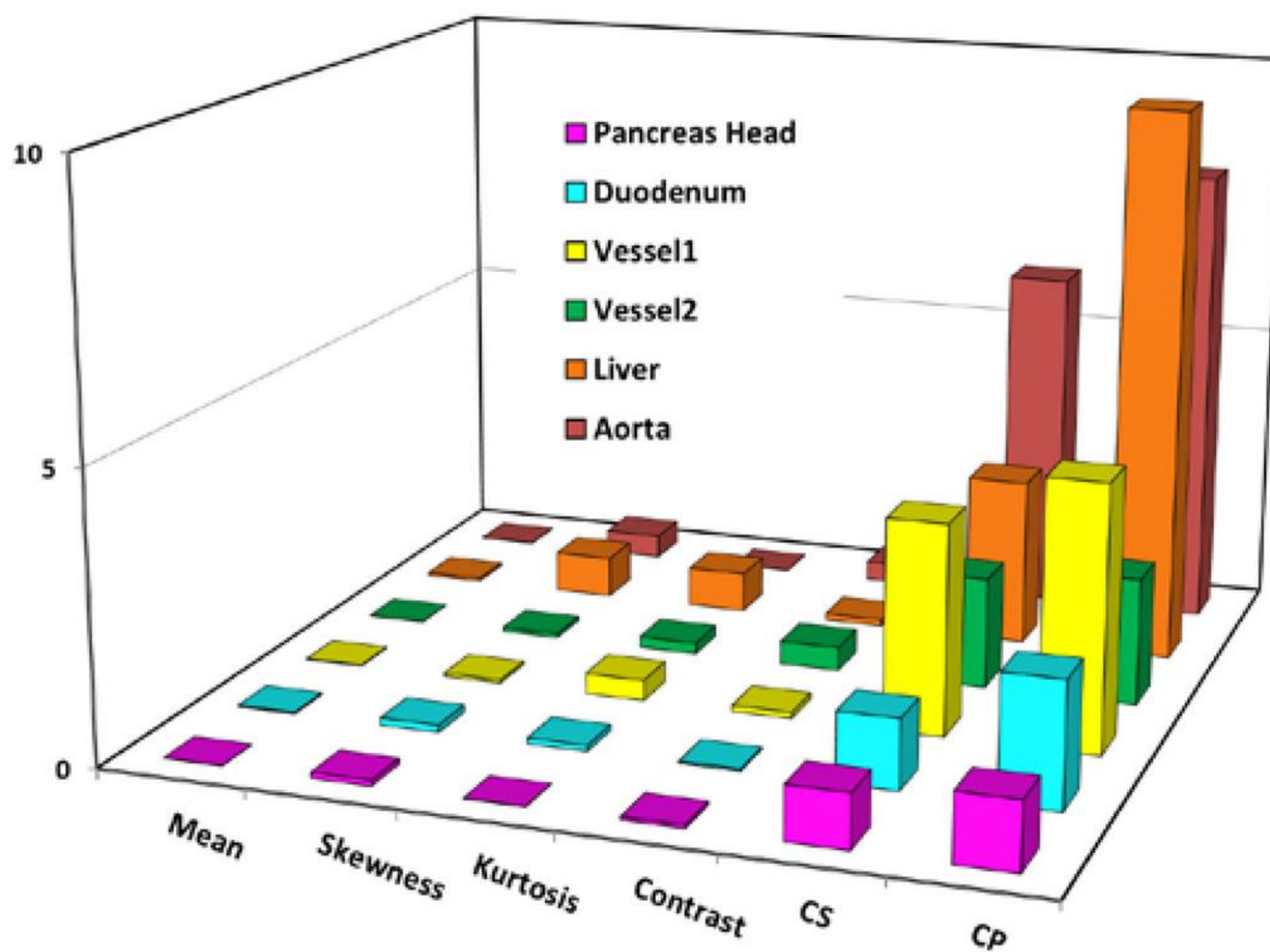


Research Publication Series

February 2020



About the Research Publication Series:

The Medical College of Wisconsin is a major national research center and the second-largest research institution in Wisconsin. Basic science, clinical, and translational researchers thrive in the unique setting of an academic medical center. The innovative work of our scientists leads to groundbreaking discovery that impacts healthcare and saves lives. The Research Publication Series is a sampling of recent publications by faculty, staff, and student investigators.



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February 2020

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“Hydroxyurea Use for Sickle Cell Disease Among Medicaid-Enrolled Children”

Kirsten M. M. Beyer, PhD, MPH, MS

“Housing Discrimination and Racial Cancer disparities among the 100 Largest US Metropolitan Areas”

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Cover Image from “Texture-based, Automatic Contour Validation for Online Adaptive Replanning: A Feasibility Study on Abdominal Organs”



David Brousseau, MD, MS

Professor of Pediatrics
 Chief, Section of Pediatric Emergency
 Medicine
 Director of Scholarly Activities
 Medical College of Wisconsin

I have been a Pediatric Emergency Medicine physician at MCW and Children’s Wisconsin for over 19 years, now serving as the Chief of Pediatric Emergency Medicine. I am a health services researcher and clinical trialist in the field of pediatric sickle cell disease, focusing on acute care utilization for patients with sickle cell disease and improving the emergency department treatment of sickle cell pain crises through both randomized clinical trials and quality improvement work. As the Director of Scholarly Activities for the MCW medical school, Director of the MCW MD/MS dual degree program and the study PI on the CTSI TL1 training program, I am also very invested in training the next generation of scholars.

“Hydroxyurea Use for Sickle Cell Disease Among Medicaid-Enrolled Children”

Brousseau DC, Richardson T, Hall M, et al. *Pediatrics*. 2019;144(1):e20183285.

Hydroxyurea use in sickle cell disease has been shown to decrease pain episodes and reduce emergency department visits and hospitalizations. Recent publications from studies in academic medical centers have shown that children of younger age or with milder forms of a sickle cell disease might benefit from hydroxyurea therapy. We undertook a multiyear, population-based, multi-state study of children with sickle cell disease enrolled in Medicaid to assess whether children with sickle cell disease were receiving hydroxyurea and if any subsequent change in utilization was occurring. We found that despite small to moderate increases in hydroxyurea use across all pediatric age groups, there was no consistent pattern of decreased utilization in this Medicaid population suggesting that the benefits of hydroxyurea use found in academic centers are not translating to the community.

Figure 1. Utilization rates 13 to 16 year-olds with increased hydroxyurea use.

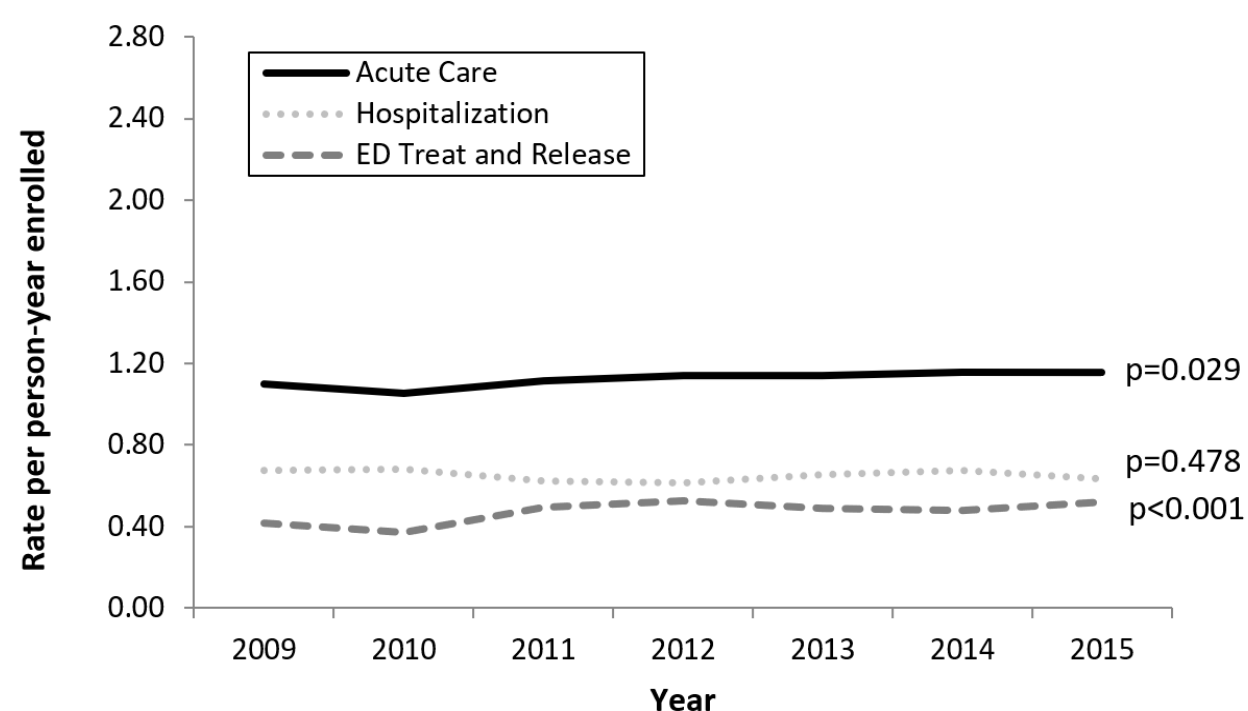
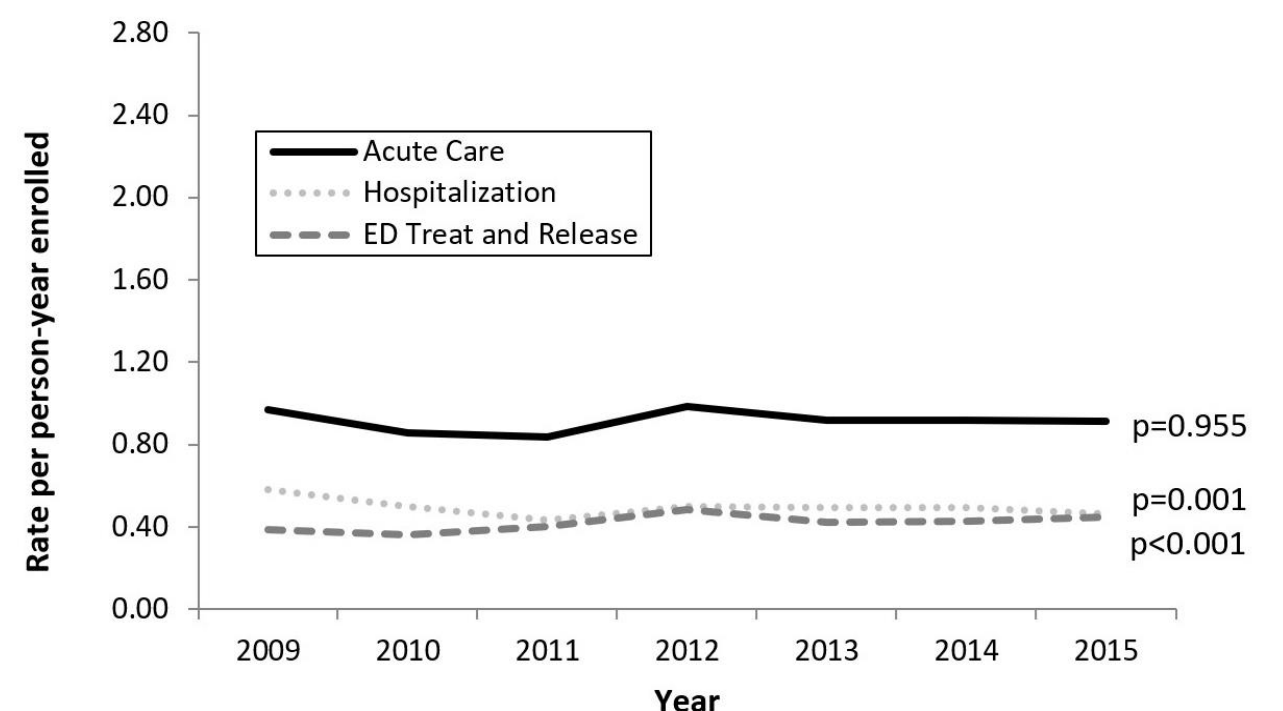


Figure 2. Utilization rates 7 to 12 year-olds with increased hydroxyurea use.





**Kirsten M. M. Beyer, PhD,
MPH, MS**

Assistant Professor
Epidemiology
Institute for Health and Equity
Medical College of Wisconsin

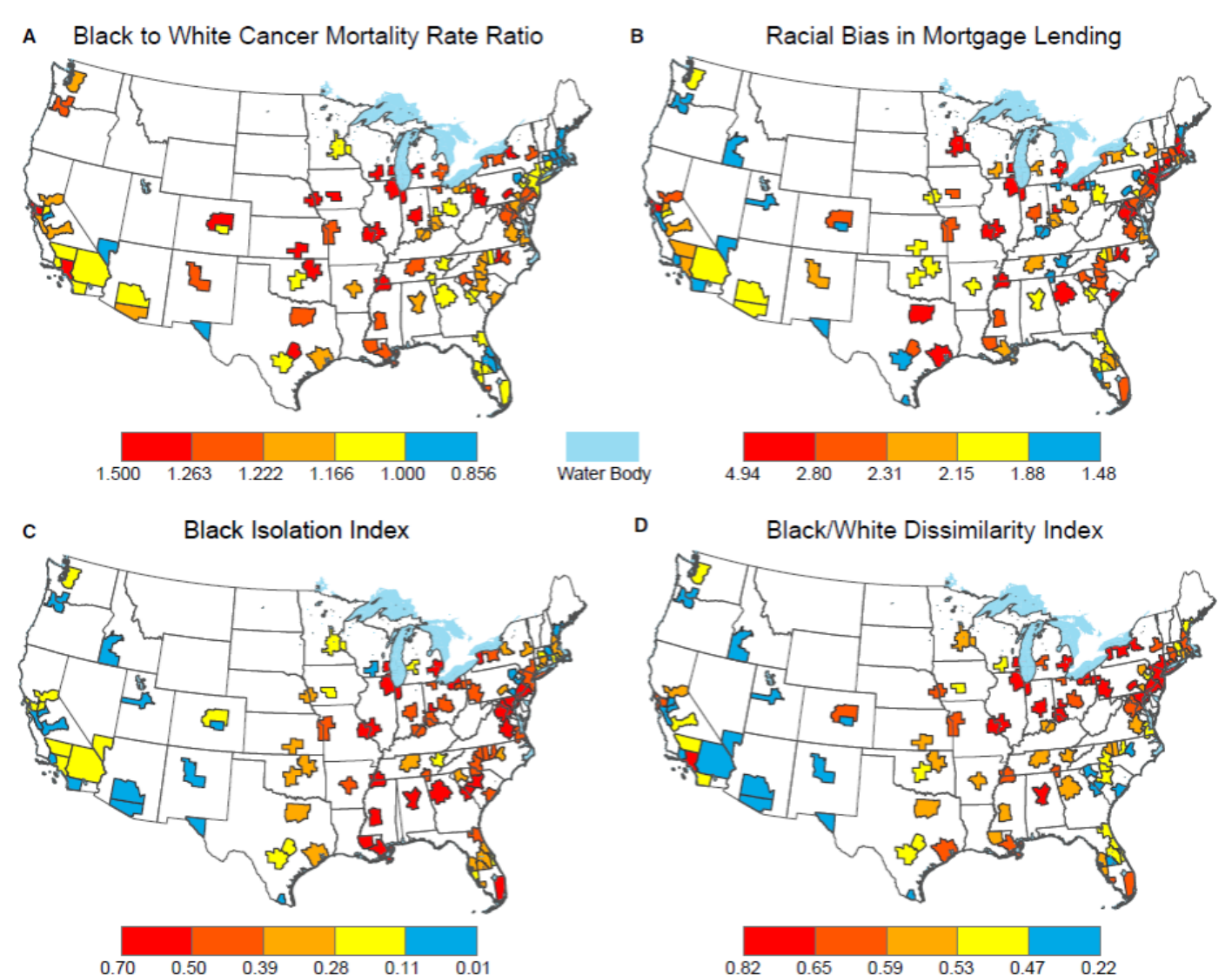
I am a health geographer interested in human-environment interaction as it relates to public health, with environment conceived broadly as including the physical (built and natural) and social environments. I use spatial, statistical and qualitative methods to identify spatial patterns of disease and understand the complex processes that create them. My research focuses on health disparities, and my current work examines the health impacts of neighborhood environmental characteristics such as green space and residential racial segregation, on cancer disparities. I have a strong interest in the role of community engagement in research and teaching and I partner with local community organizations in undertaking much of my work.

“Housing Discrimination and Racial Cancer disparities among the 100 Largest US Metropolitan Areas”

Beyer KMM, Laud PW, Zhou Y, Nattinger AB. *Cancer*. 2019;125(21):3818-3827.

Racial health disparities are a serious problem in the U.S. and have been linked to contextual factors, including racial segregation. In this research, we sought to examine the association between housing discrimination and the size of cancer mortality disparities across United States metropolitan areas. Using the Home Mortgage Disclosure Act (HMDA) database, we estimated the odds ratio of denial of a mortgage application for Black, compared to non-Hispanic White applicants, and correlated this measure of mortgage discrimination with the Black to White cancer mortality rate ratio for each metro area. In areas with greater mortgage discrimination, the gap between black and white cancer mortality rates was larger. This relationship persisted in sex-specific analyses and in models controlling for confounders. Housing discrimination is an important factor to consider in future work that seeks to explain and ultimately eliminate cancer disparities.

Figure 1. Geographic variation in structural racism and black-to-white cancer mortality disparities is illustrated across US metropolitan areas. Shown are (A) the spatial distributions of cancer mortality disparities and (B-D) 3 measures of structural racism in housing: (B) Racial bias in mortgage lending, (C) black isolation, and (D) dissimilarity. Category breaks on all maps represent quantiles, such that one-fifth of the metropolitan areas shown are represented by each color. However, to enhance interpretation, the lowest category (blue) for mortality disparities is adjusted such that blue areas represent places where blacks have equal or lower mortality than whites. In contrast, metropolitan areas where blacks have higher mortality rates than whites are shown in shades of red and yellow, with the darkest red indicating the largest disparity between blacks and whites. Of the 100 largest US metropolitan areas, information was available for all areas for structural racism measures and for all but 3 areas for mortality.





M. Bilal Abid, MD, MRCP (UK)

Assistant Professor
Divisions of Hematology & Oncology and
Transplant Infectious Diseases
Department of Medicine
Medical College of Wisconsin

I am an Assistant Professor of Medicine jointly with the divisions of Hematology/Oncology and Transplant Infectious Diseases. My clinical and translational research interests include hematological malignancies, stem cell transplantation, immunotherapy, CAR T-cells, and transplant infectious diseases. In a collaborative study involving basic scientists and clinicians from several disciplines, I am currently exploring the potential of the gut microbiome in enhancing the responses to engineered T-cell cancer therapy. I am also involved in research studies and clinical trials related to infections that develop after bone marrow transplantation and cellular therapy.

“Gut Microbiome and CAR-T Therapy”

Abid MB, Shah NN, Maatman TC, Hari PN. *Experimental Hematology & Oncology*. 2019;8:31. doi:10.1186/s40164-019-0155-8.

Considerable progress has been made in cancer therapeutics recently with targeted strategies that are efficacious and less toxic. Immunotherapy and chimeric antigen receptor (CAR) T-cells are increasingly being evaluated in a variety of tumors in the relapsed/refractory as well as frontline disease settings, predominantly in hematologic malignancies. Despite impressive outcomes in select patients, there remains significant heterogeneity in clinical response to CAR T-cells. The gut microbiome has emerged as one of the key host factors that could potentially be modulated to enhance responses to immunotherapy. Currently, it is unknown if gut microbiota modulates anti-tumor responses to CAR T-cells. Based on molecular and immunological understanding, we hypothesize that strategically manipulating gut microbiota may enhance responses to CAR T-cells. In this review, we further discuss resistance mechanisms to CAR T-cells in HM, potential approaches to overcome resistance by harnessing gut microbiota and other related novel strategies.

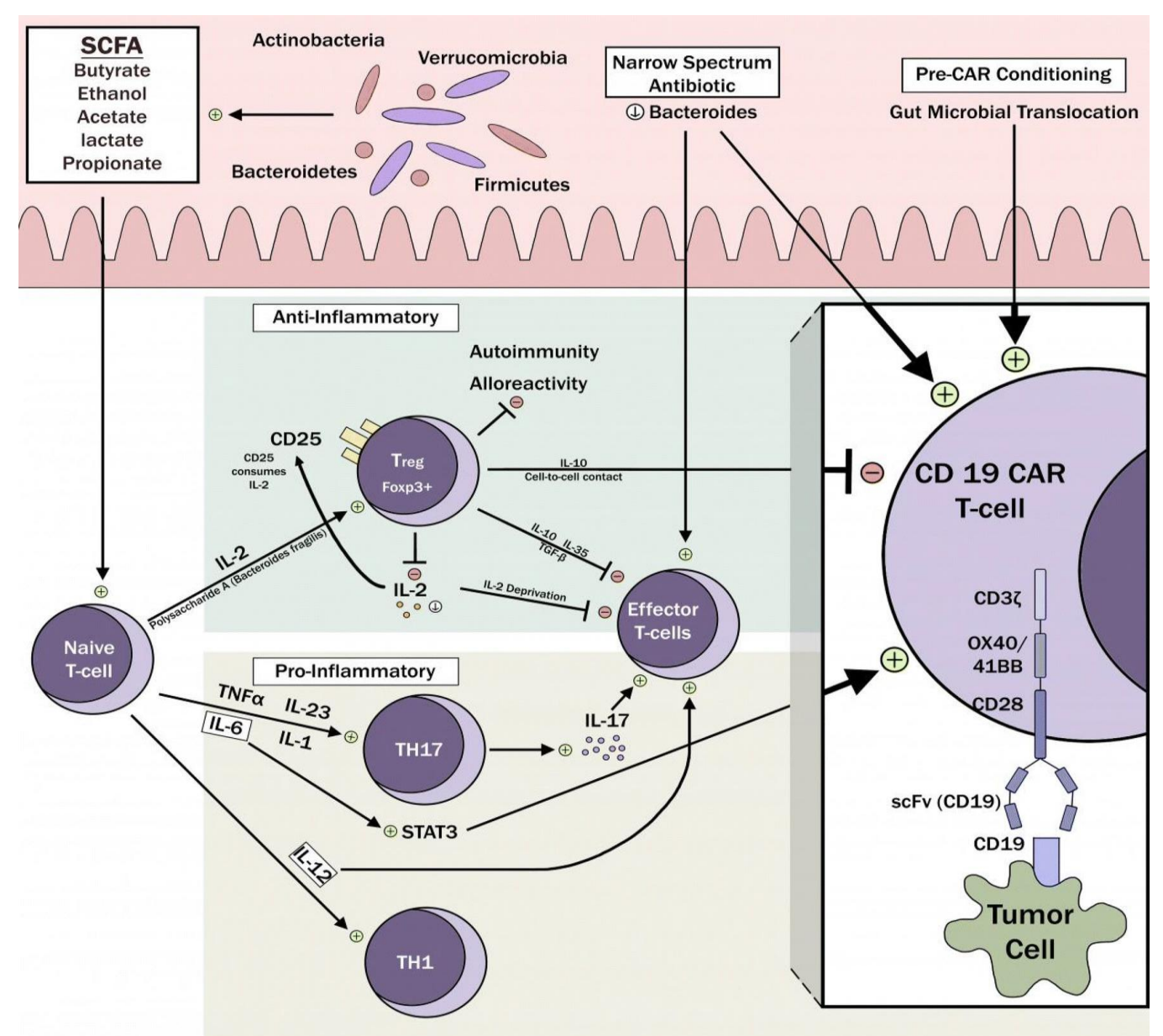


Figure 1. Gut microbiota mediates the differentiation of naive T-cells either into pro-inflammatory Th17 or anti-inflammatory, Tregs. These effector T-cells then migrate to systemic circulation from mLN. Th17 boosts effector T-cells, mainly mediated via IL-17, whereas Tregs suppress effector T-cell function, mediated via IL-10. Specific gut taxa may potentially be harnessed to enhance CAR T-cell responses in several ways (figure's left to right): By influencing pre-CAR conditioning; by using specific, narrow-spectrum antibiotics to deplete select, detrimental gut microbes; suppression of Foxp3+ Tregs and hence circumventing Treg-induced CAR T-cell suppression; upregulation of IL-6/STAT3 signature; direct activation of CAR T-cells (similar mechanism as that of endogenous T-cells)



Jennifer Gerardin, MD

Assistant Professor of Pediatrics
Division of Pediatric Cardiology
Medical College of Wisconsin

I am an Assistant Professor of Pediatrics in the Division of Cardiology. I completed training in combined Internal Medicine and Pediatrics, Pediatric Cardiology and Adult Congenital Heart Disease (ACHD). I currently care for both pediatric cardiology and ACHD patients as a part of the Wisconsin Adult Congenital Heart (WAtCH) program. The WAtCH program at MCW is an accredited Adult Congenital Heart Association comprehensive care center. During fellowship, most of my research interests were focused on transition and transfer of congenital heart disease (CHD) patients to adult care. Young adults who are lost to CHD care have worse long term outcomes compared to patients seen in referral centers. At the Herma Heart Institute, I am continuing this work by leading quality improvement efforts to reduce medication errors in ACHD patients.

“Lost in the System? Transfer to Adult Congenital Heart Disease Care- Challenges and Solutions”

Gerardin J, Raskind-Hood C, Rodriguez FH 3rd, et al. *Congenital Heart Disease*. 2019;14(4):541-548.

Our objective was to determine what percentage of CHD patients transferred to adult congenital cardiac care in Georgia using billing codes. Although most patients (76%) left pediatric cardiology care by 21 years old, only 12.1% of all patients transferred successfully to the referral affiliated adult hospital. Patients with severe disease (18.7%) were more likely to transfer to adult congenital heart disease care than nonsevere disease (6.2%). Most CHD patients did not transfer to adult congenital

cardiology care with distance to referral center being a contributing factor. Higher percent of uninsured in Georgia after 18 years old may have contributed to the higher number of patients lost to cardiology care compared to other states. Both pediatric and adult providers need to understand and address barriers in order to improve successful transfer.

Figure 1. Inclusion and exclusion criteria for study cohort.

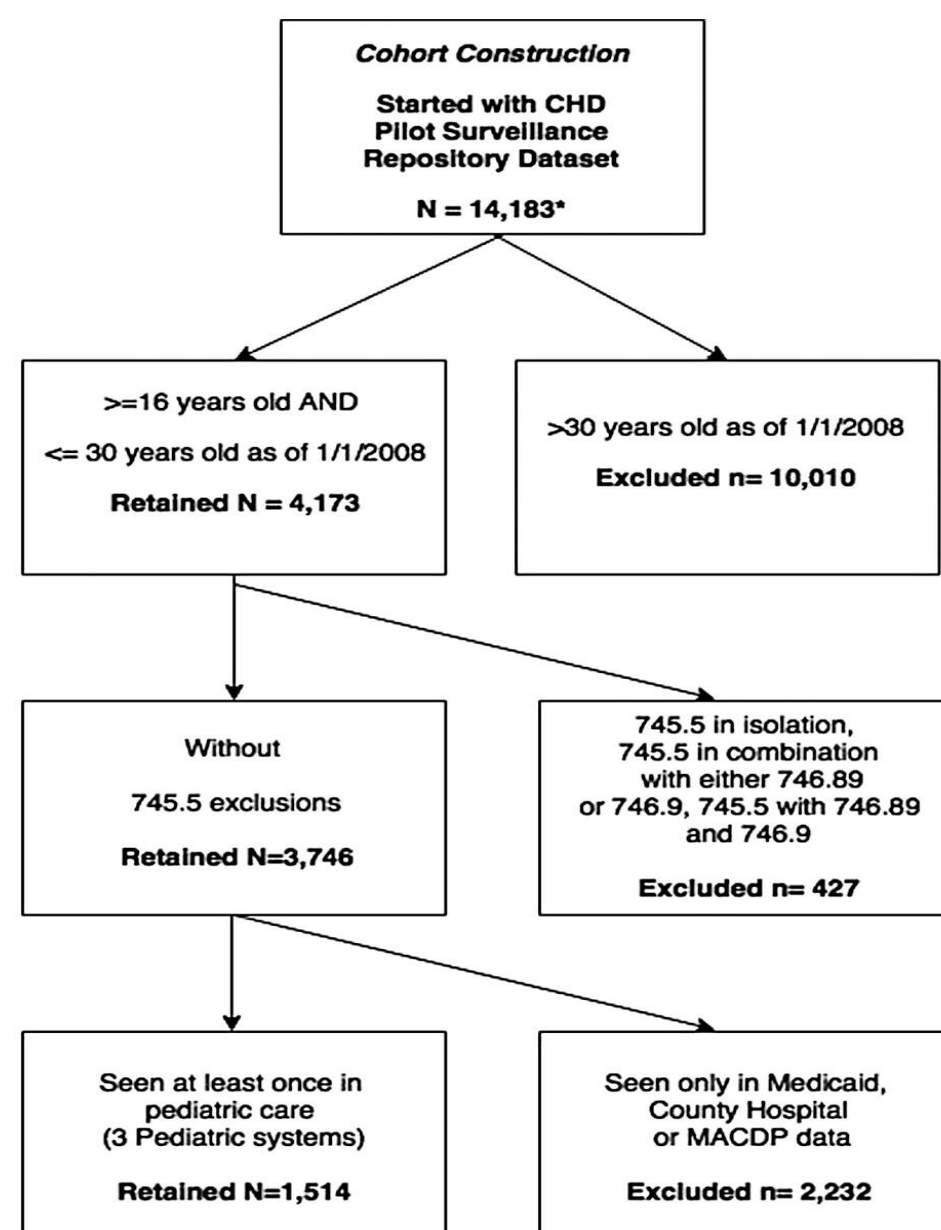
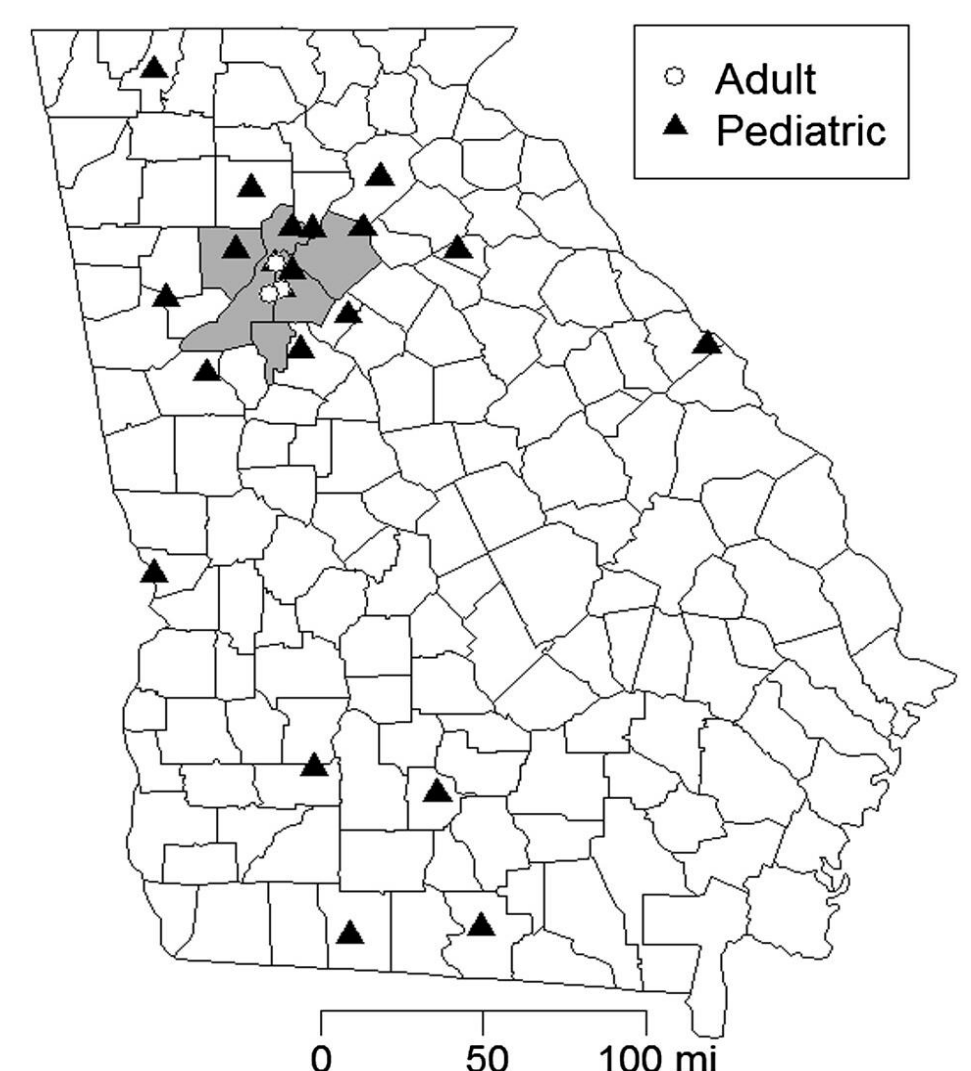


Figure 2. Locations of the studied pediatric cardiology clinics and adult congenital cardiology clinics in Georgia.



“Subcutaneous Emphysema and Vocal Fold Paresis as a Complication of a Dental Procedure”

North L, Sulman C. *International Journal of Pediatric Otorhinolaryngology*. 2019;124:76-78.

This case report details a patient with vocal cord paresis associated with significant iatrogenic subcutaneous emphysema. He originally presented to Children’s Wisconsin after having undergone third molar extraction with a turbine drill by an outside provider. During the procedure he developed significant cervicofacial subcutaneous emphysema with extension to the bilateral carotid visceral spaces and mediastinum. Treatment included intubation for airway protection, followed by transoral drainage of emphysema and intravenous antibiotics. Weeks after discharge, the patient reported persistent dysphonia and was discovered to have left vocal fold paresis. This was likely related to extensive pneumomediastinum causing irritation and/or injury to the recurrent laryngeal nerve. After a period of clinical monitoring, he underwent injection laryngoplasty with successful return of normal vocal. This is the first ever reported case of cervicofacial emphysema leading to vocal cord paresis after third molar extraction.

Lauren North, MD

Resident, PGY-3

Department of Otolaryngology



Kristin K. Magner, MSN, RN, CPNP-AC/PC, APNP

Advanced Practice Provider, W5 APP Clinical Lead
Pediatric Critical Care

“Understanding Mothers’ Perception of Child’s Illness: Adapting the CONNECT Instrument for Pediatrics”

Magner K, Bragg D, Treat R, Lee KJ. *Journal of Clinical Nursing*. 2019;28(17-18):3279-3287.

The primary objective of this study was to expand the applicability of the CONNECT Instrument to situations and populations beyond its initial conception. Secondly, we wanted to see if the discrepancies noted in the perceptions of illness that were seen in the original study were maintained in a different patient population and in a different healthcare setting. The results of our study indicate that not only is CONNECT for Pediatrics valid, but could also serve to illuminate the variation in perception that does exist between providers and parents.

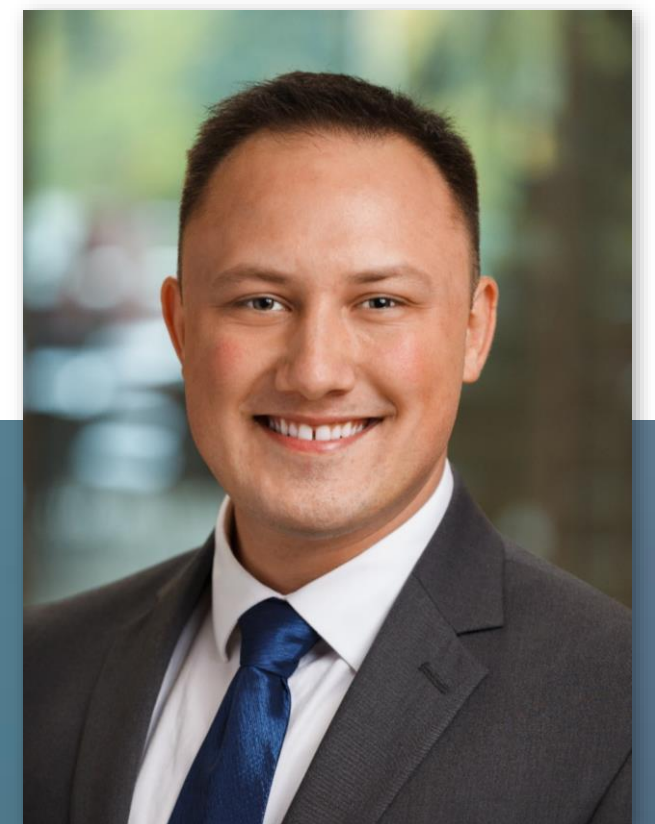
“Salt-sensitive Increase in Macrophages in the Kidneys of Dahl SS Rats”

Fehrenbach DJ, Abais-Battad JM, Dasinger JH, Lund H, Mattson DL. *American Journal of Physiology. Renal Physiology*. 2019;317(2):F361-F374.

Hypertension, or an elevated blood pressure, remains the number one modifiable risk factor for cardiovascular disease in which the role of immune system activation is becoming increasingly apparent. We used the Dahl SS rat, an animal model that recapitulates many of the phenotypes observed in human hypertensives who have salt-sensitivity of their blood pressure to investigate how macrophages, cells in our innate immune system, change when dietary salt is increased. We found that there is pronounced infiltration of macrophages into the kidney of these rats when on a high-salt diet and that these cells are skewed toward being pro-inflammatory.

Daniel Fehrenbach, PhD

Graduate, MCW Grad School
Department of Physiology



Anne Waniger

MD Candidate, Class of 2020
Department of Psychiatry

“Community and Caregiver Perceptions of Giving Care to Seniors”

Waniger A, Gale K, DeNomie M, Nelson D. *International Journal of Psychiatry in Medicine*. 2019;54(4-5):307-315.

Family caregivers of seniors and disabled adults frequently bear the responsibility of aiding in instrumental activities of daily living and locating resources, often while raising their own families. In this study, twenty-eight current and former unpaid caregivers of seniors participated in four separate focus groups to help us better understand the journey of family caregivers and identify opportunities for improvement across organizations, policies, systems, and teams. Focus groups indicated an urgent need to identify and support unpaid caregivers earlier in their trajectory of caring for a senior and to provide consistent, right-time resources over the trajectory of the senior’s lifespan.

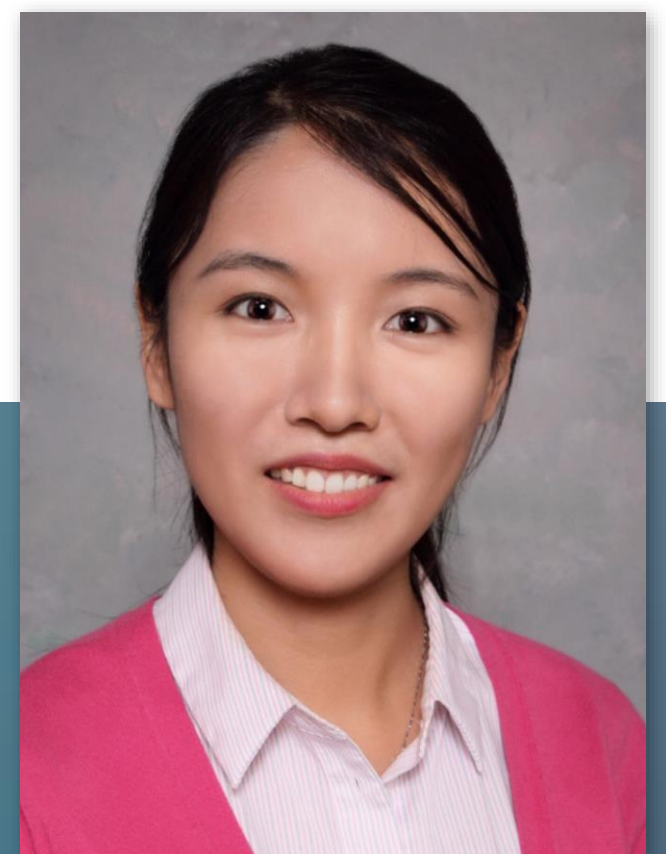
“Texture-based, Automatic Contour Validation for Online Adaptive Replanning: A Feasibility Study on Abdominal Organs”

Zhang Y, Plautz TE, Hao Y, Kinchen C, Li XA. *Medical Physics*. 2019;46(9):4010-4020.

Evaluation of contour accuracy in radiotherapy planning requires manual interaction and is one of the most limiting bottlenecks for online adaptive replanning (OLAR). In this study, we developed an automatic approach to rapidly evaluate organ contour quality based on quantitative image texture features. The feasibility and effectiveness are demonstrated using pancreas head and duodenum contours from daily CTs acquired during radiotherapy. Our model accurately classifies unseen contours as accurate or inaccurate with high sensitivity and specificity. This method may be integrated into a fully automatic pipeline for auto-segmentation, contour quality evaluation and contour correction, facilitating the routine practice of OLAR.

Ying Zhang, PhD

Medical Physics Assistant
Department of Radiation Oncology



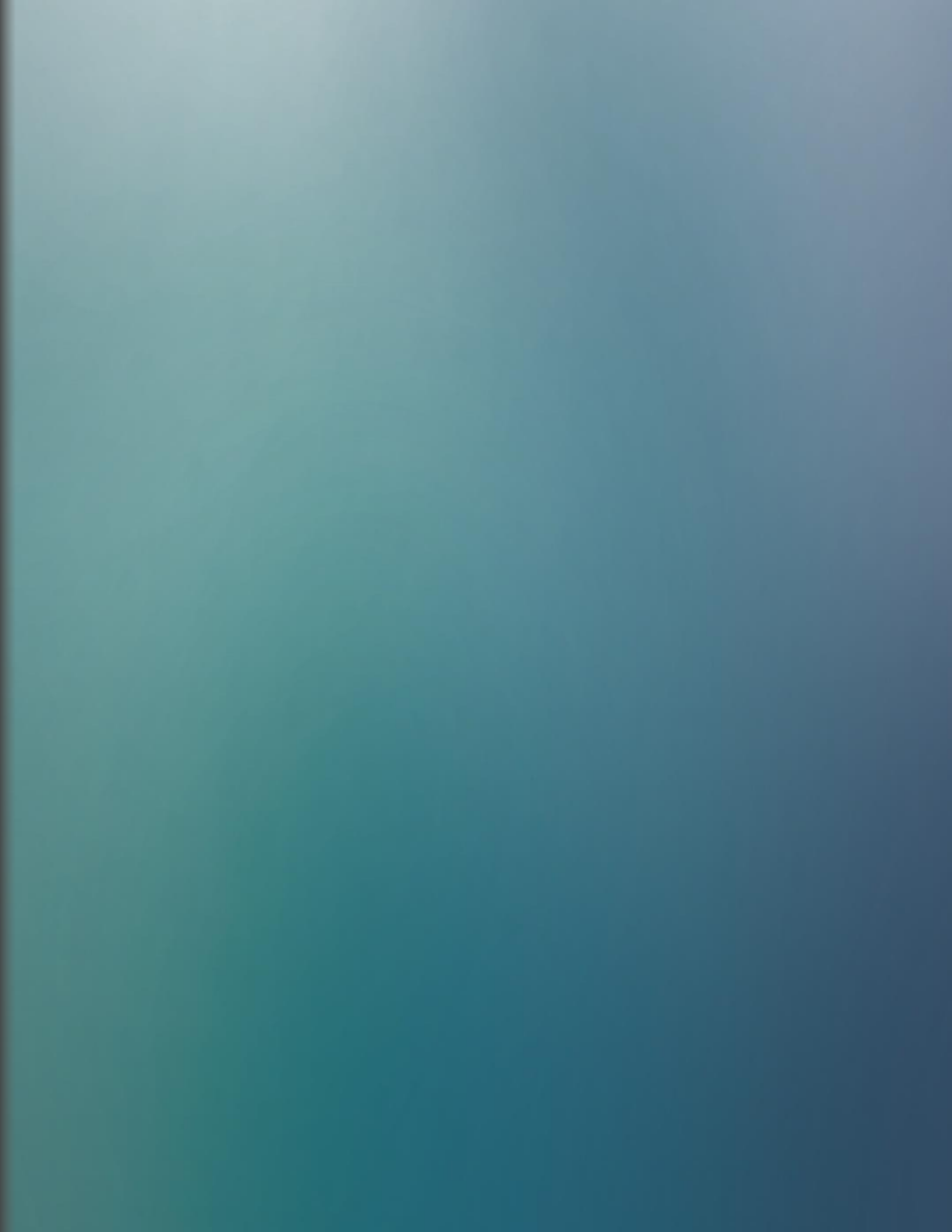
Amornluck Krasaelap, MD, FAAP

Resident
Department of Pediatrics

“Nutrition Management in Pediatric Gastrointestinal Motility Disorders”

Krasaelap A, Kovacic K, Goday PS. *Nutrition in Clinical Practice*. 2020. 10.1002/ncp.10319

Gastrointestinal (GI) motility disorders are associated with suboptimal nutrition in children, mainly because of malabsorption and symptoms limiting dietary intake. Nutrition support has a crucial role in maintaining growth and improving clinical outcomes in children. Based on recent data and guidelines, this review provides an overview of nutrition assessment and specific interventions for common pediatric GI disorders including gastroesophageal reflux disease, esophageal motility disorders, gastroparesis, chronic intestinal pseudo-obstruction, and constipation. Several approaches including diet modification, enteral nutrition (gastric vs post-pyloric, temporary vs permanent access, bolus vs continuous), and parenteral nutrition need to be tailored based on patient's nutrition and clinical assessment.





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