



Department of
Internal Medicine
Top Papers
Published in 2023



**We are delighted to announce the
Department of Internal Medicine's awards for the
Top Research Papers published in 2023.**

The 12 papers receiving recognition this year reflect the collective work of Internal Medicine trainees and faculty in Winston-Salem and Charlotte. The papers were selected on the basis of their originality and their scientific and clinical impact. The papers span the spectrum of basic, clinical, and healthcare delivery science and represent the creativity, passion, and dedication of our faculty and trainees. The papers further demonstrate the Department's commitment to improve the health of the patients we serve by advancing understanding of the mechanisms of disease, by testing novel therapies, and by building and implementing the evidence base for clinical practice. Lastly, the papers represent the Department's long-term goal of advancing a preeminent Academic Learning Health System.

Please join us in congratulating this year's awardees. But recognize that the 12 papers receiving awards this year represent just the tip of the iceberg of the wonderful research being done by so many faculty and trainees in the Department.



**Gary E. Rosenthal,
MD, FACP**

Tinsley R. Harrison
Professor and Chair
Department of
Internal Medicine



**David M. Herrington,
MD, MHS**

Dalton McMichael Chair in
Cardiovascular Medicine and
Vice Chair for Research
Department of
Internal Medicine



**Scott L. Furney,
MD, MBA**

Vice Dean for Academic
Affairs, Charlotte and
Regional Chairman
Department of
Internal Medicine



Miranda E. Orr, PhD

Senolytic Therapy in Mild Alzheimer's Disease: A Phase 1 Feasibility Trial

Citation: *Nature Medicine*. 2023 Oct;29(10):2481-2488.

Authors: Gonzales MM, Garbarino VR, Kautz TF, Palavicini JP, Lopez-Cruzan M, Dehkordi SK, Mathews JJ, Zare H, Xu P, Zhang B, Franklin C, Habes M, Craft S, Petersen RC, Tchkonja T, Kirkland JL, Salardini A, Seshadri S, Musi N, **Orr ME**

Summary: This pioneering study marked the first clinical trial of senolytics in individuals with Alzheimer's disease. It offered crucial insights into safety, brain penetrance, and initial biomarker data, laying the foundation for Phase 2 testing, currently in progress.



Parag A. Chevli, MBBS, MS

Circulating Ketone Bodies and Cardiovascular Outcomes: the MESA Study

Citation: *European Heart Journal*. 2023 May 7;44(18):1636-1646.

Authors: Shemesh E, **Chevli PA (Co-1st)**, Islam T, German CA, Otvos J, Yeboah J, Rodriguez F, deFilippi C, Lima JAC, Blaha M, Pandey A, Vaduganathan M, **Shapiro MD**

Summary: This study, which was conducted in a healthy community-based population of Multi-Ethnic Study of Atherosclerosis (MESA), demonstrated that elevated circulating ketone bodies are associated with a higher incidence of cardiovascular disease and mortality, suggesting their potential utility as a biomarker for assessing cardiovascular risk.



Michael D. Shapiro, DO



Dalane W. Kitzman, MD

Effects of Semaglutide on Symptoms, Function, and Quality of Life in Patients with Heart Failure with Preserved Ejection Fraction and Obesity: A Prespecified Analysis of the STEP-HFpEF Trial

Citation: *Circulation*. 2024 Jan 16;149(3):204-216. Epub 2023 Nov 12.

Authors: Kosiborod MN, Verma S, Borlaug BA, Butler J, Davies MJ, Jon Jensen T, Rasmussen S, Erlang Marstrand P, Petrie MC, Shah SJ, Ito H, Schou M, Melenovský V, Abhayaratna W, **Kitzman DW**; STEP-HFpEF Trial Committees and Investigators

Summary: In patients with HFpEF (heart failure with preserved ejection fraction) and obesity, the use of semaglutide GLP-1a was associated with improvements in heart failure-related symptoms, physical limitations, exercise function, inflammatory markers, body weight, and N-terminal pro-brain natriuretic peptide. The benefits of semaglutide were seen across all levels of baseline health status and across all domains of the Kansas City Cardiomyopathy Questionnaire, a widely accepted quality of life instrument.



Peter M. Voorhees, MD

Addition of Daratumumab to Lenalidomide, Bortezomib, and Dexamethasone for Transplantation-Eligible Patients with Newly Diagnosed Multiple Myeloma (GRIFFIN): Final Analysis of an Open-Label, Randomised, Phase 2 Trial

Citation: *Lancet Haematology*. 2023 Oct;10(10):e825-e837.

Authors: **Voorhees PM (Co-1st)**, Sborov DW, Laubach J, Kaufman JL, Reeves B, Rodriguez C, Chari A, Silbermann R, Costa LJ, Anderson LD Jr, Nathwani N, Shah N, Buma N, Efebera YA, Holstein SA, Costello C, Jakubowiak A, Wildes TM, Orlowski RZ, Shain KH, Cowan AJ, Dinner S, Pei H, Cortoos A, Patel S, Lin TS, Usmani SZ, Richardson PG

Summary: In a phase 2 open label trial in transplantation-eligible patients with newly diagnosed multiple myeloma, the addition of daratumumab to a regimen of lenalidomide, bortezomib, and dexamethasone (RVd) improved the depth of response and progression-free survival. The two regimens had similar rates of serious adverse event. These results justify further evaluation in phase 3 studies.



Gordon R. Reeves, MD

Frailty and Effects of a Multidomain Physical Rehabilitation Intervention Among Older Patients Hospitalized for Acute Heart Failure: A Secondary Analysis of a Randomized Clinical Trial

Citation: *JAMA Cardiology*. 2023 Feb 1;8(2):167-176.

Authors: Pandey A, Kitzman DW, Nelson MB, Pastva AM, Duncan P, Whellan DJ, Mentz RJ, Chen H, Upadhyya B, **Reeves GR**

Summary: In this prespecified secondary analysis of the REHAB-HF trial, older patients with acute decompensated heart failure (ADHF) with worse baseline frailty status had more robust improvement in physical function in response to an innovative, early, transitional, tailored, multidomain physical rehabilitation intervention. These findings suggest that frail patients with ADHF may derive greater benefit from early physical rehabilitation intervention.



Kendrah Kidd, MS

Autosomal Dominant ApoA4 Mutations Present as Tubulointerstitial Kidney Disease with Medullary Amyloidosis

Citation: *Kidney International*. 2024 Apr;105(4):799-811. Epub 2023 Dec 12.

Authors: Kmochová T, **Kidd KO (Co-1st)**, Orr A, Hnízda A, Hartmannová H, Hodaňová K, Vylet'al P, Naušová K, Brinsa V, Trešlová H, Sovová J, Barešová V, Svojšová K, Vrbacká A, Stránecký V, Robins VC, Taylor A, Martin L, Rivas-Chavez A, Payne R, Bleyer HA, Williams A, Rennke HG, Weins A, Short PJ, Agrawal V, Storsley LJ, Waikar SS, McPhail ED, Dasari S, Leung N, Hewlett T, Yorke J, Gaston D, Geldenhuys L, Samuels M, Levine AP, West M, Hůlková H, Pompach P, Novák P, Weinberg RB, Bedard K, Živná M, Sikora J, **Bleyer AJ Sr (corresponding)**, Kmoch S



Anthony J. Bleyer, MD, MS

Summary: This study reported the identification of mutations in the APOA4 gene as a cause of inherited kidney disease in five different families in the US and Canada. ApoA4 is an apolipoprotein that is filtered at the glomerulus and undergoes proximal tubular reabsorption. Mutations in ApoA4 affect its conformation and result in its deposition and the formation of renal medullary amyloidosis, leading to end-stage kidney disease later in life.



Shalini Mishra

A Liquid Biopsy-Based Approach to Isolate and Characterize Adipose Tissue-Derived Extracellular Vesicles from Blood

Citation: *ACS Nano*. 2023 Jun 13;17(11):10252-10268.

Authors: Mishra S, Kumar A, Kim S, Su Y, Singh S, Sharma M, Almousa S, Rather HA, Jain H, Lee J, Furdui CM, Ahmad S, Ferrario CM, Punzi HA, Chuang CC, Wabitsch M, Kritchevsky SB, Register TC, **Deep G**

Summary: This research introduces a pioneering ‘liquid biopsy’ approach for hard-to-access tissues that involves the isolation of adipose tissue-specific extracellular vesicles from blood and the characterization of molecular biomarkers. The approach provides a profound opportunity to understand the links between visceral adiposity and chronic diseases, as well as aging-related disorders.



Gagan Deep, PhD

Report of the First Seven Agents in the I-SPY COVID Trial: A Phase 2, Open Label, Adaptive Platform Randomised Controlled Trial

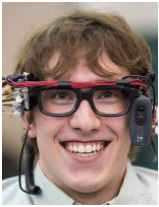
Citation: *EClinicalMedicine*. 2023 Apr;58:101889.

Authors: I-SPY COVID Consortium

Summary: The study reported results of the I-SPY COVID program, which was a phase 2 open label platform trial of agents targeted to discover novel therapies to improve outcomes of hospitalized patients with COVID-19. For this study, Wake Forest team led site training, served as the central IRB, and directed the agent selection committee and the trial operations. Of the 12 agents evaluated using a novel trial design, no agents moved forward to phase 3 testing in COVID, though some agents are being further tested in non COVID lung injury.



D. Clark Files, MD



Thomas E. Tavolara,
PhD

One Label is All You Need: Interpretable AI-Enhanced Histopathology for Oncology

Citation: Seminars in Cancer Biology. 2023 Dec;97:70-85.

Authors: Tavolara TE, Su Z, Gurcan MN, Niazi MKK

Summary: This manuscript reviewed the application of AI-enhanced histopathology interpretation, which has important clinical implications for oncology by simplifying the analysis of histopathology slides through the use of a single label without detailed tissue annotations. While this technology reduces research and clinical costs and enhances personalized medicine, it faces challenges such as validation, explainability, and the need for robust computational resources.



M. Khalid Khan Niazi,
PhD

Self-Reported Experiences of Discrimination and Incident Dementia

Citation: Alzheimers & Dementia. 2023 Jul;19(7):3119-3128.

Authors: Banks MP, Byrd GS, Caban-Holt A, Fitzpatrick AL, Forrester SN, Hayden KM, Heckbert SR, Kershaw KN, Rapp SR, Sachs BC, Hughes TM

Summary: This study examined associations between experiences of discrimination in education, employment, housing, and policing and the incidence of dementia in the Multi-Ethnic Study of Atherosclerosis (MESA), a racially/ethnically diverse cohort of over 6800 adults from six communities. The study found that discrimination was highly prevalent in Black (> 60% experiencing discrimination) and Hispanic (> 50%) adults and that experiencing discrimination in multiple domains was associated with a 40% higher adjusted risk for dementia.



Timothy M. Hughes,
PhD



Heidi D. Klepin, MD,
MS

External Validation of Risk Factors for Unplanned Hospitalization in Older Adults with Advanced Cancer Receiving Chemotherapy

Citation: *Journal of the National Comprehensive Cancer Network.* 2023 Mar;21(3):273-280.

Authors: Mohamed MR, Loh KP, Mohile SG, Sohn M, Webb T, Wells M, Yilmaz S, Tylock R, Culakova E, Magnuson A, Sun CL, Bearden J, Hopkins JO, Faller BA, **Klepin HD**

Summary: In a cohort of older adults who received cancer chemotherapy, this study validated seven risk factors for incident hospitalization within 3 months of treatment. Higher numbers of risk factors were associated with increased odds of unplanned hospitalization. The association was largely driven by two factors (impairment in ADLs and low albumin level).



Bradley A. Rowland
Jr., MD

Impact of Continuous and Wireless Monitoring of Vital Signs on Clinical Outcomes: A Propensity-Matched Observational Study of Surgical Ward Patients

Citation: *British Journal of Anaesthesia.* 2024 Mar;132(3):519-527. Epub 2023 Dec 21.

Authors: **Rowland BA**, Motamedi V, Michard F, Saha AK, Khanna AK

Summary: In this propensity-matched analysis, continuous and wireless monitoring (with ViSi devices) of adult surgical patients was associated with a reduced risk of in-hospital mortality and ICU admission, compared with standard of care intermittent monitoring. The improvement in patient outcomes associated with continuous wireless monitoring may be secondary to the decreased risk of severe adverse events, consequent to earlier detection of vital signs changes.

