor complex karyotype (P = .09) with significantly greater proportion harboring -17/17p (46.2% vs. 33.8%; P = .031) and TP53 VAF>25% (85.6% vs. 76.4%; P = .042) compared to those without -7/7q. The median duration of follow up (from diagnosis of TP53MUT MN to study exit) was 6.2 months (range: 0.0–72.8 months) with 77.0% receiving frontline non-intensive therapies, mostly HMA-based. First-line response was evaluable in 251 patients with 28.7% achieving CR, 24.7% had partial response, and 46.6% had non-response/stable-progressive disease. -7/7q was not associated with inferior frontline response (P = .35) in the entire cohort as well as in the intensively-treated subgroup (P = .92). Significantly greater proportions of those lacking -7/7q went on to receive alloSCT (20.7% vs. 11.1%; P = .023). In the entire cohort OS24 analysis, -7/7q was associated with inferior overall survival (HR = 1.5 [1.2–2.0]; Pfpm = .002; N = 298). In separate analysis by blast count and therapies, the adverse impact was restricted only to those subgroups with either high blast count or intensive therapy (See figure 1). [Formula presented] [Formula presented] Conclusions: Presence of -7/7q adversely impacts the prognosis of TP53MUT MN, an effect which is accentuated in patients receiving intensive chemotherapy and ≥20% blast count at diagnosis, supporting its prognostic utility in this context.

Pathology and Laboratory Medicine

Dhillon J, Lobo A, Akgul M, Acosta A, Chumbalkar V, Vosoughi A, Xu H, Al-Ahmadie H, **Al-Obaidy K**, Amin M, Aron M, Arora S, Ayyanar P, Bakshi N, Balzer B, Bardia A, Baweja P, Chakrabarti I, Cheng L, Cima L, Colecchia M, Collins K, Compérat E, Das D, Dixit M, Downes M, Elhence P, Epstein J, Galea L, Gandhi J, Giannico G, Gordetsky J, Gupta G, Gupta N, Haider A, Hansel D, Hartmann A, Ho-Yen C, Iczkowski K, Jain E, Jain R, Jha S, Kao CSS, Kaushal S, van Leenders G, Kamalesh l, Lopez J, Lopez-Beltran A, Luthringer D, Maclean F, Magi-Galluzzi C, Malik V, Manini C, Martignoni G, Mehta B, Menon S, Misra S, Mohanty S, Montironi R, Nayak S, Nguyen J, Ntala C, Oliveira P, Osunkoya A, Patil S, Picken M, Prachi D, Pradhan D, Prendeville S, Queipo F, Quiroga-Garza G, Rao BV, Rao P, Raspollini MR, Sabnis S, Sancheti S, Sanchez DF, Sarungbam J, Satarkar R, Satturwar S, Sayyed NK, Shah R, Sharma I, Sharma N, Sharma S, Sirohi D, Sobti P, Soni S, Sreeram S, Sundaram S, Tamboli P, Tanveer N, Tickoo S, Tiwari A, Tomar R, Tretiakova M, Trpkov K, Tsuzuki T, Warrick J, Zhou M, Sangoi A, Williamson S, and Mohanty S. 790 Current Reporting Trends, Practices, and Resource Utilization in Penile Cancer: A Survey among Genitourinary Pathologists. *Lab Invest* 2025; 105(3). Full Text

Background: Efforts have been made to standardize the reporting and terminology of penile squamous lesions. This applies to grading, utilization, and interpretation of immunohistochemical stains (IHCs) and testing for HPV. Design: To understand the current trends, practices and resource utilization we conducted an online survey asking 30 questions related to practice. Results: Survey was sent to 143

uropathologists world-wide of which 117 (82%) responded. The survey was fairly distributed in terms years of experience. Responses were received from across the world (Figure 1). More than 50% respondents see >20 cases/year. Only 22% of pathologists submit the entire partial penectomies for microscopic examination. 50% of pathologists make a diagnosis of condyloma acuminatum (CA) with dysplasia whereas 33% never make this diagnosis. Penile intraepithelial neoplasia (PeIN) terminology is used by majority (83%). PeIN is usually subtyped by majority (85%) and never by 11%. No consensus was reached for grading HPV-associated penile carcinoma (PC) although 63% would grade basaloid type as poorly differentiated (PD). Some senior pathologists do not grade HPV-associated PC. No consensus was reached on the minimum % of PD foci required in a well to moderately differentiated PC to grade it as PD (Figure 1). About 25% pathologists either do not or rarely use IHCs to diagnose or to subclassify PeIN. HPV testing in PCa is not routinely done by all (Figure 2). P16 IHC is the most common method used to test for HPV. HPV RNA ISH is done by 37%. 63% agreed that HPV-associated PC has better prognosis than HPV-independent. PDL-1 testing is done only when requested by clinicians and ≥1 CPS is used by 51% to call it positive and 5% report the value without interpreting it further. 54% agreed to subclassify PD 1 as low positive (1-19) and high positive (≥20). There was no consensus on cut off criteria to report p53 IHC positive (Figure 2). [Formula presented] [Formula presented] Conclusions: The survey has consensus and differences as follows: 1. PeIN terminology is used by most uropathologists. 2. p16 IHC is the most common method used to subtype PC as HPV-associated. 3. Need criteria for dysplasia in CA. 4. Need guidelines for a uniform grading system for subtypes of HPV-associated PC. 5. Need guidelines on minimum % of PD foci required in a well to moderately differentiated PC to grade it as PD. 6. Need criteria for reporting p53 IHC positive in PC. 7. There is limited experience among uropathologists with PDL-1 reporting.

Pathology and Laboratory Medicine

Diaz AL, **Agarwal P**, **Hassan O**, **Al-Obaidy K**, Alhamar M, **Dadhania V**, and **Gupta N**. 842 Is Grading of Small Volume of High Grade Prostatic Adenocarcinoma on Needle Biopsy Accurate? Correlation with Radical Prostatectomy Findings. *Lab Invest* 2025; 105(3). Full Text

Background: Grading of prostatic adenocarcinoma (PCa) is recommended on needle biopsies (Nbx) for tumors of any given volume. Highest tumor grade on needle core set plays a critical role in subsequent patient management. High grade PCa is often associated with high volume disease and involves multiple biopsy cores. In such scenarios, correlation with final radical prostatectomy (RP) score is excellent. Our aim in this study was to determine the correlation of grades assigned to high grade PCa when present in low volumes on Nbx with the final grade and other adverse parameters on RP. Design: All consecutive NBx from 2012 to 2019 were reviewed for patients showing 1 or 2 positive cores in the biopsy set with Grade Group (GG) 3 and higher grades. Only cases with subsequent RP were included. 55 cases met our inclusion criteria. Cases were divided into four groups: 1 positive (+) core with < 10% tumor length (TL)involvement ; 1 + core with 10%-50% TL; 1 + core with > 50% TL; 2 + positive cores with any TL. Tumor grade, stage, margin status, presence or absence of lymphovascular invasion (LVI) and lymph node metastasis (LNM) were recorded from RP. Results: Needle biopsy and RP findings are summarized in the Table below. 55 cases of high grade PCa were identified, 11 cases were identified in the smallest tumor volume group (1+ core < 10%). These cases showed least incidence (27%) of extraprostatic extension (EPE) compared to groups with higher tumor volumes (43-64%). The likelihood of downgrade in GG was highest amongst this group (64%) compared to 33% in cases with 1 + core with 10 - 50% TL or 2 + cores and 18% downgrade in cases with 1+ core with > 50% TL. The correlation of biopsy grade with Final RP (No change in final grade) improved as the sampled %TL increased in the core ranging from 48-55% in these groups. No significant correlation was found between these groups and SVI, LVI, and LNM. Margin positivity did not show an increasing trend as the Nbx % TL increased with 18-19% M+ in up to 50% TL involvement vs 33-45% M+ when >50% or 2 cores were involved. [Formula presented] Conclusions: Grading performed on small foci of PCa especially < 10% TL does not correlate with the final RP grade with significant downgrade rate. This data is also supported by lower incidence of EPE and margin positivity in these cases compared to those seen in similar grade tumors with higher volumes on single cores. In such scenarios, we suggest that pathologists add a disclaimer in the report to alert the urologist regarding this lack of correlation and high likelihood of downgrade of the final grade at RP.

Pathology and Laboratory Medicine

Gao H, Ren D, Giannico G, Khani F, Galea L, **Al-Obaidy K**, Falzarano S, Wobker S, Barry-Holson K, Chan E, McHenry A, and Sangoi A. 801 Do Urinary Bladder Smooth Muscle Neoplasms Show Morphologic and Immunophenotypic Features of Their Uterine Fumarate Hydratase-Deficient Counterparts? *Lab Invest* 2025; 105(3). Full Text

Background: Leiomyomas of the urinary bladder constitute <1% of all bladder tumors. While the morphologic and immunophenotypic features of smooth muscle neoplasms of the uterus and skin have been well-described in relationship to Fumarate Hydratase (FH) deficiency (FHD) and hereditary leiomyomatosis and renal cell cancer (HLRCC), a potential association of urinary bladder smooth muscle tumors with FHD/HLRCC has not been previously investigated. Design: Given an index urinary bladder transurethral resection (TURBT) leiomyoma which showed some of the purported morphologic features seen in uterine HLRCC-associated leiomyomas, herein we performed a multi-institutional search for bladder leiomyomas to further evaluate any potential HLRCC association. Slides from all cases were re-reviewed for the presence of the following well-described HLRCC-associated cytomorphologic features: macronucleoli (“cherry red”) surrounded by halo, isolated nuclear pleomorphism (“symplastic” nuclei), cytoplasmic eosinophilic globules, staghorn vasculature, alveolar-pattern edema, and chain-like distribution of smooth muscle fibers. Tumors with available material underwent whole-slide staining for FH and 2SC immunohistochemistry (IHC). Results: A total of 32 leiomyomas from were collected from 7 institutions, each from a unique patient (20 males, 12 females) aged 30-85 years (mean age: 54.6 years). Figure 1 highlights key clinicopathologic findings. Among the 32 study cases, cytoplasmic eosinophilic globules were seen most frequently (25%), followed by “cherry-red” macronucleoli with halos (19%), staghorn vasculature (13%), “symplastic” nuclei (9%), and alveolar-pattern edema (6%); no cases exhibited chain-like muscle fibers. Of the stained tumors, all (100%) showed retained FH expression and negative 2SC immunoreactivity (Figure 2). [Formula presented] [Formula presented] Conclusions: Although a subset of bladder leiomyomas show overlapping morphologic features with uterine FHD/HLRCC-associated leiomyomas, they do not appear to harbor FHD or an association with HLRCC. In the absence of a gynecologic origin for a bladder leiomyoma, despite a close anatomic location and some shared histology, it may not be necessary to pursue IHC for FHD status/HLRCC screening. Instead a focus on lineage confirmation and an evaluation for malignancy should be prioritized.

Pathology and Laboratory Medicine

Kaushal S, Dhillon J, Malik V, Akgul M, Acosta A, Lobo A, Smith S, Aron M, **Al-Obaidy K**, Williamson S, Sangoi A, Cheng L, Amin M, Lotan T, and Mohanty S. 821 Post-therapeutic Squamous Cell Transformation of Metastatic Prostatic Adenocarcinoma with Paired Molecular Profiling: A Multi-Institutional Cohort of an Under-reported Entity. *Lab Invest* 2025; 105(3). Full Text

Background: Transformation of primary prostatic adenocarcinoma (PCa) to squamous cell carcinoma (SCC) after initial treatment, at the metastatic site, is extremely rare and results in rapid treatment-refractory disease progression and death. Unlike neuroendocrine transdifferentiation of a PCa, scant literature is available on this entity with near absence of comprehensive molecular studies. Design: Patients with SCC transformation at the metastatic site with a primary diagnosis of PCa were collected in an international cohort. The patient's age, PSA levels, tumor's characteristics at the primary and metastatic site and additional clinicopathological details were recorded. Targeted NGS (Illumina® HiSeq 4000) platform was used for DNA and RNA NGS. Single nucleotide variants/substitutions, indels, and copy number variations in 426 cancer-associated genes, and gene rearrangements, microsatellite instability, and tumor mutational burden (TMB) were assessed. The tumors were sequenced to high uniform depth (targeting 500X median coverage with 99% coverage 100X. Somatic genomic alterations were observed in all tumors (both treatment-naive PCa specimen and SCC specimens). Results: Nine patients were collated. The mean age at the primary diagnosis was 66.5 years, with the serum PSA level ranging from 59 to1450 ng/ml. The patients presented with either primary or metastatic disease at the time of initial presentation and received hormonal/androgen-derivation, chemo, and/or radiation therapy. Mean serum PSA at the time of SCC transformation was 0.8 ng/ml (range = 0.04 to 2.13 ng/ml). Duration of SCC transformation ranged from 0.9 to 7 years. Table 1 summarizes the clinicopathologic and molecular characteristics of the cohort. Figure 2 shows a heatmap depicting molecular profiles of paired PCa and SCC samples of the cohort. [Formula presented] [Formula presented] [Formula presented]

Conclusions: 1. Post-treatment SCC transformation in a metastatic PCa is rare and portends an aggressive clinical course and treatment resistance. 2. An erroneous misdiagnosis of a secondary SCC can be made, particularly when the clinical data is unavailable. 3. We observed similar mutations in the PCa and subsequent SCC components along with some additional mutational hits involving CCND3, TP53, EGFR, MAP2K7, and PIK3CA genes, which might trigger SCC transformation and be the potential therapeutic targets. 4. Interestingly, presence of TMPRSS2::ERG rearrangement in the SCC component, supports a transformation from the pre-existing adenocarcinoma

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Kisha S, **Tawil T**, **Azordegan N**, **Yuan L**, **Gaba A**, **Schultz D**, and **Zhang Z**. 354 HPV Cotesting of Unsatisfactory ThinPrep Pap Tests: A Study on Assurance of Negative HPV Results and Compliance with American Society of Colposcopy and Cervical Pathology (ASCCP) Management Guidelines. *Lab Invest* 2025; 105(3). Full Text

Background: The 2019 guidelines from ASCCP continue to recommend that individuals with an unsatisfactory Pap test (UPT) and negative HPV cotesting undergo repeat age-based screening within 2 to 4 months. This recommendation is based on the rationale that a negative HPV result in the context of a UPT may indicate an inadequate sample rather than a true negative result. Despite this, only a few studies have examined adherence to these recommended guidelines. Some research suggests that women with UPT and negative HPV may be safely called back for screening at intervals longer than 4 months. This study aims to assess the reliability of negative HPV results in cases of UPT and evaluate our institution's adherence to the ASCCP guidelines. Design: We conducted a retrospective study, selecting all unsatisfactory ThinPrep Pap cases from January 2021 to December 2023. We gathered data on the causes of UPTs, HPV results, and follow-up information for the available cases. The criteria for determining sample adequacy were based on the 2014 Bethesda System. Results: Out of a total of 169,896 Pap tests, 480 UPTs were identified, with an age range of 20 to 83 years. The overall unsatisfactory rate was 0.3%. Among these, 423 cases (88.1%) were attributed to paucicellularity: 170 of these (40.2%) were related to bloody specimens, 72 (17.0%) resulted from inappropriate lubricant usage, and 181 (42.8%) did not show recognizable causes. Additionally, 57 cases (11.9%) were caused by excessive inflammation. Of the 480 cases, 271 had available HPV results: 239 (88.2%) were HPV negative, while 32 (11.8%) were HPV positive. Follow-up data indicated that 205 of the 480 cases were subsequently repeated, with intervals ranging from two weeks to 11 months; 165 cases (34.4%) were repeated within 4 months. Among the repeated samples, 115 cases underwent HPV retesting, and unexpectedly, 6 of these cases (5.2%) converted from initial HPV negative to positive. The time intervals for these conversions ranged from 4 to 11 months. Conclusions: This study provided institutional follow-up data on HPV cotesting for unsatisfactory ThinPrep Pap tests. Compliance with ASCCP follow-up recommendations was low (34.4%), and a small percentage (5.2%) of negative HPV results converted to positive upon retesting. These conversions may stem from initial sampling issues or new infections. It is important that women with negative HPV results in the context of UPTs adhere to ASCCP management guidelines for ongoing monitoring.

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Lobo A, Sangoi A, **Al-Obaidy K**, Akgul M, Acosta A, Kandukuri S, Jha S, Kaushal S, Satturwar S, Osunkoya A, Parwani A, Dhillon J, Williamson S, Shah R, Cheng L, and Mohanty S. 843 Expanding Horizons: A Deeper Dive into the Morphologic and Genomic Landscape of ALK-Rearranged Renal Cell Carcinomas. *Lab Invest* 2025; 105(3). Full Text

Background: Heterogeneous morphology and rarity of ALK-rearranged renal cell carcinoma (ALK-RCC) hinders their diagnosis solely based on histopathology leading to classifying these tumors into the RCC,NOS category. ALK oncogene rearrangement as seen in this neoplasm is a therapeutic target and the patients potentially benefit from ALK-inhibitors. Therefore, we attempt to elucidate the clinicopathologic characteristics of a cohort of ALK-RCC through an international collaboration. Design: Sixteen cases were collated to comprehend the overarching clinical, gross, microscopic, immunohistochemical (IHC), molecular features (DNA and RNA sequencing, FISH, microsatellite instability and tumor mutational burden) and follow-up data. Results: Clinical presentation: There were 9 males and 7 females, tumor size ranging from 2 to 12.2cm (mean=7.1cm). (Table 1) Histopathologic

features: All tumors were solid, tan-white with focal cystic changes and gelatinous appearance. Necrosis was seen in 6 tumors. Heterogeneous pattern was observed; mucinous tubular spindle (7),papillary (5), tubulocystic (2), pleomorphic epithelioid cells (6), sarcomatoid (2), rhabdoid (4) and intranuclear pseudoinclusions (6). (Figures 1 and 2) Detailed histopathologic features, IHC, molecular profile, treatment and follow-up are given in Table 1 and Figures 1 and 2. [Formula presented] [Formula presented] [Formula presented] Conclusions: 1. Our study further expands the clinicopathologic, morphologic and molecular genetic spectrum of ALK-RCC. 2. This is the largest series till date, enrolling 16 tumors through a multi-institutional collaboration. 3. This series adds to the growing body of literature on this distinct entity, supporting and expanding upon the observations by previous studies. 4. ALK-RCC can be morphologically heterogeneous and mimic other well established entities (mucinous tubular and spindle cell RCC, tubulocystic RCC, papillary RCC, clear cell papillary tumor, BAP1 deficient RCC, TFE3-rearranged RCC, and others) posing a misdiagnosis if appropriate IHC and/or molecular studies are not performed. 5. Accurate diagnosis is of clinical significance as patients with this neoplasm may potentially benefit from ALK-inhibitors, particularly in a metastatic setting. 6. As TFE3 immunoreactivity is not uncommon in ALK-RCC, a molecular assay of ALK gene rearrangements either by FISH or NGS is mandatory for a definite diagnosis.

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Lobo A, Tiwari A, Agaimy A, Akgul M, Sangoi A, Kandukuri S, Acosta A, **Al-Obaidy K**, Jha S, Kaushal S, Satturwar S, Dhillon J, Osunkoya A, Williamson S, Pradhan D, Shah R, Parwani A, Cheng L, and Mohanty S. 844 Perivascular Epithelioid Cell Tumors of the Urinary Bladder: A Clinicopathologic and Comprehensive Molecular Analysis including Microsatellite Instability Status and Tumor Mutational Burden in a Contemporary Cohort of 21 cases. *Lab Invest* 2025; 105(3). Full Text

Background: Perivascular epithelioid cell tumor (PEComa) of the urinary bladder is a rare neoplasm showing distinct melanocytic and smooth muscle differentiation. PEComas have been described arising in most organ systems; however, only a small number of bladder PEComas have been reported. Although majority of them behave in an indolent fashion, a small subset may develop metastasis and cause death. Herein, we sought to describe the clinicopathologic and molecular characteristics in a cohort of 21 such tumors. Design: Twenty-one urinary bladder PEComa cases were collated. Clinicopathologic, IHC, molecular and outcome data were analysed. DNA and RNA NGS, FISH, microsatellite instability (MSI) and tumor mutational burden (TMB) was assessed in 17 tumors. Results: There were 21 patients (13 females, 8 males), with age ranging from 17-81 years (mean=47.6 years). Clinical follow-up data was available for 17 patients, follow-up period range 5-60 months (mean=19.4 months). Figures 1 and 2 summarize the microscopic, IHC and NGS results and Table 1 summarize the clinicopathologic features and matches it with the outcome data. TRIM63 ISH showed high sensitivity (89%) with poor specificity (11%) for TFE3 rearrangements by NGS. 17/17 PEComas showed mutations by NGS which are as follows: PSF::TFE3 fusion (7/17, 41%) and TSC1/2 missense and nonsense mutations (6/17, 35%), MTOR (3/17, 18%), and co-mutations of TSC/MTOR (2/17,12%). Additionally, co-mutations involving p53 were noted in 2 tumors (1 with PSF::TFE3/p53; 1 with MTOR/p53). The morphologic features significantly associated with metastatic disease included >2 mitoses/high-power field (n=7,88%; p=0.01), atypical mitoses (n=7,88%; p=0.01), necrosis (n=7,88%; p=0.01), ≥70% atypical epithelial cells (n=6, 75%; p=0.05) and vascular involvement (n=6, 75%; p=0.05). Four TFE3-rearranged tumors developed metastasis (OR=4.67), while 6 TSC/MTOR mutated tumors had metastatic disease (OR=0.19). [Formula presented] [Formula presented] [Formula presented] Conclusions: 1. The metastatic potential of bladder PEComas has a significant association with morphologic parameters such as ≥70% atypical epithelial cells, >2 mitoses/10 hpf, atypical mitoses, necrosis and vascular invasion. 2. TFE3-rearranged tumors have a slightly higher propensity towards an aggressive outcome in comparison to TSC/MTOR altered tumors. 3. Furthermore, as there is much genetic diversity within these tumors in the form of TSC/MTOR and TFE3-rearranged alterations, assessment of the molecular signature is essential for therapy selection and prognostication.

Pathology and Laboratory Medicine

Ozcan GG, Alhamar M, **Dadhania V**, **Hassan O**, **Gupta N**, and **Al-Obaidy K**. 808 Histological Sampling Protocols for Transurethral Resection of Prostate Specimens. *Lab Invest* 2025; 105(3). Full Text

Background: Lower urinary tract symptoms (LUTS) due to bladder outlet obstruction associated with benign prostatic hyperplasia (BPH) are among the most common conditions in men, and their prevalence increases with age. Transurethral resection of the prostate (TURP) has been the gold standard for the surgical treatment of LUTS. As an alternative to TURP, other treatment technologies have been introduced, such as holmium laser enucleation of the prostate (HoLEP). Incidental prostate carcinoma (PCA) can be seen in up to 10% of TURP specimens, with the majority being Grade Group (GG) 1. Current guidelines recommend submitting the entire specimen for cases involving less than 12 grams (six blocks), with an additional 2 grams (one block) for each additional 5 grams beyond the initial 12 grams. Oversampling can lead to increased workload for both the laboratory and the pathologist. Design: From our institutional database, patients treated with endoscopic surgery (TURP, HoLEP) for LUTS were retrospectively selected between 2015 and 2022. Patients with histologically confirmed prostate cancer were included. All H&E and IHC slides were reviewed. Results: A total of 2,508 patients were included, of whom 150 (6%) were diagnosed with PCA on TURP (n=111) or HoLEP (n=39). The mean age was 73 (49-97 years). The mean resected tissue volume was 27.1 grams, the mean initial submitted block count was 12 (1-40). GG1 was the most common tumor type (n=72, 48%), followed by GG2 (n=32, 21.4%), GG3 (n=8, 5.3%), GG4 (n=2, 1.3%), and GG5 (n=34, 22.7%). Two patients had a treatment history, grading wasn`t performed. 72 patients with GG1, 53/72 (74%) and 66/72 (92%) were detected in the first 5 and first 10 blocks, respectively. All patients with GG2 and GG3 were detected in the first 5 blocks (40/40, 100%). Finally, of the 36 patients with GG4 and GG5, 35 (97%) were detected in the first 5 blocks, the remaining one identified in the 7th cassette, which had very low tumor content (5%). Thus, all GG4 and GG5 patients were detected in the first 10 blocks. Two patients with treatment effects were detected in the first 5 blocks (2/2, 100%). [Formula presented] Conclusions: In our cohort, PCA detected in TURP/HoLEP specimens was mainly of the GG1 category, the vast majority of which could be detected in the first 10 blocks. Similarly, all clinically significant PCA (GG2 and higher) could be detected in fewer cassettes than the current protocol requires. Therefore, in our opinion, current sampling protocols for TURP/HoLEP specimens need to be reevaluated.

Pathology and Laboratory Medicine

Ozcan GG, **Gagnon L**, **Azordegan N**, **Zhang Z**, and **Yuan L**. 335 Prevalence of Atypia of Undetermined Significance (AUS) in Thyroid Fine Needle Aspirations Before and After Implementation of the 2023 Bethesda System for Reporting Thyroid Cytopathology. *Lab Invest* 2025; 105(3). Full Text

Background: The 2023 Bethesda System for Reporting Thyroid Cytopathology (TBSRTC) now subclassifies atypia of undetermined significance (AUS) into nuclear atypia (AUS-nuclear) and non-nuclear (AUS-other) subcategories. As a heterogeneous category of TBSRTC, the AUS rate varies greatly among different laboratories (from 1% to over 20%) and has at best only fair reproducibility. The recommendation about the upper limit of the AUS diagnostic category to no more than 10% of thyroid FNAs in the 2017 edition of TBSRTC continues unchanged. A suggestion about AUS:malignant ratio ≤ 3.0 as a laboratory quality control was included in the 2023 edition. The new subclassification of AUS into nuclear and other is designed to improve reproducibility and to better reflect the risk of malignancy and subsequent management. Design: At our institution, the 2023 TBSRTC was implemented in September 2023. A retrospective review of thyroid FNAs from our center from January 2020 to August 2024 was performed. Results were stratified by year and an annual rate and overall rate of AUS over a four-year period before the implementation of the 2023 TBSRTC and one-year period after the implementation were calculated. The inclusion criteria was any diagnosis of atypical, AUS, or follicular lesions of undetermined significance (FLUS) before September 2023, and AUS-nuclear, AUS-other afterwards. Results: Among 4662 cases of thyroid FNA cytology performed in our institution from January 2020 to August 2023, 755 cases were diagnosed as atypical. The overall rate of AUS in this four-year period was 16.2%. The annual rate of AUS had increased from 10.3% to 24.7%. After the implementation of 2023 TBSRTC in September 2023 (one-year period 9/2023-8/2024), the annual rate of AUS has decreased to 19.7%. The AUS/malignant (A/M) ratio was 4.74 in 2023 before the implementation of 2023 TBSRTC; the A/M ratio decreased to 2.98 in the one-year period afterwards. [Formula presented] Conclusions: In the present study AUS rate is 19.7% after the implementation of the 2023 TBSRTC. It is higher than the recommended upper limit, but the 2023 TBSRTC appeared helpful in reducing AUS rate in our institution. AUS/malignant ratio is a useful quality measure and our A/M ratio of 2.98 was within the recommended

range of ≤ 3. Reporting AUS results and AUS/malignant ratio as we have done could potentially establish the acceptable range of AUS within an institution and limit AUS interpretations.

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Ozcan GG, **Vitale A**, **Tawil T**, **Gagnon L**, **Zhang Z**, and **Yuan L**. 336 Endobronchial Ultrasound-Guided Transbronchial Needle Aspiration Without Rapid On-site Evaluation Performed: A Retrospective Study with Cytologic-Histologic Correlation Comparing Main Campus Versus Regional Hospitals. *Lab Invest* 2025; 105(3). Full Text

Background: Endobronchial ultrasound transbronchial needle aspiration (EBUS-TBNA) is a safe and minimally invasive procedure for evaluating lung nodules and lymph nodes. The reported sensitivity and specificity of EBUS-TBNA with rapid on-site evaluation (ROSE) are variable at 85-90% and 90-95%, respectively. We employed a method for performing EBUS without ROSE at our institution with staffing and cost benefit. We're a tertiary care center with a main campus and peripheral sites. The aim of this study is to determine the diagnostic value of our EBUS-TBNA without ROSE method and access the effectiveness of this method at the peripheral sites. Design: Cells were collected by pulmonologists; all passes were put in Saccomanno preserve and sent to Cytology lab. The cells were then drained through tissue bag to collect tissue fragments for making cell blocks. The liquid portion was used for making ThinPrep slide. All consecutive EBUS cases, including FNA of the lung nodules, hilar/mediastinal masses, and lymph nodes between 5/2022-4/2023 at our institution (main campus and peripheral sites) were included. Pathological findings and clinical information were collected from pathology archives and medical records, respectively. Results: In the study period, 1805 EBUS cases from 676 patients were identified at main campus site, including 364 lung/ mediastinal masses and 1441 lymph nodes. Cytology diagnosis were non-diagnostic (ND) in 203 (11%), benign (1124, 62%), atypical (65, 3.6%), suspicious (12, 0.7%), and positive (399, 22%). When histology was taken as the gold standard, the sensitivity and specificity of our method (EBUS without ROSE) were 90.8% and 97%, respectively. Molecular and PD-L1 were ordered on 72 and 71 positive cyto cases, respectively, all adequate. At peripheral sites, 210 EBUS cases from 96 patients were identified including 70 lung/ hilar masses and 140 lymph nodes. Cytology diagnosis were ND in 47 (22%), benign (99, 47%), atypical (8, 3.8%), and positive (56, 27%). The sensitivity and specificity for EBUS-TBNA at our peripheral sites were 86.4% and 97.9%, respectively. Molecular testing were ordered on 4 positive cyto cases (3 adequate); PDL-1 were ordered on 5 positive cyto cases (all adequate). [Formula presented] Conclusions: EBUS without ROSE method at our institution provided sufficient adequacy for ancillary testing and rendering diagnosis, with excellent sensitivity and specificity even at the peripheral sites. This method also provided excellent tumor cellularity for molecular and PDL-1 testing.

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Ozcan K, **Theisen B**, **Khan G**, **Chang Q**, and **Ahsan B**. 1613 Adenosquamous Carcinoma of the Pancreas: A Clinicopathologic Analysis of 33 Cases. *Lab Invest* 2025; 105(3). Full Text

Background: Adenosquamous carcinoma (ASC) of the pancreas is a rare subtype of cancer. Clinicopathologic and molecular data on this entity remains limited. Here we identify and describe clinical and molecular features on a population of ASC. Design: We identified 33 cases of ASC and performed a detailed analysis of clinicopathologic features and molecular results. ASC cases were compared with a cohort of 70 consecutive conventional pancreatic ductal adenocarcinoma (PDAC) cases. Next Generation Sequencing assay (NGS) was performed on a subset of ASC. Results: Clinicopathologic features of pancreatic ASC and PDAC are summarized in Table. There were slightly more male patients than female patients diagnosed with ASC. Compared to PDAC, ASC patients were older (median: 74, range 54-81, p<.0005), with larger tumor size (median: 4.3 cm, range 1-8.2, p<.00001), higher T stage (T3 or T4: 63% vs 23%, p<.001), and higher clinical stage (Stage III or IV: 60% vs 28.6%, p<.0003). However, ASC did not show higher rate of nodal metastases when compared with PDAC (60.9% vs 54.4%). ASC of the pancreas was more frequently located in the body/tail (51.6% vs 18.6%, p<.01). Radiologic findings of all available patients showed hypodense lesions, with 21% significant for central necrosis. Squamous differentiation was detected on fine needle aspiration for 12 patients and reported as "(adeno)carcinoma with squamous differentiation". In all cases, CK 5/6, p40 or p63 were used to highlight the squamous component. Squamous cell carcinoma was the predominant component in one case. NGS data were

available for 13 cases. Most commonly encountered mutations included KRAS (69.2%), TP53 (53.9%), CDKN2A (30.8%), SMAD4 (23.1%), KMT (23.1%) and PIK3CA (15.4%). On follow up, ASC had significantly worse prognosis when compared to PDAC. 27 patients died of disease with a median survival of 6 months (range: 0-39). Only 6 patients were alive with disease with a median follow up of 15.5 months (range: 1--28 months)(Figure 1). Clinicopathologic features of adenosquamous carcinomas of the pancreas and pancreatic ductal adenocarcinomas [Formula presented] [Formula presented] Conclusions: Adenosquamous carcinoma of the pancreas is an aggressive malignancy with an even worse prognosis than PDAC. It presents as a larger mass, in older patients with higher T and clinical stages and has a higher propensity for body/tail. Although an arbitrary 30% cut-off is typically used to diagnose ASC, it is also known that presence of any squamous component is associated with a worse prognosis which aligns with our findings that ASC group diagnosed on FNA having similar behavior with the rest of ASC cohort.

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Ozcan K, **Xu Z**, **Bava EP**, **Chang Q**, **Lai Z**, **Theisen B**, and **Ahsan B**. 1612 Interobserver Agreement in Pathologic Assessment of Pancreatic Ductal Adenocarcinoma Post-Neoadjuvant Chemotherapy: A Comparative Study of Scoring Systems and Stromal Changes. *Lab Invest* 2025; 105(3). Full Text

Background: The majority of pancreatic ductal adenocarcinoma (PDAC) are diagnosed at an advanced stage, and neoadjuvant chemotherapy (NACT) followed by surgery is the preferred treatment. Assessing the pathologic status of PDAC after NACT presents one of the most challenging tasks for pathologists due to issues including how to process specimens, evaluate and score tumor response, and achieve consistency and reproducibility. Design: Forty-five cases were included in our study. H&E slides were reviewed by 4 pathologists who were asked to evaluate the following parameters: tumor regression score (TRS) using College of American Pathologists (CAP) and Becker scoring systems as well as stromal changes such as fibrosis, exocrine atrophy and inflammatory response. All stromal changes were categorized as: none, mild, moderate and severe. All pathologists were blinded to original interpretation and interpretation of others. Relevant clinical and pathologic data were collected. Interobserver agreement and survival data were analyzed using Fleiss Kappa and Kaplan-Meier respectively. Results: In our cohort, F:M ratio was 20:25. The median age was 67 (range 55-75) and the median tumor size was 1.8 cm (range: 0-6 cm). Expert recommendations on complete/near-complete grossing of post-treatment cases were followed. There was substantial agreement between all four pathologists for CAP ($\kappa = 0.76$) and Becker scoring systems ($\kappa = 0.70$). Regarding the evaluation of stromal changes, there was substantial agreement for exocrine atrophy ($\kappa = 0.76$), fair agreement for fibrosis ($\kappa = 0.21$) and inflammation ($\kappa = 0.24$). When CAP regression scores 0, 1 and 2 were combined, they had significantly better prognosis compared to CAP score 3 ($p = 0.02$) (Figure 1). Stromal changes, like exocrine atrophy, fibrosis, and inflammatory response did not correlate with survival. For PDACs status post NACT, it is suggested that, 1 cm could be a better cut off between T1 and T2. When we analyzed our results, we noted that T1c had a prognosis similar to T1a and T1b, and was significantly better than T2 (Figure 2). [Formula presented] [Formula presented] Conclusions: NACT is increasingly utilized in PDAC treatment, therefore clear guidelines on grossing the tumor as well as better TRS systems need to be established. CAP-TRS system, while reproducible, does not aid in risk stratifying patients which may be a weakness. Due to being highly subjective, around 60% of the evaluated cases are reported as CAP Grade 2, making over-utilization of this category reducing its analytical significance

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Pandiri M, Kaur A, Rojek A, Symes E, Velmurugan S, Arber D, Badar T, Chang H, **Ghosh S**, Menon M, Nawas M, Pan Z, Patel J, Patel A, Sojitra P, Tariq H, Tjota M, Stock W, Wang P, Wiredja D, Zhang J, Bell R, Perry A, and Venkataraman G. 1272 A 4-Gene Co-Alteration Signature (SIG4) Predictive of Favorable Outcomes in High-Grade TP53 Mutated Myeloid Neoplasms: An International TP53 Investigators Network (iTIN) Study. *Lab Invest* 2025; 105(3). Full Text

Background: We recently proposed an adverse EPI6 6-gene co-mutation signature (CUX1, U2AF1, EZH2, TET2, CBL, or KRAS) in high-grade TP53-mutated myeloid neoplasms (≥ 10% blasts). In this expanded cohort of 324 individuals with TP53-mutated MDS/AML and AML, we asked if there are any pre-therapy molecular determinants of better outcomes. Design: All participating centers collected clinical, pathological, somatic genetic, and cytogenetic information. Genes shared across ten centers were

examined to identify potential gene sets capable of delineating a favorable risk group. The primary outcome was 24-month overall survival (OS24) from the time of diagnosis, with a secondary focus on assessing frontline composite complete response (cCR1; see Table 1). Results: We included 324 patients with a median age at diagnosis of 68.6 years (range: 13.5–92.6 years). A 4-gene co-mutation signature (termed 'SIG') with pathogenic mutations in BCOR, IDH1, IDH2, or DDX41 was identified in 11.1% (36/324) of the cohort with no significant difference in baseline characteristics stratified by SIG4 status (Table 1). SIG4+ individuals had less frequent complex karyotype (60.6% vs. 81.1%; P = .007) as well as marginally infrequent TP53 VAF >25% (69.4% vs. 81.9%; P = .08). First-line response was evaluable in 253 patients with 28.5% (72/253) achieving a cCR1. In the response-evaluable subgroup, only a monosomal karyotype (22.2% vs. 39.5% CR1 in 0-1 Monosomy; P = .005) and EPI6 (16.4% vs. 31.8% CR1 in Absent EPI6; P = .025) predicted inferior CR1 but not SIG4 (P = .94) although SIG4 showed a marginally favorable cCR1 in venetoclax-treated patients (61.5% vs. 35.1% CR1 in SIG4 Absent; P = .07). In age-adjusted OS24 analysis, SIG4 was favorable (HR = 0.5 [0.3–0.8]; P = .005) while EPI6 predicted inferior OS24 (HR = 1.7 [1.3–2.3]; P < .001); See Figure 1 for subset analysis by blast counts and therapy groups. Among the 51(15.7%) allo-transplanted patients, SIG4+ patients experienced a trend towards superior overall survival (not reached vs. 15.3 mos.; PLog-rank = .06). In a forward stepwise multivariable Cox model including both signatures (EPI6 & SIG4), were retained in the final model (P = .0001). [Formula presented] [Formula presented] Conclusions: Our work highlights the prognostic value of the novel SIG4 signature in this high-risk cohort. When combined with the adverse EPI6, it offers a powerful tool for accurately identifying individuals who could benefit from personalized frontline treatment strategies.

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Qadir H, **Inamdar K**, **Ghosh S**, **Shen Y**, **Gomez-Gelvez J**, **Kuriakose P**, and **Liu W**. 1279 Re-Classification of Acute Myeloid Leukemia Based on Latest World Health Organization & International Consensus Classifications and Its Clinical Impact in a Population-Based Comparative Study. *Lab Invest* 2025; 105(3). Full Text

Background: Significant changes in acute myeloid leukemia (AML) classification were made in the latest World Health Organization and International Consensus 2022 classifications (WHO22 and ICC22), underpinning the biology of diseases. Whether the classification is in line with clinical outcomes has yet to be fully elucidated. Design: From a pathology database,116 consecutive AML cases with complete data from 1/1/2020 to 12/31/2022 were reclassified based on WHO22 and ICC22. The clinical impact, with a focus on AML-MRC (renamed as AML-MR), was assessed, correlating with ELN2022 genetic risk stratification, post-induction therapy responses and overall survivals. Results: Of 116 AML patients (median age 67, M/F=1:1), 46 (39.7%) were with recurrent genetic abnormalities (RGA), 44 AML-MRC (37.9%), and 26 AML-NOS (22.4%) by WHO2016, most changes in the latter two categories. AML-NOS narrowed down to include 21 patients by WHO22, 17 by ICC22. 54 patients (46.6%) were reclassified as AML-MR by WHO22, including 10 previously classified as AML-NOS (rAML-MR). Most (53.7%, n=29) had both cytogenetic and molecular abnormalities, while 15 had only molecular, 7 had only cytogenetic changes, and 3 neither. Complex karyotype (43.3%, n=26) and ASXL1 mutation (30.2%, n=13) were the most common. Under ICC22, 39 patients (33.6%, also including 10 rAML-MR) were reclassified as AML-MR, 19 patients (16.3%) as AML-TP53, in comparison to WHO22 showing similar genetic composition (data not included). Under WHO22, rAML-MR (n=10) showed significantly higher rate of non-response to treatment than that of AML-NOS (66.6% vs 0%, p=0.0015) while no difference than that of remainder AML-MR (60.0%, p=0.68), with all (100%) concordantly classified in the adverse risk group by ELN2022 (vs 28.6% AML-NOS [p<0.0001] and vs 90.9% remainder AML-MR [p>0.9999]). Of note, while overall survival (OS) was significantly different by WHO22 among AML-NOS, rAML-MR and remainder AML-MR (42 vs undefined vs 704 days, p=0.001), no significance reached between AML-NOS and rAML-MR (p=0.16). Results from ICC22 were similar in addition to that AML-TP53 showed the shortest OS than those with rAML-MR, remainder AML-MR and AML-NOS subgroups (42 vs undefined vs 133 vs 488 days, p=0.0005). Conclusions: While rAML-MR showed significantly worse treatment response and associated with adverse risk by ELN2022, OS was not significantly different from that of AML-NOS. Additional studies are warranted.

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Rizkalla C, Tretiakova M, Suarez C, Williamson S, **Al-Obaidy K**, Acosta A, Idrees M, Chan E, Potterveld S, and Sangoi A. 883 Osteoclast-Rich Undifferentiated Urothelial Carcinoma: An Expanded Immunohistochemical and Molecular Profiling with Classification Re-assessment. *Lab Invest* 2025; 105(3). Full Text

Background: Osteoclast-rich undifferentiated carcinoma of the urinary tract (ORUC) is a rare tumor currently classified under the "poorly differentiated urothelial carcinoma" subtype. Neoplasms with similar morphology have been reported in bone, soft tissue, synovium, and visceral organs. To date, only limited study into the immunoprofile of ORUC has been performed without assessment of novel histiocytic/osteoclastic markers. Moreover, there is limited data on the molecular profiling of ORUC. Design: Clinicopathologic features of 14 ORUCs were recorded with immunohistochemistry (IHC) performed using CD68, CD163, PU.1, SATB2, cathepsin K, pankeratin, p63, GATA3, H3.G34W, and HCG. In situ hybridization (ISH) for CS1 was also performed. Semi-quantitative staining results for both the mononuclear (MN) and giant cell (GC) components of ORUC were scored (0-3). Comparative staining was performed on 6 urothelial carcinomas (UC) with trophoblastic differentiation and 5 UC with pleomorphic giant cells. Next-generation sequencing (NGS) was performed on 4 ORUC tumors. Results: All ORUCs showed classic biphasic morphology of osteoclast-like giant cells intermixed with mononuclear cells. The extent of ORUC elements in the urothelial carcinomas ranged from 5% to 95% (mean=44%), and often included other UC morphologies (Figure 1). IHC revealed distinct profiles with some overlap for MN and GC (Figure 2). The MN cells averaged high scores for histiocytic markers (CD68, CD163, PU.1) and osteoclastic markers (SATB2, cathepsin K, CSF1 ISH), was moderate for urothelial markers (GATA3, p63), and low for pankeratin. In contrast, the GCs showed variable scores for both histiocytic and osteoclastic markers and no staining for urothelial markers or pankeratin. Both MN/GC were negative for H3.G34W and HCG. The multinucleated cells from all UC with trophoblastic differentiation and UC with pleomorphic GCs were negative for histiocytic and osteoclastic markers. NGS from all 4 tested ORUC showed mutations consistent with urothelial carcinoma without any fusions identified. [Formula presented] [Formula presented] Conclusions: The expression ofUC markers in the MN component along with a molecular profile and concomitant backgroundUC histology overall support urothelial origin to ORUC. Moreover, as ORUC exhibits both morphologic and immunophenotypic overlap with other tumor types (e.g., tenosynovial giant cell tumor, giant cell tumor of bone, giant cell tumor of soft parts), it may warrant re-categorization as UC with osteoclast-rich differentiation.

Pathology and Laboratory Medicine
Tavberidze N, Jennings L, Duckett D, Volek M, Alexiev B, Castaneda C, Weisman P, Kapinski E, Isaacson A, **Keller C**, Fritchie K, and Buehler D. 91 Novel Low-Grade Fibroblastic Neoplasm with Co-Expression of MUC4 and Beta-catenin: Clinicopathologic and Molecular Characterization of Eight Cases. *Lab Invest* 2025; 105(3). Full Text

Background: To date, MUC4 immunostain has been a highly specific marker in separating low-grade fibromyxoid sarcoma (LGFMS) from its known fibroblastic mimics, including desmoid fibromatosis. Here, we present clinicopathologic, molecular genetic, and epigenetic features of a novel low-grade fibroblastic neoplasm showing co-expression of MUC4 and nuclear beta-catenin by IHC. Design: Eight spindle cell neoplasms with co-expression of MUC4 and nuclear beta-catenin were analyzed by RNA/DNA sequencing and DNA methylation profiling. A control group of sporadic (CTNNB1 exon 3 mutated) and familial adenomatous polyposis (FAP)-related desmoid fibromatoses were stained with MUC4. Results: The tumors occurred in 5F and 3M patients (median age 25 years; range 17-60) without personal or family history of FAP, as masses of deep axial or appendicular soft tissue (7) and lung (1), with a mean size of 8.6 cm (range 2.5-10). The tumors uniformly consisted of short, banal fibroblasts in a loosely fascicular or storiform pattern within a densely collagenous stroma containing compressed vessels and scattered mast cells. All cases with evaluable margins (7/7) showed sharp circumscription with minimal or no peripheral infiltration. Strong, diffuse MUC4 and nuclear beta-catenin co-expression was present in all cases (8/8) while 9 sporadic and 8 FAP-associated desmoid fibromatoses were negative for MUC4 (0/17). RNA sequencing revealed no gene fusions in all 6 cases tested; the remaining 2 cases were negative for FUS and FUS/EWSR1 rearrangements by FISH, respectively. Preliminary DNA sequencing showed a pathogenic APC mutation in 1 of 2 cases tested (6 not yet completed) and no CTNNB1 mutations in 4 of

4 cases tested. Four tumors analyzed by DNA methylation profiling formed a distinct cluster separate from desmoid fibromatosis and LGFMS on unsupervised clustering. Of those, the methylation array showed recurrent chromosome 5q deletions in 3 cases; the last case had inconclusive findings. Seven cases were resected with negative (1), positive (3) and unspecified (3) final margins. No recurrences or metastasis have been reported (mean follow-up of 11.6 months (range 2-38)). [Formula presented] [Formula presented] Conclusions: Low-grade fibroblastic neoplasms with MUC4 and beta-catenin co-expression appear to be a unique fibroblastic tumor with a DNA methylation signature distinct from desmoid fibromatosis and LGFMS even though they overlap by histology and immunophenotype. Long-term follow-up is needed to determine the biologic potential of this novel neoplasm.

Pathology and Laboratory Medicine
Wu D, Akgul M, Williamson S, Acosta A, **Al-Obaidy K**, Amin M, Berney D, Brimo F, Cheng L, Colecchia M, Compérat E, Cornejo K, Dhillon J, Downes M, Epstein J, Hirsch M, Jimenez R, Lobo A, Kaushal S, Lopez-Beltran A, Mohanty S, Mehra R, Paner G, Rao P, Reuter V, Shah R, Shen S, Smith S, Tretiakova M, Trpkov K, Wobker S, Tamboli P, Zynger D, and Sangoi A. 917 Interobserver Reproducibility of Hilar Soft Tissue Invasion in Testicular Germ Cell Tumors Among Genitourinary Pathologists. *Lab Invest* 2025; 105(3). Full Text

Background: Compared to lymphovascular invasion (LVI), hilar soft tissue invasion (HSTI) is a relatively novel pT2 staging parameter in testicular germ cell tumors (GCT). There is however diagnostic variability in how pathologists interpret HSTI, and we sought to explore interobserver reproducibility among genitourinary (GU) pathologists. Design: Twenty digitally-scanned GCT slides were pre-classified as HSTI (n=10) or not HSTI (n=10) by internal consensus of the survey authors; slides with concomitant LVI were excluded. A survey (surveymonkey.com) was distributed to invited GU pathologists. All 20 slides consisted of tumors grossly approaching the hilum. Participants were asked follow-up questions pertaining to HSTI diagnosis. Results: Thirty of 50 GU pathologists completed the survey. A majority agreement (≥67% participants) was achieved in 17/20 (85%) slides, with strong consensus (≥80% participants) achieved in 16/20 (80%). In the 2 slides not reaching consensus, 63% and 60% of participants agreed with the design team's HSTI designation, whereas 1 slide was nearly divided (53%/47%). In their respective daily practices, 57% of participants "occasionally encountered" HSTI without LVI, and 77% perceived that there are no clear-cut guidelines regarding HSTI staging on pathologic assessment. If the gross impression was HSTI but histologic sections were not supportive, 27% would still render HSTI (pT2) diagnosis. Histologic criteria used for HSTI designation included invasion beyond rete (62%), invasion to a level parallel to hilar adipose tissue (55%), and invasion beyond level parallel to hilar adipose tissue and directly abutting fat (66%). A minority (13%) considered epididymis invasion synonymous with HSTI. A majority (72%) evaluated HSTI independently of other parameters, but for some participants (28%), if stage pT2 was established via LVI or epididymis invasion, their threshold to also diagnose HSTI lowers. GCT subtype did not alter the diagnostic threshold for HSTI for great majority (93%). Akin to "EPE" (extraprostatic extension) for prostatectomy staging, the term "ETE" (extratesticular extension) as a proposed replacement to HSTI was met with mixed opinion (56% opposed the descriptor). [Formula presented] Conclusions: Although a good consensus exists among genitourinary pathologists on HSTI assessment, clarifying the diagnostic guidelines with specific set of criteria included in pathologic staging systems should improve its diagnosis.

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Xu Z, **Ahsan B**, **Theisen B**, and **Chang Q**. 1471 Loss of Canal of Hering, a Feature of Early Chronic Rejection in Liver Allograft Transplantation. *Lab Invest* 2025; 105(3). Full Text

Background: T-cell mediated chronic rejection (CR), occurring weeks to years post-transplantation, causes damage to bile duct and blood vessel and eventually causes allograft failure. Chronic rejection is categorized into early chronic rejection (ECR) and late chronic rejection (LCR). Differentiating them is clinically important, as ECR is reversible. Interlobular bile duct injury and ductopenia is hallmark feature of CR. Canals of Hering (CoH) are strings of small cholangiocytes located in acinus zone 1 or 2. Because of their more proximal location in bile draining pathway, it is reasonable to assume that loss of CoH (LOH) would be prior to interlobular bile duct injury as an earlier feature of ECR. Design: A search of pathology database from our institution was conducted to select cases that contain "chronic rejection" in final

diagnosis including comment section. Slides were reviewed to determine the ECR histological features. The features included bile duct loss in < 50% of all portal tracts, foamy cell change in perihilar hepatic artery branches, perivenular zone 3 hepatocyte dropout and mild perivenular fibrosis or perivenulitis. Meanwhile, CK7 and CK19 stains were evaluated to assess the LOH. Clinical information was collected from electronic medical records. Results: Our cohort contained 31 patients with 13 male and 18 female patients (M:F ratio 1:1.4), ranged from 20 to 73 years with a median of 54.5. Of the 31 patents, ductal paucity (< 50% portal tract loss) was seen in 7 patients, LOH presented in 5 of them. 2 patients showed foamy cell change in the intima of artery, and both demonstrated concurrent LOH. Perivenular hepatocyte drop-out was seen in 8 patients, among which 2 patients showed LOH. Perivenular fibrosis or perivenulitis was seen in 7 patients, among which 3 patients showed LOH. 4 patients demonstrated ductopenia and were diagnosed as chronic rejection. 3 of them showed LOH. In reports of 9 patients, CR was listed as top 3 differential diagnosis. LOH was seen in 5 of them. See Table. [Formula presented] [Formula presented] Conclusions: LOH evaluated by CK19 and CK7 stains has a strong correlation with ductopaucity and arterial foamy cell change, features of ECR, as well as ductopenia, features of LCR. In contrast, correlation with perivenular hepatocyte drop out and perivenulitis or fibrosis is weak. In summary, LOH is probably one of the earliest features of chronic rejection in liver allograft transplantation.

Public Health Sciences
Finkel K, **Lin CH**, **Sitarik A**, **Kim H**, **Eapen A**, **Baptist A**, **Levin A**, **Cassidy-Bushrow A**, **Johnson C**, and **Zoratti E**. Associations between genetic ancestry and serum Immunoglobulin E trajectory, allergen-specific IgE sensitization, and asthma at 10 years among Black children in the WHEALS birth cohort. *J Allergy Clin Immunol* 2025; 155(2):AB269-AB269. Full Text

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Public Health Sciences
Schutt M, Gadd S, Senter J, Barrera L, Cho S, Pongracic J, Liu AD, Gruchalla R, Kercsmar C, Hershey GK, **Zoratti E**, **Johnson C**, Teach S, Kattan M, Bacharier L, O'Connor G, Gern J, Visness C, Coleman A, Gergen P, Becker P, Jackson D, Altman M, and Kumar R. PAI-1 genotype and regulation of airway PAI-1 in vivo: relationships with patterns of airway gene expression during illness. *J Allergy Clin Immunol* 2025; 155(2):AB279-AB279. Full Text

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Research Administration

Lanfear DE, Lowry J, Amendola L, **Trepanier A**, **Aurora L**, **Ferrari H**, **Cabral W**, Kesari A, Rajkumar R, Chawla A, Coffey A, Hostin D, Huertas-Vazquez A, Perry D, Longoni M, and Taft R. CLINICAL GENOME SEQUENCING IN ROUTINE CARDIOLOGY: INITIAL FINDINGS OF THE CARDIOSEQ STUDY. *J Am Coll Cardiol* 2025; 85(12):1364. Full Text

Background Cardiovascular disease (CVD) is multifactorial and includes monogenic and polygenic contributors to onset and severity. Clinical genetic testing in practice seldom meets guideline recommendations, in part due to test limitations, disease heterogeneity and uncertainty about the utility of positive findings. The CardioSeq study was designed to evaluate the diagnostic yield and clinical impact of comprehensive clinical genome sequencing (cGS) spanning hundreds of genes and genetic disorders, risk factors and potential care modifiers in patients presenting with CVD. Methods A prospective, open-label, single-center clinical trial was conducted at Henry Ford Health. Inclusion required a diagnosis of at least one among: cardiomyopathy or heart failure, aortopathy, arrhythmia, coronary or peripheral artery disease, and/or dyslipidemia. The cGS test included 215 CVD-associated genes, 4 common genetic variants associated with increased CVD risk, 35 optional non-CVD ACMG secondary findings genes, pharmacogenomic variants and a coronary artery disease (CAD) PRS. Results Of the 1,000 participants who received cGS testing, 501 were assigned male sex at birth (median age 69, IQR 61-75) and 499 were assigned female (median age 70, IQR 62-76). The most common self-reported races were white (57.9%) and African American (39.2%). Cardiomyopathy or heart failure accounted for 33.5% of the entire cohort. A total of 74 participants received a monogenic finding, roughly half of which were due to variants in three genes: TTR (n = 16, 21.6%), TTN (n = 14, 18.9%), and LDLR (n = 8, 10.8%). The TTR p.Val142Ile variant accounted for 20.3% of positive cases. Unadjusted diagnostic yield was highest in African American cases (11.5%). Risk allele findings were reported in 10.1% of study participants, secondary findings in 1.4%, and pharmacogenomic findings in <99%. An elevated CAD PRS was reported in 4.6% of participants. Conclusion A single comprehensive cGS test can provide useful diagnostic and genetic risk data across a broad range of CVD phenotypes and genetic ancestries. The investigation of the impact of cGS findings on clinical management is ongoing and will be reported at CardioSeq study completion.

Research Administration

Sabbah HN, **Gupta RC**, **Zhang KF**, and **Lanfear DE**. Abnormalities Of Mitochondria! Function In Renal Epithelial Cells Of Dogs With Chronic Heart Failure And Dogs With Cardiorenal Syndrome. *J Card Fail* 2025; 31(1):2. Full Text

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Surgery

Chamseddine H, **Shepard A**, Constantinou C, **Nypaver T**, **Weaver M**, **Boules T**, **Kavousi Y**, **Onofrey K**, **Peshkepija A**, **Halabi M**, and **Kabbani L**. Preoperative smoking cessation improves carotid endarterectomy outcomes in asymptomatic carotid stenosis patients. *J Vasc Surg* 2025; 81(3):650-657. Full Text

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Objective: Smoking cessation has been suggested as having the potential to improve the outcomes of carotid endarterectomy (CEA) and mitigate the risk of long-term stroke in patients with asymptomatic carotid stenosis (ACS). This study aims to compare the perioperative and long-term outcomes of CEA in patients with ACS across different smoking status groups. Methods: All patients receiving an elective CEA for ACS between 2013 and 2023 were identified in the Vascular Quality Initiative (VQI). Patients with an ipsilateral carotid stenosis <70% and those receiving a concomitant coronary artery bypass graft were excluded. Patients were then classified according to their smoking status: never smokers, former smokers (defined as those who have stopped smoking more than 30 days prior to their operation), and current smokers. Patient characteristics and outcomes were compared using the $\chi 2$ or Fischer exact test as appropriate for categorical variables and the analysis of variance or Kruskal-Wallis test as appropriate for continuous variables. Cox regression analysis was used to study the association between smoking status and the primary outcomes of long-term stroke and major adverse cardiac events (MACE) defined as the composite outcome of stroke, myocardial infarction, and/or mortality. Results: A total of 77,664 patients received a CEA for ACS, of which 19,416 patients (25%) were never smokers, 39,374 patients (51%) were former smokers, and 18,874 patients (24%) were current smokers. Patients in the three groups had similar rates of perioperative stroke (P = .79), myocardial infarction (P = .07), mortality (P = .23), and MACE (P = .17). At 18-month follow-up, former and never smokers had similar rates of stroke (former 0.9% vs never 0.8%; P = .92), with former smokers exhibiting a lower stroke risk than current smokers (former 0.9% vs current 1.5%; P = .001). At 18 months, former smokers had a significantly lower rate of MACE compared with current smokers (former 11.8% vs current 13.2%; P = .03), but a higher rate compared with never smokers (former 11.8% vs never 8.7%; P < .001). On multivariate Cox regression analysis, compared with current smokers, former smokers were independently associated with a lower risk of stroke (hazard ratio [HR], 0.68; 95% confidence interval [CI], 0.53-0.87; P = .002), mortality (HR, 0.79; 95% CI, 0.74-0.84; P < .001), and MACE (HR, 0.77; 95% CI, 0.70-0.83; P < .001). No difference in long-term stroke risk was observed between former and never smokers (HR, 1.06; 95% CI, 0.82-1.38; P = .65). Conclusions: This study demonstrates that preoperative smoking cessation in patients with ACS significantly reduces the risk of stroke, mortality, and MACE following CEA compared with continued smoking, aligning their outcomes more closely with those of never smokers. Optimizing patients with ACS prior to surgery should include smoking cessation counseling. Vascular surgeons play a critical role in encouraging smoking cessation, as their guidance can significantly improve patient outcomes following CEA.

Surgery

Nguyen F, **Fadel R**, **Cowger JA**, **Nemeh H**, and **Basir MB**. AORTIC VALVE THROMBUS ASSOCIATED WITH LEFT ATRIAL VENOARTERIAL EXTRACORPOREAL MEMBRANE OXYGENATION (LAVA-ECMO) WHILE ON BIVALIRUDIN. *J Am Coll Cardiol* 2025; 85(12):3322. Full Text

Background LAVA-ECMO is an ECMO configuration that uses a single trans-septal cannula to provide biventricular unloading. Despite its advantages, the risk of thrombosis remains. Case A 32-year-old male with a history of nonischemic cardiomyopathy and recurrent venous thromboses on apixiban was admitted with decompensated heart failure. Right heart catheterization showed elevated filling pressures and very reduced cardiac output. He is started on diuretics and afterload reducing agents. On hospital day #4, he develops worsening cardiogenic shock with severe lactic acidosis and acute hypoxic respiratory failure requiring intubation. He is taken urgently for LAVA-ECMO. Decision-making Given the patient's thrombosis history, body habitus, and difficulties maintaining heparin at therapeutic range, heparin was switched to bivalirudin after cannulation. After 3 days, his mental status declines. A transesophageal echocardiogram was performed revealing severe smoke around the aortic valve and root, suspicious for thrombus. A CT head was performed showing an acute infarct in the right frontal lobe. Bivalirudin is switched back to heparin. Discussions of durable support are expedited, and patient is taken for LVAD. He is subsequently extubated and demonstrated intact neurologic function. Conclusion In this patient with thromboembolic history, bivalirudin may not have provided adequate anticoagulation while on ECMO. Improving protocols for anticoagulation for ECMO may help reduce this risk. [Formula presented]

Surgery

Walji M, **Cieslak R**, **Abuzahrieh O**, **Phillips C**, and **Arnautovic J**. PREPARED FOR THE WORST, HOPE FOR THE BEST: COLLABORATIVE MEDICINE AGAINST A MASSIVE PULMONARY EMBOLISM IN A YOUNG WOMAN. *J Am Coll Cardiol* 2025; 85(12):3815. Full Text

Background Approximately 900,000 Americans experience pulmonary embolisms (PEs) each year, with 5-10% of those classified as high-risk or massive PE. The mortality risk for an untreated massive PE is alarmingly high, ranging from 30-60% within hours of onset. Even with prompt treatment, it remains one of the leading causes of cardiovascular death. Treatment requires a multifaceted, coordinated team approach that considers the patient's clinical condition, risk factors, and contraindications (CIs). Case A 24-year-old woman with a past medical history of obesity, oral contraceptive therapy, and back pain presented to a communityhospital with tachycardia, lightheadedness, and shortness of breath after a recent epidural spinal injection (ESI). She was diagnosed with a massive saddle PE and quickly became hemodynamically unstable with hypoxia and hypotension. A STAT echocardiogram demonstrated a severely dilated right ventricle (RV) with evidence of strain and a small, hyperdynamic left ventricle. Decision-making Neurosurgery was consulted due to the relative CI for thrombolysis after an ESI and determined the patient to be at an acceptable risk to proceed with thrombectomy and anticoagulation. She was urgently transported to the catheterization lab. A cardiothoracic surgeon (CTS) was present during the case with cardiopulmonary bypass prepped along with a pharmacist with thrombolysis if needed. Patient underwent a successful transfemoral embolectomy and was closely monitored. She was later initiated on oral anticoagulation. At her two-month follow-up, she was doing well with her echocardiogram demonstrating an exceptional, complete recovery of her RV. Conclusion This case emphasizes the importance of collaborative multidisciplinary care in a rural-hospital setting, especially in high-risk cases. Obtaining Neurosurgery clearance in an urgent manner helped expedite treatment. Having CTS and their team on standby, as well as a pharmacist with thrombolysis, allowed for alternative treatment options that could be seamlessly initiated. Coordinating care to this degree is uncommon, but vital in optimizing the utilization of all available resources when dealing with a massive PE.

Urology

Hwang C, **Symanowski J**, **Shore N**, **Russell D**, **Kral P**, **Elsouda D**, **El-Chaar N**, and **Karsh L**. CHARACTERISTICS, TREATMENT PATTERNS, AND OUTCOMES OF AFRICAN AMERICAN VERSUS CAUCASIAN PATIENTS WITH METASTATIC CASTRATION-RESISTANT PROSTATE CANCER: POST HOC ANALYSIS OF TRUMPET REGISTRY. *Urol Oncol* 2025; 43(3):7. Full Text

Introduction: Racial disparities exist in the treatment of prostate cancer in the US, and robust data for African American (AA) vs Caucasian (CAU) patients with metastatic castration-resistant prostate cancer (mCRPC) are scarce. This study explored characteristics, treatment patterns, and outcomes of AA vs CAU patients with mCRPC in the real-world setting. Methods: TRUMPET, a prospective, observational, multicenter study, enrolled 1028 patients who initiated CRPC treatment at 147 urology and oncology sites in the US (2015[sbnd]2019). The post hoc analysis included patients with mCRPC who identified as AA or CAU. Patients were enrolled within 90 days of the decision to treat or treatment initiation. Characteristics and treatment patterns were analyzed descriptively; radiographic progression-free survival (rPFS), prostate-specific antigen PFS (PSA-PFS), overall survival (OS), and time to skeletal-related events (SREs) were analyzed using Kaplan–Meier methods and adjusted Cox proportional hazards models. An exploratory sub-analysis compared outcomes by race in patients initially treated with androgen receptor pathway inhibitors (ARPIs). Results: In total, 133 AA vs 661 CAU patients with M1 CRPC at baseline were included: median age, 69.0 vs 74.0 years; hypertension, 72% vs 66%; diabetes, 32% vs 23%; osteoporosis, 5% vs 12%; other cancers, 6% vs 24%; PSA at diagnosis, 48.8 vs 13.9 ng/mL; N1 tumors, 17% vs 11%; M1 tumors, 29% vs 23%. Primary treatment before CRPC diagnosis (AA vs CAU patients): surveillance, 12% vs 19%; radical prostatectomy, 18% vs 36%; radiation, 48% vs 41%. Initial mCRPC treatment: chemotherapy, 12% vs 6%; ARPI, 62% vs 57%; immunotherapy, 29% vs 41%. After treatment initiation, a trend toward improved clinical outcomes was seen in AA vs CAU patients (Table). In the exploratory analysis, AA patients initiating ARPIs showed a trend toward improved OS vs CAU patients (adjusted median time to death [95% CI]: 41.86 [33.25, not estimable] vs 32.30 [28.62, 40.08] months; adjusted HR [95% CI]: 0.71 [0.45–1.14]). Conclusions: AA patients were younger, had higher rates of some comorbidities and more severe disease, and were more likely to receive ARPIs or chemotherapy.

Despite our initial hypothesis predicting differences favoring CAU patients, we observed generally similar treatment patterns and a trend toward better outcomes in AA patients. Further research is needed to better understand the outcomes of AA patients with mCRPC.