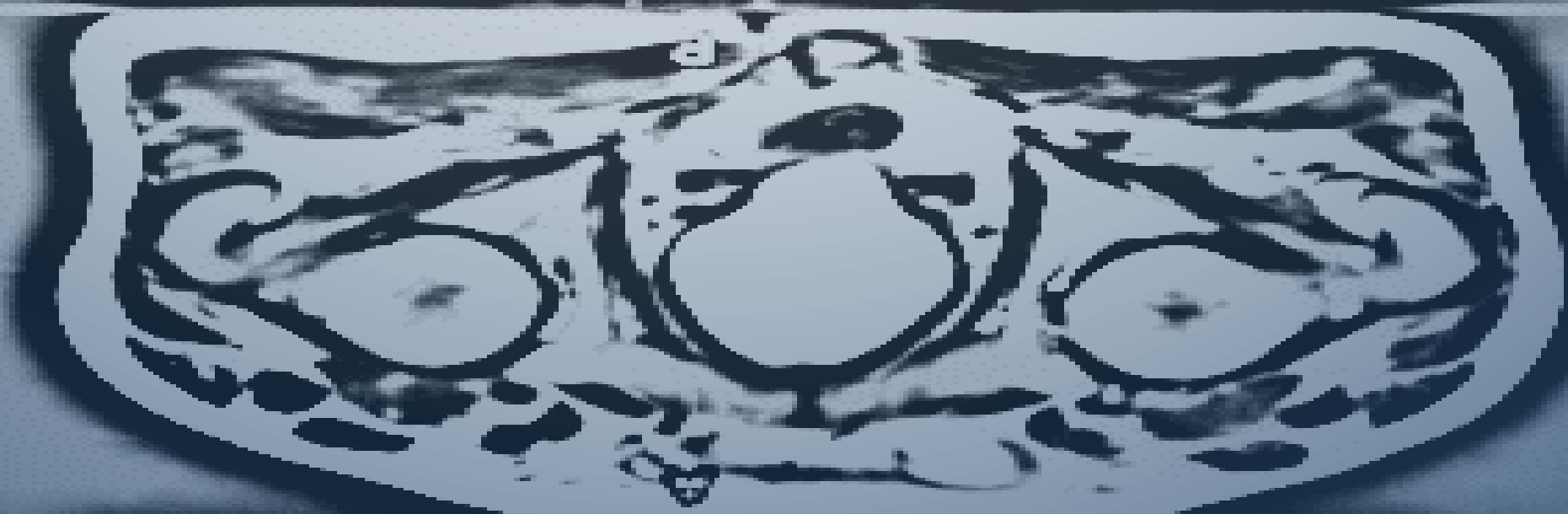
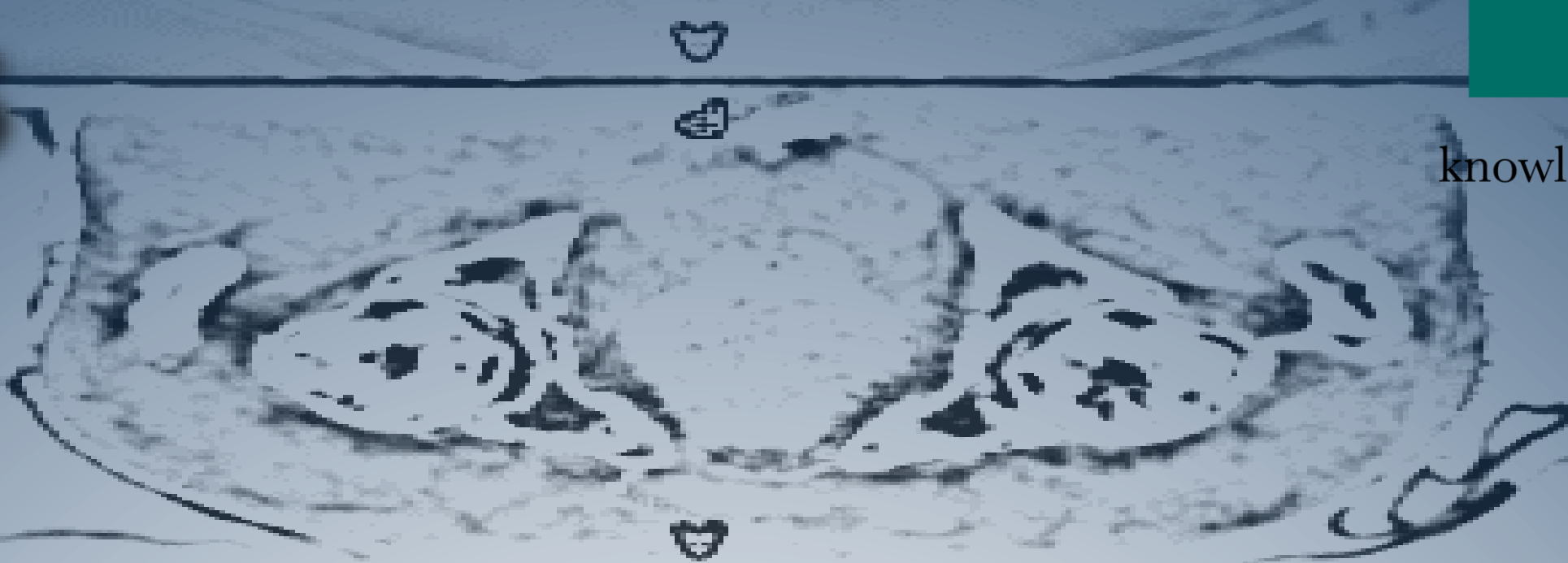


# Research Publication Series

June 2019



knowledge changing life



## 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.



MCW Collaborative Highlights, indicated with the puzzle piece icon, call out articles that are produced by multidisciplinary teams. These articles represent collaborative efforts between researchers from different departments, centers, divisions, or fields of study.



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## Publication Stats: June 2019

Publication Type	May Total
Articles	130
Editorial Material	12
Reviews	19
<b>Total</b>	<b>161</b>

Publications in Top Quartile Journals
<b>118 out of 161 (73.3%)</b>

Total Publications Fiscal Year to Date:
<b>1,517</b>

Publication stats are pulled by the MCW Libraries for the previous month using the Science Citation Index and Social Sciences Citation Index. For inclusion, one or more authors must be institutionally affiliated with MCW. Letters and abstracts are excluded from the data. The MCW Fiscal Year runs from July 1 – June 30.

Research Publication Series:  
**June 2019**

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**Michael Andrew Kron, MD, MScCTM, FACP**

"Persistence of Schistosoma japonicum DNA in a Kidney-Liver Transplant Recipient" 

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**Peter Frommelt, MD, FACC, FAHA, FASE**

"Impact of Initial Shunt Type on Echocardiographic Indices in Children After Single Right Ventricle Palliations: The SVR Trial at 6 Years"

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**Ergun Ahunbay, PhD**

"A Technique to Rapidly Generate Synthetic Computed Tomography for Magnetic Resonance Imaging-Guided Online Adaptive Replanning: An Exploratory Study"

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**Michael Muriello, MD**

"Growth hormone deficiency, aortic dilation, and neurocognitive issues in Feingold syndrome 2"

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"Adipose-only sentinel lymph nodes: a finding during the adaptation of a sentinel lymph node mapping algorithm with indocyanine green in women with endometrial cancer" 

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Cover Image from "A Technique to Rapidly Generate Synthetic Computed Tomography for Magnetic Resonance Imaging-Guided Online Adaptive Replanning: An Exploratory Study"



I am a Professor of Medicine in the Division of Infectious Diseases. My professional research interests have been for more than 30 years in the areas of tropical medicine and parasitology, global health, host-parasite interactions and the structure and function of parasite tRNA synthetases, novel immunomodulators evolved by parasites to evade the host immune response.

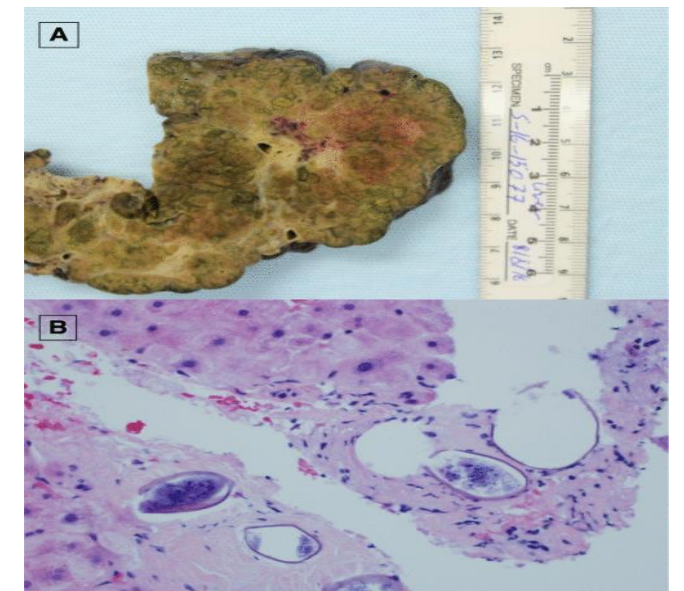
## Michael Andrew Kron, MD, MScCTM, FACP

Professor  
Division of Infectious Disease  
Department of Medicine  
Medical College of Wisconsin

### “Persistence of *Schistosoma japonicum* DNA in a Kidney-Liver Transplant Recipient”

Kron M, Gordon C, Bauers T, et al. *American Journal of Tropical Medicine and Hygiene*. 2019;100(3):584-587.

Schistosomiasis is a tropical parasitic disease that affects more than 250 million people worldwide. We applied knowledge of variations in the schistosome NADH1 mitochondrial gene to study a patient we diagnosed with schistosomiasis. The patient had not visited schistosomiasis-endemic countries for more than 35 years and had no idea where she became infected. Unusual clinical features included the absence of egg granulomas in tissue and persistence of noncalcified eggs that appeared viable despite multiple praziquantel (PZQ) treatments over 7 years. DNA sequence analysis of parasite DNA obtained from colonoscopy biopsies that contained eggs, revealed that it was a Philippine strain of *S. japonicum*. Future studies using stored DNA may provide new insight into why some persons do not respond well to PZQ, the only drug available to treat this disease.



**Figure 1.** (A) Gross appearance of explanted liver from patient with *Schistosoma japonicum* infection. (B) Histological findings in liver and subsequent colon biopsies demonstrated noncalcified ova without granuloma formation (magnification  $\times 400$ ).



**Figure 2.** (A) Phylogenetic tree constructed using the maximum likelihood method to compare *Schistosoma japonicum* strains based on mitochondrial NADH1 sequences. Included in this comparison are sequences from the patient, *S. japonicum* from China (Hunan, Jiangxi) and the Philippines (Sorsogon, Mindoro, Leyte), *Schistosoma mekongi*, *Fasciola gigantica*, and *Schistosoma bovis*. The phylogenetic tree demonstrates that the patient’s parasite is most closely related to *S. japonicum*. This method does not take into account the single-nucleotide polymorphisms used to design PCR primer pairs (SJ1 and SJ2) that distinguish between the Chinese and Philippine strains of *S. japonicum*. Accession numbers are listed for each strain at the left of the sequence. (B) DNA sequence alignments representing *S. japonicum* strains from China (Jiangxi, Hunan) and the Philippines (Leyte, Sorsogon, Mindoro) compared with the DNA sequence obtained from the patient. Single-nucleotide polymorphisms (highlighted in gray) in specific regions of the NADH1 dehydrogenase one mitochondrial gene allow for the design of PCR primer sets that differentiate Chinese *S. japonicum* from *S. japonicum* found in the Philippines. Accession numbers are listed at the left of each sequence. (C) Agarose gel electrophoresis of PCR products identified *S. japonicum* DNA in two of three colonoscopy biopsy samples (lanes 3 and 4) using SJ2 primers but no amplicons were generated using SJ1 primers (lanes 5, 6, and 7) that are specific for Chinese *S. japonicum*. Lane 1 contains positive control PCR products using SJ2 primers with Philippine *S. japonicum*, and Lane 8 shows positive control PCR products obtained with SJ1 primers and *S. japonicum* DNA from China. DNA molecular weight markers are displayed on the far left.



**Peter Frommelt, MD, FACC,  
FAHA, FASE**

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

Director of Pediatric Echocardiography  
Children's Hospital of Wisconsin

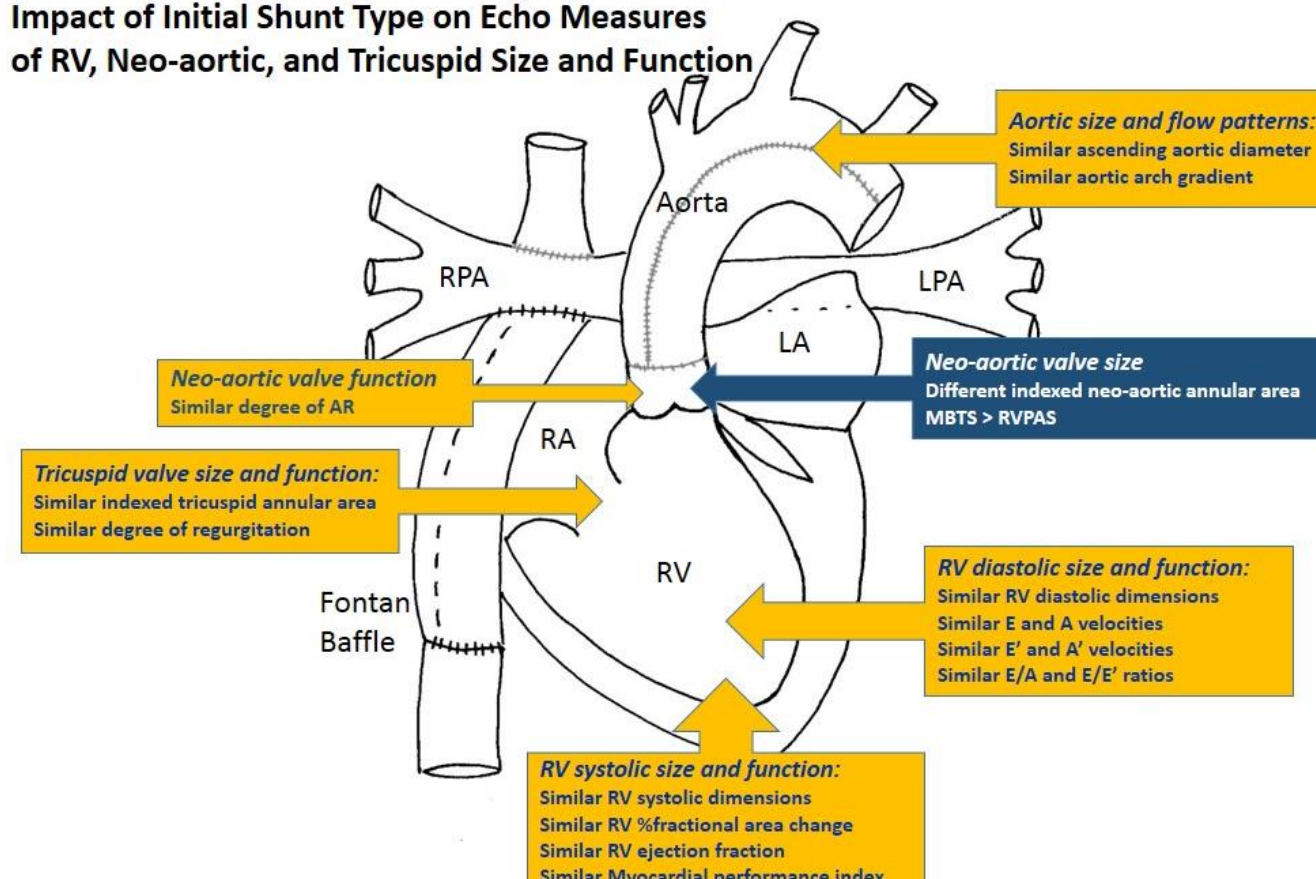
I am a pediatric cardiologist in the Herma Heart Institute at CHW and Professor of Pediatrics for the Division of Pediatric Cardiology at MCW. I am Director of Pediatric Echocardiography (since 1991) at CHW and Director of the Pediatric Echocardiography Core Research Laboratory (since 2004) at MCW. I have had extensive involvement with the NIH through the Pediatric Heart Network, as our Echocardiography Research lab has served as the core lab for several Pediatric Heart Network-initiated multicenter trials involving echocardiography, with longitudinal studies specifically focused on echocardiographic assessment of the infant and child with single ventricle heart disease. My focus of practice and research has always been on understanding and optimizing clinical outcomes of pediatric heart disease.

**“Impact of Initial Shunt Type on Echocardiographic Indices in Children After Single Right Ventricle Palliations: The SVR Trial at 6 Years”**

Frommelt PC, Hu C, Trachtenberg F, et al. Circulation. Cardiovascular Imaging. 2019;12(2):e007865.

The Single Ventricle Reconstruction (SVR) trial sought to answer a critical question in surgical management of infants with Hypoplastic Left Heart Syndrome undergoing a Norwood procedure: which shunt (the right-ventricular-to-pulmonary-artery shunt or modified Blalock-Taussig shunt) was associated with better outcomes? After 6 years of longitudinal follow-up, that answer remains unclear. This report summarizing the echocardiographic characteristics of the SVR cohort supports the notion that neither shunt is unequivocally superior, with no shunt-related survivor benefit at 6 years. Specifically, we found that initial shunt type did not significantly impact echocardiographic indices of right ventricular, neo-aortic, and tricuspid valve size and function. Encouragingly, these data suggest that there is actually beneficial remodeling of right ventricular size/function, and neo-aortic and tricuspid valve size/function over time, regardless of shunt type.

**Hypoplastic Left Heart Syndrome at 6 years after Surgical Palliations—  
Impact of Initial Shunt Type on Echo Measures  
of RV, Neo-aortic, and Tricuspid Size and Function**





## Ergun Ahunbay, PhD

Associate Professor  
Medical Physicist  
Department of Radiation Oncology  
Medical College of Wisconsin

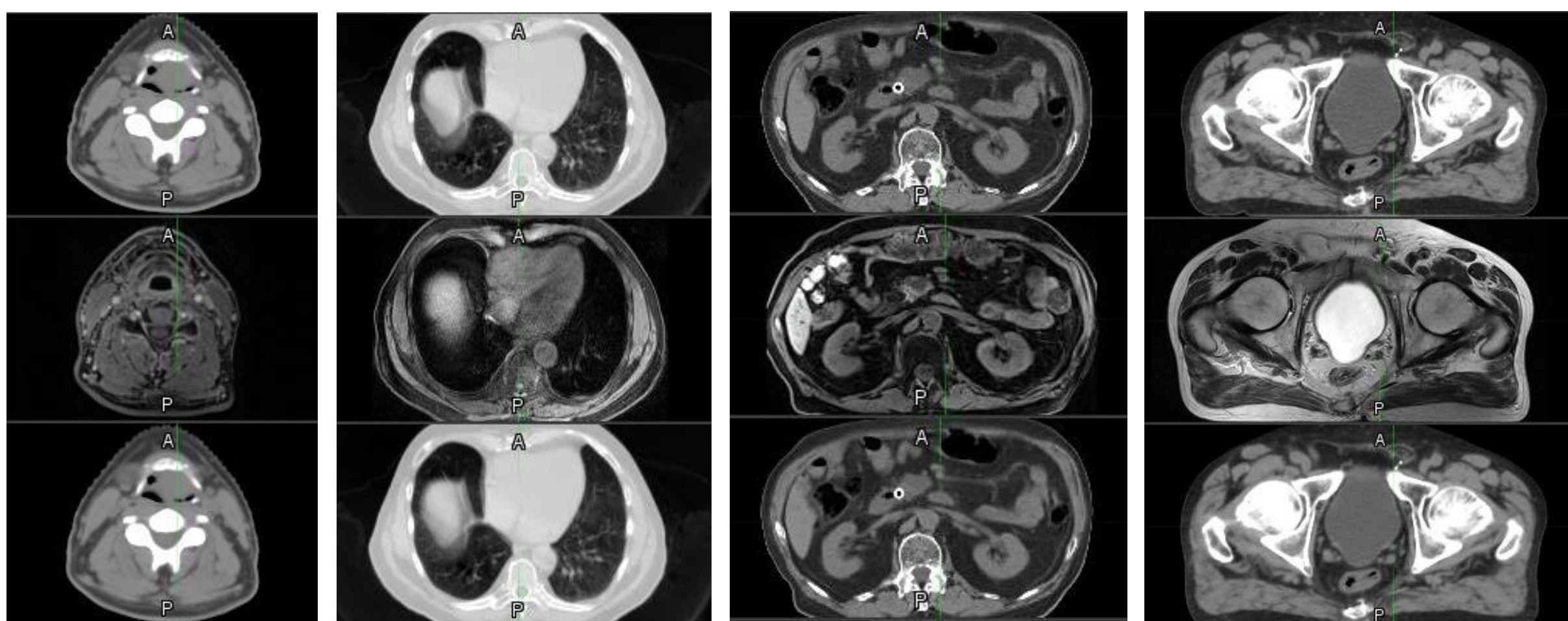
I am a medical physicist working at the department of Radiation Oncology. I have been working in this profession since the last 16 years. My research interests are Image Guided Radiation Therapy, Adaptive Radiotherapy, Magnetic Resonance Guided Radiotherapy. I also work clinically as well as on research and working on improving the accuracy and quality of delivery of radiation dose to tumors.

## “A Technique to Rapidly Generate Synthetic Computed Tomography for Magnetic Resonance Imaging-Guided Online Adaptive Replanning: An Exploratory Study”

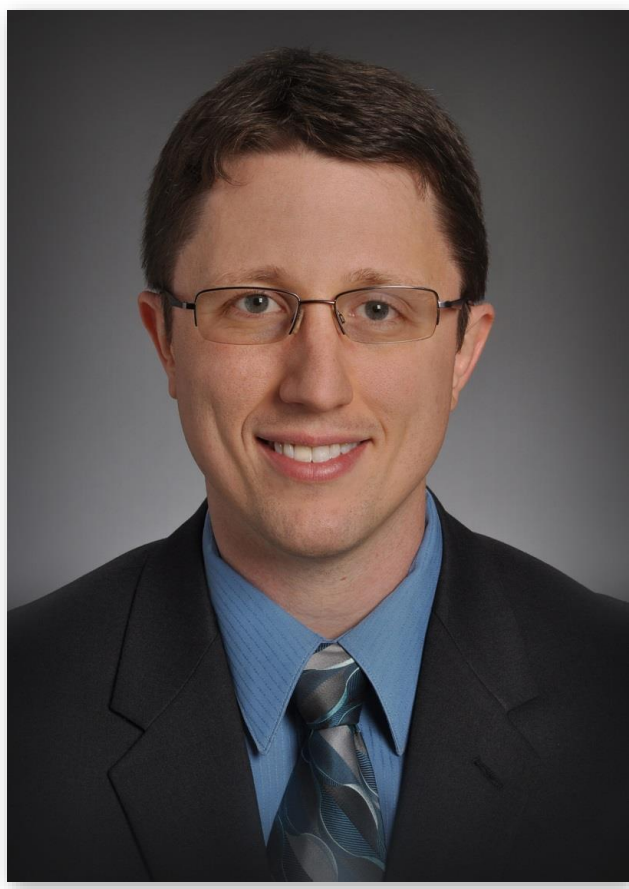
Ahunbay EE, Thapa R, Chen X, Paulson E, Li XA. *International Journal of Radiation Oncology, Biology, Physics*. 2019;103(5):1261-1270.

In this research we tried to generate an automatic and accurate method to generate Computed Tomography (CT) images from Magnetic Resonance images that are acquired on the MR-Linac. CT images are needed for calculating the doses and perform adaptive replanning on the daily anatomy. We used an atlas based method which uses CT images of the same patient acquired at an earlier time. A major challenge was the air pockets that occurs in the body randomly, which were handled by some thresholding method. We were able to generate CT images, that were able to reach very high dosimetric accuracy while can be performed fully automatically.

**Figure 2.**



The axial images from different image sets: Columns from left to right: Head and Neck, Thorax, Abdomen, and Pelvis. The rows from top to bottom: Reference CT, Daily MR, Synthetic CT generated from daily MR.



## Michael Muriello, MD

Assistant Professor  
Division of Genetics  
Department of Pediatrics  
Medical College of Wisconsin

I am an Assistant Professor of Pediatrics at the Medical College of Wisconsin and a medical geneticist specializing in rare and undiagnosed disease and genomic research. I attended Rush Medical College and went on to conduct a fellowship in Medical Genetics at the Johns Hopkins University School of Medicine.

## “Growth hormone deficiency, aortic dilation, and neurocognitive issues in Feingold syndrome 2”

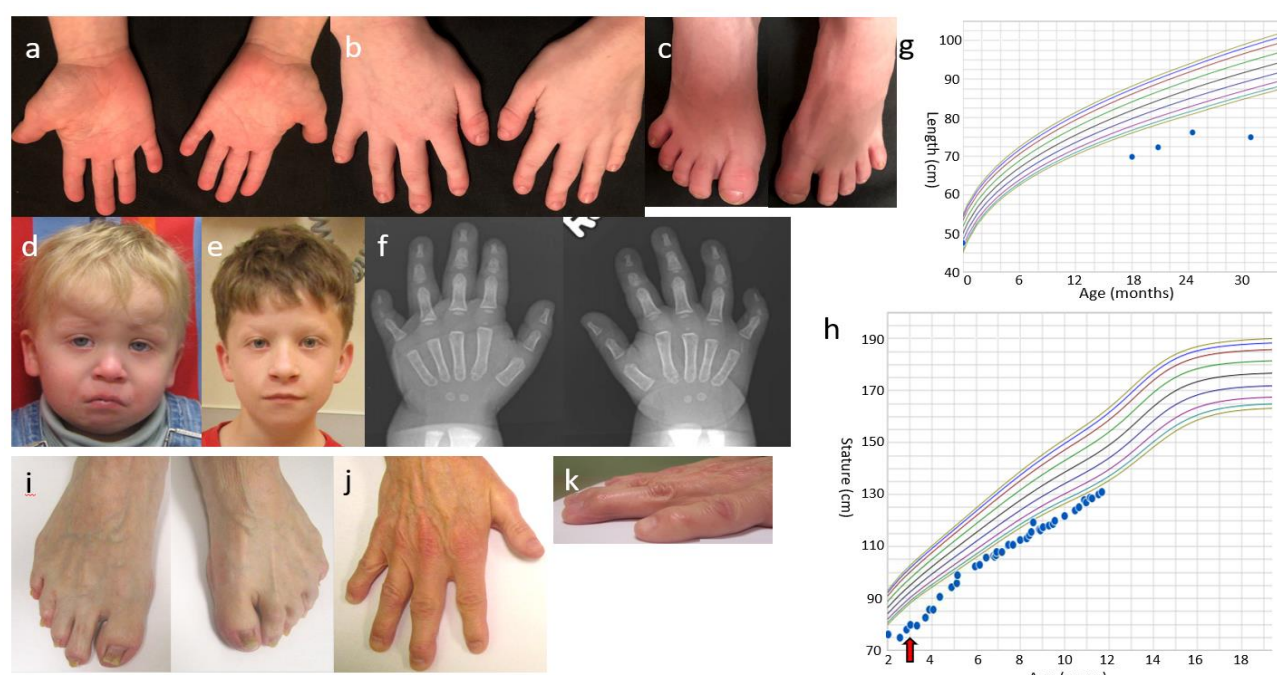
Muriello M, Kim AY, Sondergaard Schatz K, Beck N, Gunay-Aygun M, Hoover Fong JE. *American Journal of Medical Genetics, Part A*. 2019;25(1): 73-85.

We report three cases of Feingold 2 syndrome with the novel features of growth hormone deficiency associated with adenohypophyseal compression, aortic dilation, and phalangeal joint contractures, in addition to the typical features of microcephaly, brachymesophalangy, toe syndactyly, short stature, and cardiac anomalies. Microdeletions of chromosome 13q that include the MIR17HG gene were found. One of the patients was treated successfully with growth hormone. These three patients expand the phenotype of Feingold 2 syndrome.

**Table 1. Summary of clinical features of the patients reported herein in addition to the patients FG2 reviewed previously**

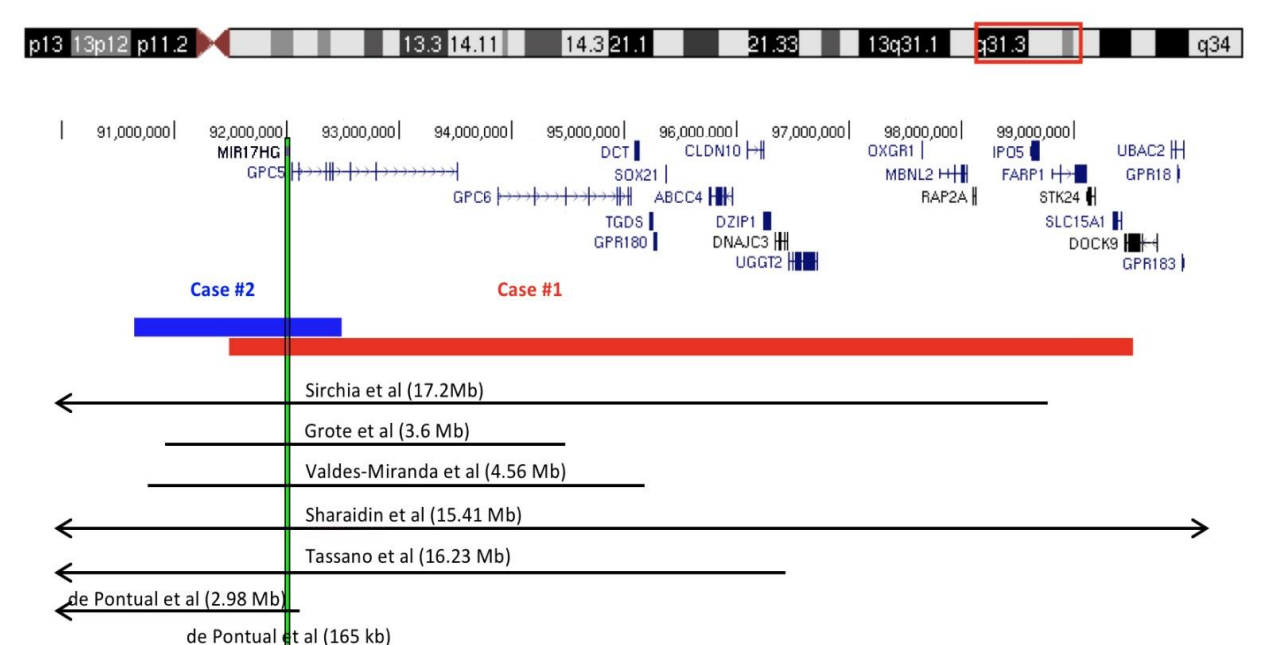
Features	Patient 1	Patient 2	FG2	FG1
Deletion Size	8 Mb	1.84 Mb	165 kb to 17.2 Mb	Deletions/duplications in 10%
Gender	Male	Male	6M:11F reported	
Microcephaly	Y	Y	94% (15/16)	89%
Short stature	Y	Y	93% (13/14)	60%
DD/ID/LD	Y	Y	100% (16/16)	51%
Brachymesophalangy	Y	Y	100% (17/17)	100%
5th finger clinodactyly	Y	Y	100% (9/9)	100%
Thumb hypoplasia	N	N	33% (4/12)	17%
Toe Syndactyly	N	Y	64% (9/14)	97%
Gastrointestinal atresia	N	N	0% (0/18)	55%
Cardiac defect	Y*	Y**	40%*** (4/10)	15%
Deafness/hearing deficit	N	N	2/3 reported	10%
Keratoconus	N	N	1 patient	NR
Strabismic amblyopia	N	Y	1 patient	NR
Compressed adenohypophysis	Y	N	1 patient	NR
Memory impairment	N	Y	1 patient	NR
Insomnia	N	Y	1 patient	NR

**Figure 1.**



Patient 1's hands (a,b), feet (c), profile age 2 years 5 months (d), age 10 years 11 months (e), hand radiographs (f), and growth charts (g: infant 0–24 months, h: child 2–12 years). Red arrow indicates initiation of GH therapy. Feet (i) and hand (j,k) of patient 3.

**Figure 3.**



Schematic representation of the deletions identified in Patients 1 and 2 and the genes in the region (only those with OMIM phenotype are included), above the deletions reported in the literature. The vertical bar shows the location of MIR17HG.



## Vikash Kumar, PhD

Instructor

Department of Physiology

Medical College of Wisconsin

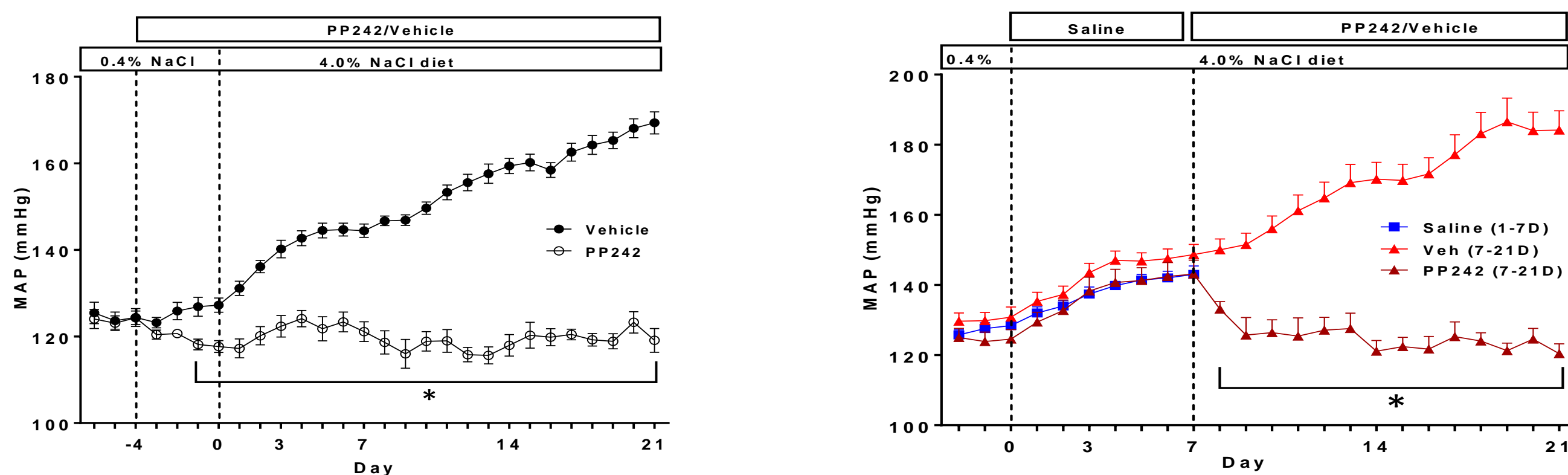
My research interests are primarily focused on cardiovascular disease, with a particular interest in the role of mTOR signaling in salt-sensitive hypertension and Pappa2 gene in kidney development and functional consequences on hypertension. I used combination of molecular and renal physiological studies to understand the mechanisms by which mTOR signaling contributes primary cause and/or a secondary consequence of salt-induced hypertension. My current research is utilizing genetically modified Dahl salt-sensitive rats and applying several laboratory skills such as immunohistochemistry, in situ hybridization, fluorescent microscopy, and ex vivo kidney culture to determine the role of Pappa2 in nephrogenesis and nephron number. This study will enable me to develop a novel genetic rat model to examine the functional consequence of low nephron number on hypertension and kidney disease.

## “Therapeutic Suppression of mTOR (Mammalian Target of Rapamycin) Signaling Prevents and Reverses Salt-Induced Hypertension and Kidney Injury in Dahl Salt-Sensitive Rats”

Kumar V, Evans LC, Kurth T, et al. *Hypertension*. 2019;73(3):630-639.

Mammalian target of rapamycin complex 2 (mTORC2) pathway is involved in the regulation of renal tubular sodium and potassium transport but its role in hypertension has remained largely unexplored. In our recent publication we used PP242 drug to inhibit mTORC2 and found that it not only completely prevented but also reversed salt-induced hypertension and kidney injury in Dahl salt-sensitive (SS) rats. PP242 exhibited potent natriuretic actions and chronic administration tended to produce a negative Na<sup>+</sup> balance even during high salt feeding. The results indicate that mTORC2 and the related downstream associated pathways play an important role in regulation of sodium balance and arterial pressure regulation in SS rats. Therapeutic suppression of the mTORC2 pathway represents a novel pathway for the potential treatment of hypertension.

Figure 1.



**LEFT:** Mean arterial pressure (MAP; 24 hrs average) was measured by telemetry in rats fed a 0.4% NaCl diet for 7 days the final 4 days of which rats were treated with PP242 or vehicle prior to switching to 4.0% NaCl diet for 21 days. Open circles represent PP242 (n=7) and black circles represent vehicle (n=7) treated SS rats. **RIGHT:** MAP was measured by telemetry in rats fed a 4.0% NaCl diet for 7 days treated with saline (blue square, n=6) and then treated with PP242 (brown triangle, n=7) or vehicle (red triangle, n=7) for 14 days. \* Significant difference between vehicle and PP242 treated SS rats ( $p < 0.05$ ) as determined using a two-way RM ANOVA; Holm-Sidak post hoc.



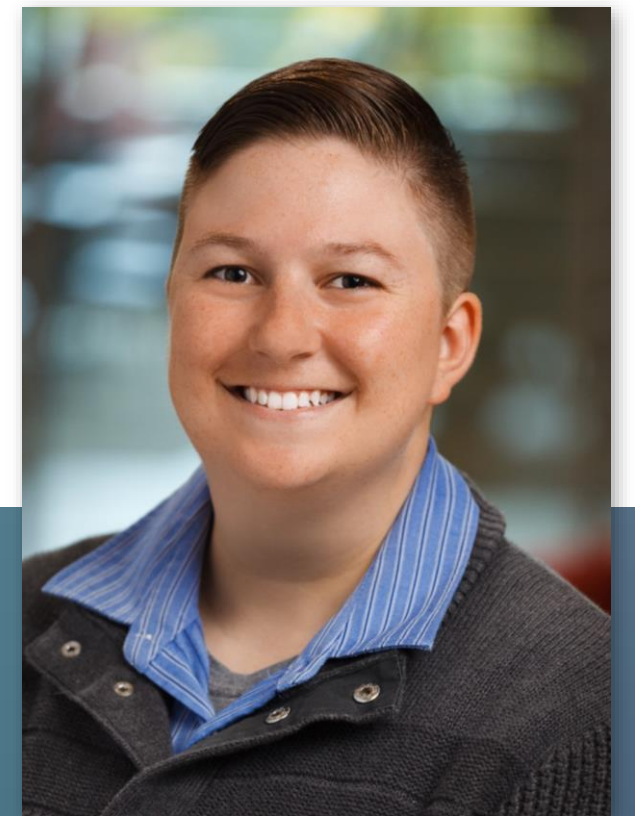
## “miR-21-5p regulates mitochondrial respiration and lipid content in H9C2 cells”

Nasci VL, Chuppa S, Griswold L, Goodreau KA, Dash RK, Kriegel AJ. *American Journal of Physiology. Heart & Circulatory Physiology*. 2019;316(3):H710-H721.

Cardiovascular-related pathologies are the leading cause of death in chronic kidney disease (CKD) patients. Previously, we found that a rat model of CKD has augmented microRNA miR-21-5p levels in the left ventricle, which negatively regulates peroxisome proliferator-activated receptor- $\alpha$  and alters transcripts involved with fatty acid oxidation and glycolysis. In this study we evaluated the potential for miR-21-5p manipulation to regulate lipid content, lipid peroxidation, and mitochondrial respiration in H9C2 cardiac cells. Our results indicate that overexpression of miR-21-5p reduces lipid content and lipid peroxidation. This likely occurs by reducing lipid uptake and shifting cellular metabolism toward reliance on glycolysis.

### Victoria Nasci

Graduate Student  
Department of Physiology  
Kriegel Lab



### Ashima Singh, PhD, MS

Research Scientist  
Department of Pediatrics  
Division of Hematology/Oncology/BMT

## “Use of the new pediatric PROMIS measures of pain and physical experiences for children with sickle cell disease”

Singh A, DasGupta M, Simpson PM, Panepinto JA. *Pediatric Blood & Cancer*. 2019;66(5):e27633.

The Patient-Reported Outcomes Measurement Information System (PROMIS) recently added new domains to assess pain and physical functioning in the pediatric population. Our study objective was to establish psychometric properties of the new PROMIS domains for children with sickle cell disease (SCD). Validity of the new domains was determined by comparing scores between known groups and describing their correlations with previously validated PROMIS measures. We determined reliability using Cronbach's alpha and item response theory reliability. Our results show that new PROMIS domains of pain behavior, pain quality(sensory), physical stress experience and strength impact are valid and reliable for children with SCD.

## “Staphylococcal Superantigen-like protein 11 mediates neutrophil adhesion and motility arrest, a unique bacterial toxin action”

Chen C, Yang C, Barbieri JT. *Nature Scientific Reports*. 2019;9(4):4211.

Methicillin resistant *Staphylococcus aureus* (MRSA) is a major human pathogen. Neutrophils are the most abundant leukocytes in the blood and are the first defense mechanism against *S. aureus* infections. Here we show Staphylococcal Superantigen-Like protein 11 (SSL11) from MRSA mediated differentiated human neutrophil-like cells (dHL60) motility arrest by inducing cell adhesion and "locking" cells in adhesion stage, without inducing oxidative burst. This is the first description of a bacterial toxin inhibiting neutrophil motility by inducing adhesion and "locking" cells in an adhesion stage. Therefore, this study might provide a new target against *S. aureus* infections.

### Chen Chen, MD, PhD

Postdoctoral Fellow  
Department of Microbiology &  
Immunology



### Gary C. Mouradian, Jr., PhD

Parker B. Francis Postdoctoral Fellow  
Department of Physiology

## “Acute and chronic changes in the control of breathing in a rat model of bronchopulmonary dysplasia”

Mouradian GC Jr, Alvarez-Argote S, Gorzek R, et al. *American Journal of Physiology. Lung, Cellular and Molecular*. 2019;316(3):L506-L518.

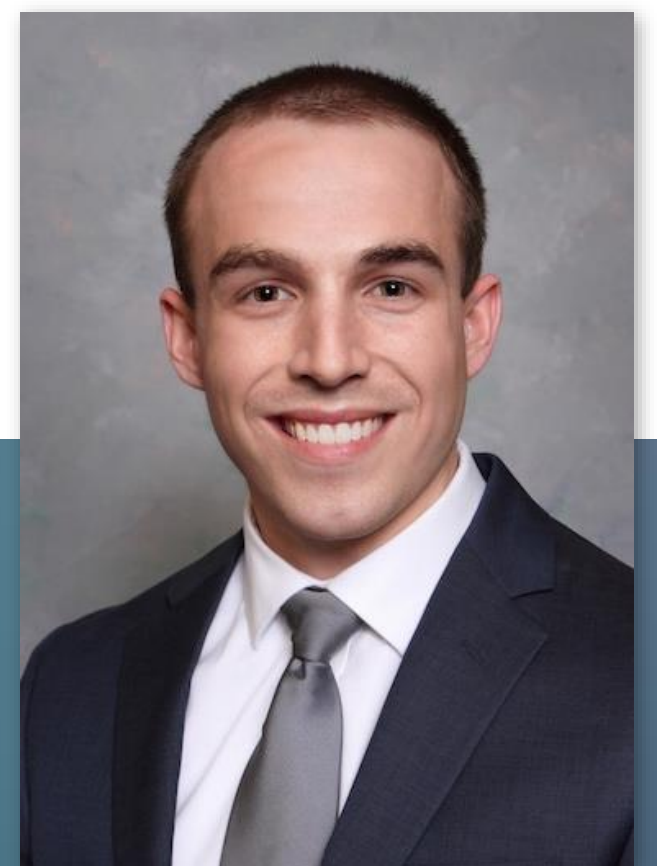
Infants born very prematurely (<28 weeks gestation) have underdeveloped lungs and a neural respiratory control network often necessitating respiratory interventions such as supplemental oxygen (hyperoxia). Although lifesaving, hyperoxia can facilitate bronchopulmonary dysplasia (BPD), a chronic lung disease. We sought to determine how the ventilatory control system adapts to BPD using a hyperoxia-induced BPD rat model. Our results indicate hyperoxia causes chronic increases in room air and hypoxic ventilation, age dependent changes in breathing stability, and reduces SpO<sub>2</sub> upon hypoxic challenges. These physiologic changes are associated with astrogliosis within respiratory control nuclei. Our results suggest chronically altered ventilatory control in BPD.

## “Impact of Medical Scribes on Provider Efficiency in the Pediatric Emergency Department”

Addesso LC, Nimmer M, Visotcky A, Fraser R, Brousseau DC. *Academic Emergency Medicine*. 2019;26(2):174-182.

We conducted an observational study comparing one year of pre-scribe and post-scribe clinical productivity metrics in the Children’s Hospital of Wisconsin Emergency Department (ED). Following scribe implementation, overall provider efficiency increased by 0.24 pts/hr (11.98%) and 0.72 wRVUs/hour (20.14%). The largest efficiency increase (0.36 pts/hour, 0.96 wRVUs/hour) occurred in January – March, when ED census peaked. Visit duration and patient satisfaction were unchanged. Among providers, 88% preferred working with a scribe and 82% felt their skills were used more effectively when working with a scribe, decreasing their likelihood of experiencing burnout.

**Luke Addesso, MD**  
MD Graduate, Class of 2019  
Department of Pediatrics



**Laxman Mainali, PhD**  
Research Scientist II  
Department of Biophysics

## “Detection of cholesterol bilayer domains in intact biological membranes: Methodology development and its application to studies of eye lens fiber cell plasma membranes”

Mainali L, O’Brien WJ, Subczynski WK. *Experimental Eye Research*. 2019;178:72-81.

Pure cholesterol bilayer domains (CBDs) are detected in model membranes only at a very high cholesterol content. Such a high cholesterol content is observed only in fiber cell plasma membranes forming eye lenses. Earlier we detected these domains in membranes made of the total lipid extracts from human lenses. Recently, we developed the method based on the EPR spectroscopy with ASL spin labels, which allowed to detect CBDs in intact fiber cell membranes of human eye lenses. We hypothesize that the high cholesterol content and especially the presence of CBDs is necessary for the normal functioning of the eye lens.

## “Risk Factors Linked to Central Catheter-Associated Thrombosis in Critically Ill Infants in the Neonatal Intensive Care Unit”

Lambert I, Tarima S, Uhing M, Cohen SS. *American Journal of Perinatology*. 2019;36(3):291-295.

Our study identified risk factors for the development of clinically identifiable catheter-associated thrombosis (CT). We performed a retrospective cohort study of neonates in whom a central catheter was present. 1,475 catheters were identified in 766 patients during a 36-month study period. The incidence of CT was 1.17 per 100 neonates. In multiple logistic and Cox’s regression analyses, three factors continued to be significantly associated with OR or HR of thrombi formation: line size, femoral location, and cholestasis. We conclude that clinically identifiable CT is rare in the neonatal population. Furthermore, catheter-specific characteristics are predictive for CT and require further investigation.

### Isabella Eiler, MD (Lambert)

MD Graduate, Class of 2019  
Department of Pediatrics



### Justin A. Harold, MD

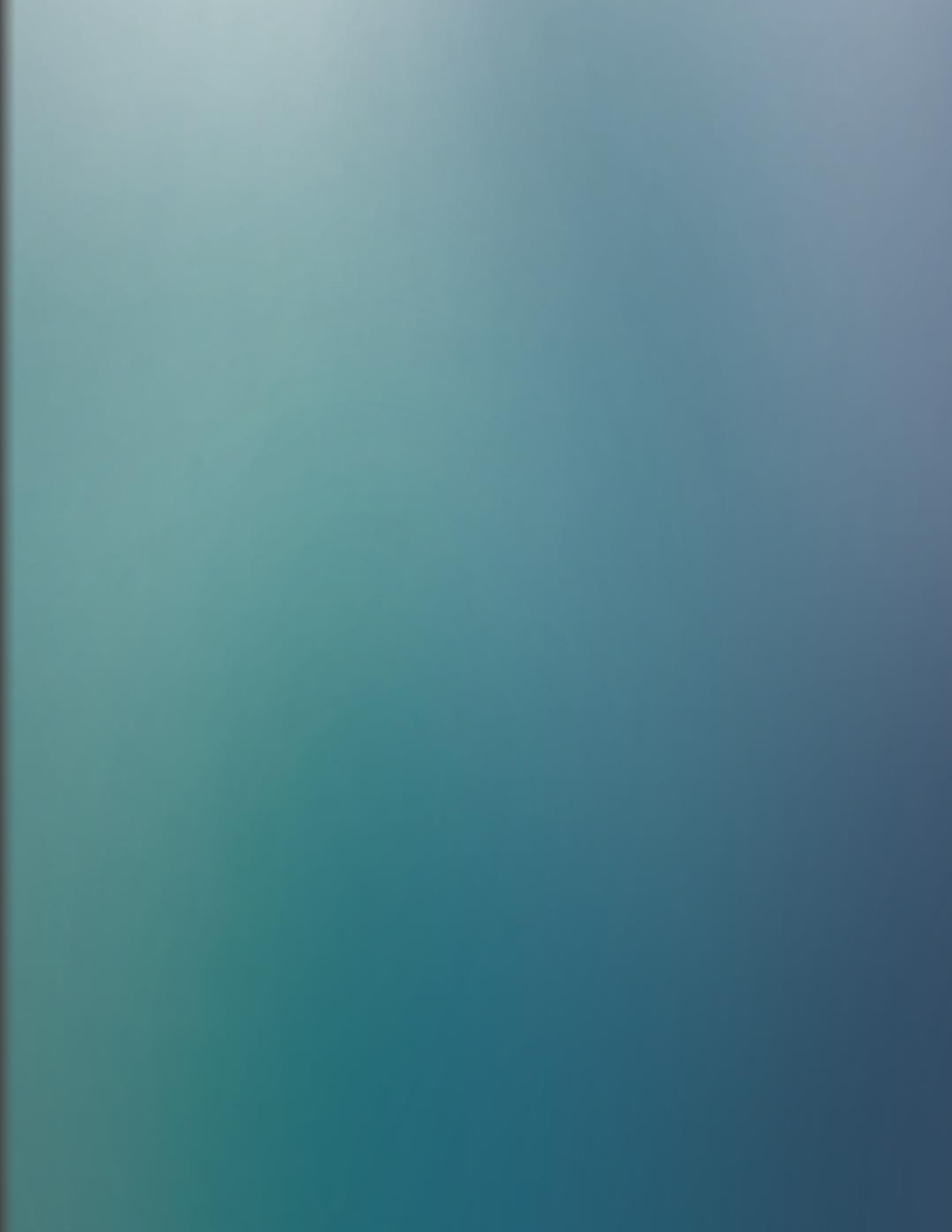
PGY-3

Department of Obstetrics & Gynecology

## “Adipose-only sentinel lymph nodes: a finding during the adaptation of a sentinel lymph node mapping algorithm with indocyanine green in women with endometrial cancer”

Harold JA, Uyar D, Rader JS, et al. *International Journal of Gynecological Cancer*. 2019;29(1):53-59.

The objective was to identify factors that affect unintended adipose-only sentinel lymph node (AOSLN) identification in women with endometrial cancer. All cases were planned laparoscopic hysterectomies with the robotic system utilizing indocyanine green, a proven sentinel lymph node (SLN) identification method. AOSLN specimens were defined as SLN specimens without a pathologically identified lymph node. 202 patients were identified; the rate of AOSLN identification decreased from 37% in the first 10 cases to 9% after 30 cases ( $P = 0.006$ ). AOSLNs were more likely with increased time from cervical injection to SLN specimen harvest. The median difference was 5 minutes longer ( $P = 0.02$ ). This finding represents a potential barrier to SLN biopsy in endometrial cancer but decreases with experience.





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