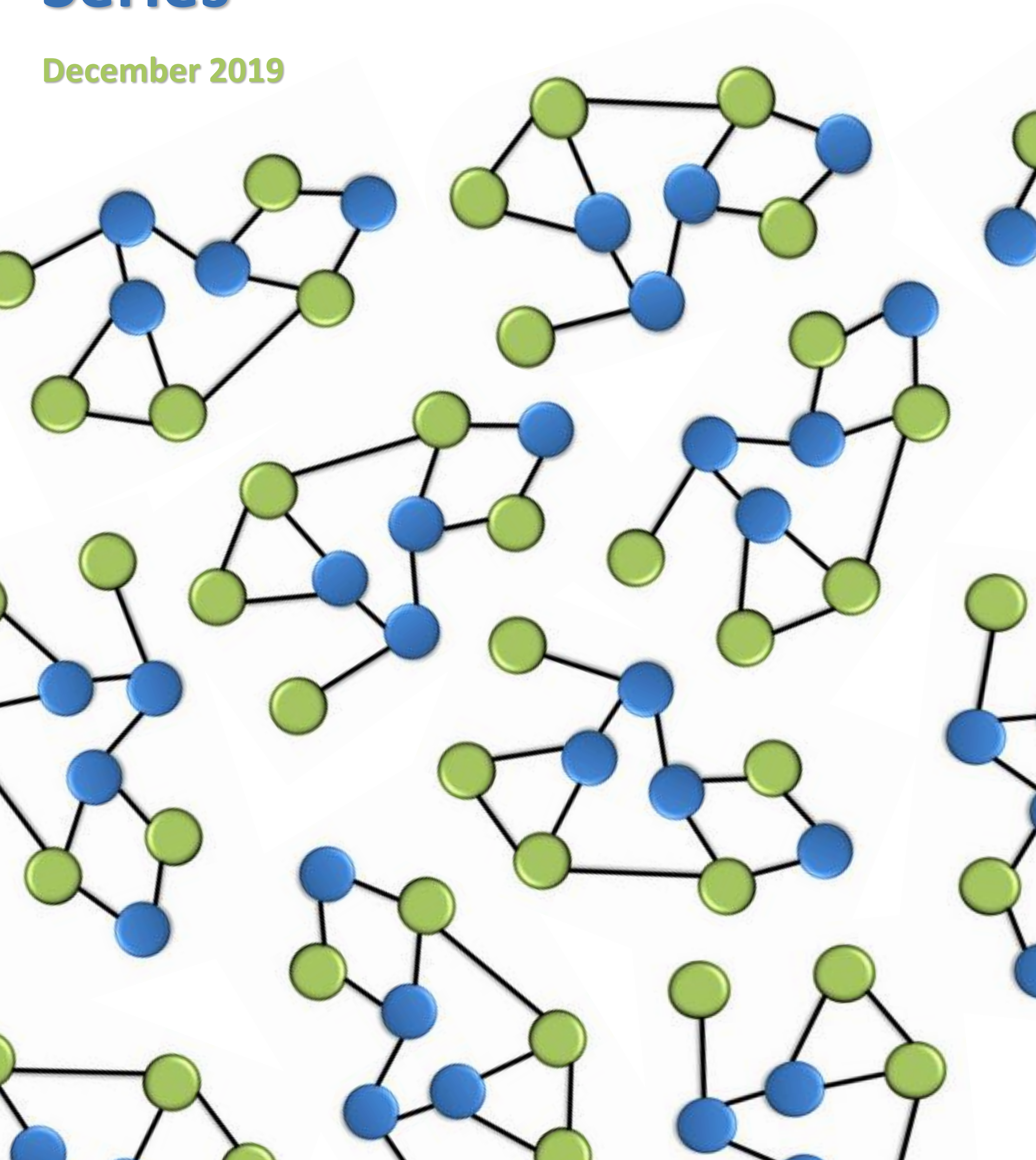


# Research Publication Series

December 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.



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**December 2019**

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**Kulwinder Dua, MD, DMSc, FRCP (Edinburgh), FRCP (London), FASGE**

“A Phase III, Multicenter, Prospective, Single-blinded, Noninferiority, Randomized Controlled Trial on the Performance of a Novel Esophageal Stent with an Antireflux Valve”

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**Stacey Lerret, PhD, RN, CPNP-AC/PC, CCTC, FAAN**

“A Clinical Description of Children with Solid Organ Transplants Who Present with Feeding Disorder”

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“RITAN: Rapid Integration of Term Annotation and Network Resources”

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**Kulwinder Dua, MD, DMSc,  
FRCP (Edinburgh), FRCP (London), FASGE**  
Professor of Medicine and Pediatrics  
Chief, Division of Gastroenterology and  
Hepatology, VAMC  
Director, Adv. Endoscopy Training Prgm  
Medical College of Wisconsin

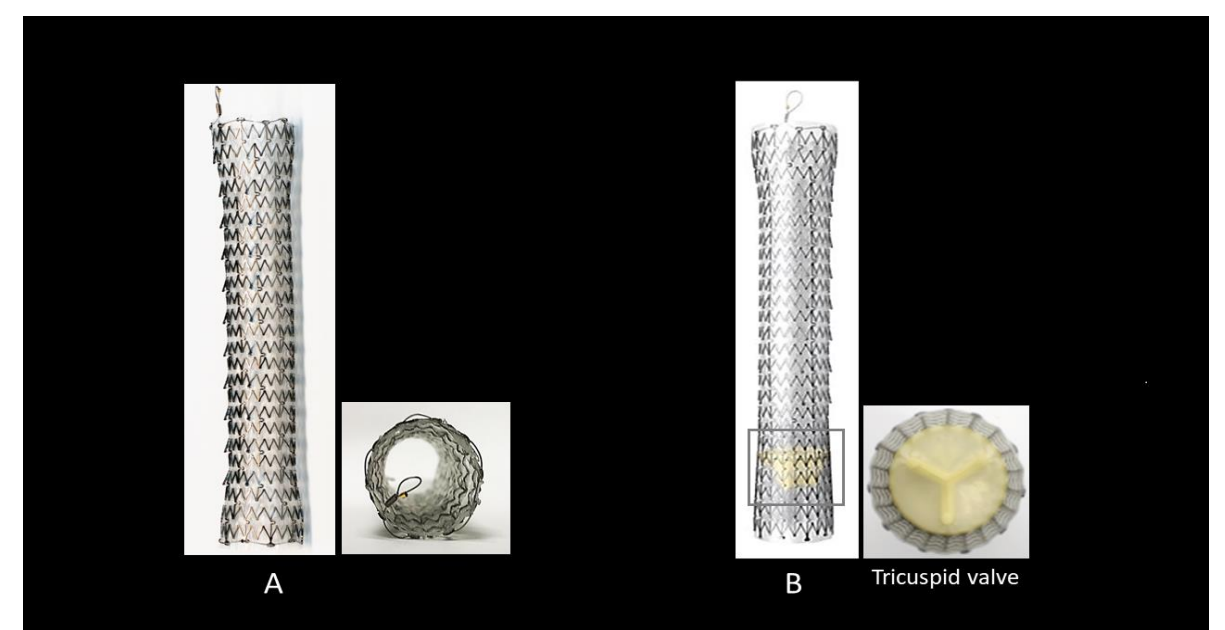
I completed my medical training in India and GI fellowship in the U.K. Currently I am a Professor of Medicine and Pediatrics. My primary interests are in interventional endoscopy and airway defense mechanisms against aspiration. I hold patents on many FDA-cleared inventions. Some of my accomplishments include regenerating the first human esophagus with tissue engineering (published in *The Lancet* in 2016), receiving the prestigious Master of Endoscopy award, Vakil Memorial gold medal, and the Poona Oration Gold Medal. I have been on the America's Best Doctor's list since 2002. I am regularly invited to participate in several international therapeutic GI endoscopy courses and was the American Society of Gastrointestinal Endoscopy's ambassador to Ecuador. I've held several positions such as the President of the International Dysphagia Research Society, President, Midwest Endoscopy society, and Vice-chair, ASGE International Committee. Hobbies include flying – I have a private pilot's license.

## “A Phase III, Multicenter, Prospective, Single-blinded, Noninferiority, Randomized Controlled Trial on the Performance of a Novel Esophageal Stent with an Antireflux Valve”

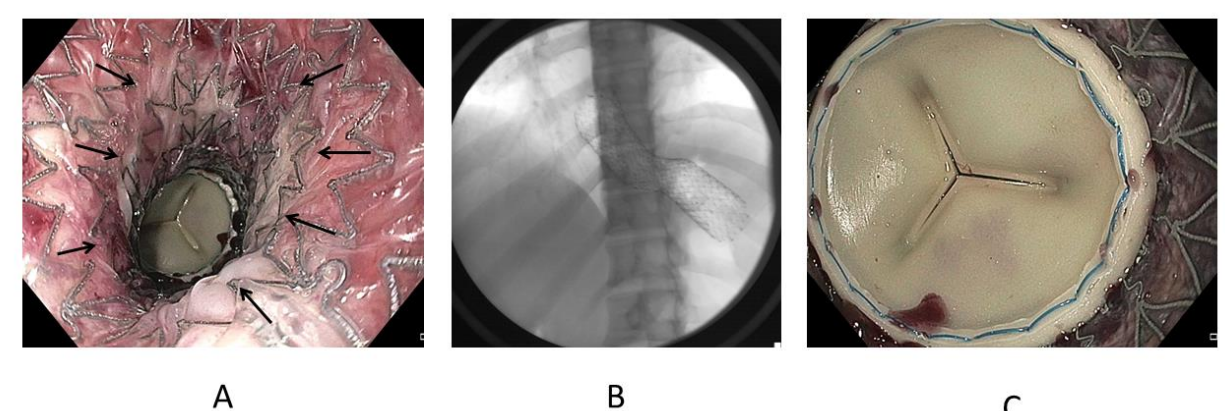
Dua KS, DeWitt JM, Kessler WR, et al. *Gastrointestinal Endoscopy*. 2019;90(1):64-74.

The incidence of adenocarcinoma of the esophagus has risen by over 60%. Majority of these patients present with difficulty in swallowing (dysphagia). Since these cancers are usually located near the gastro-esophageal junction (GEJ), self-expanding metal esophageal stents (SEMS) to palliate dysphagia have to be placed across the GEJ. Besides relieving dysphagia, this also allows gastric contents to freely reflux into the esophagus and risk aspiration. A SEMS with a tricuspid anti-reflux valve (SEMS-V) is available for use in Europe. The aim of this study was to evaluate the efficacy and safety of this stent. A phase 3, multicenter, prospective, non-inferiority, trial was conducted on 60 patients with malignant dysphagia who were randomized to receive SEMS with valve (SEMS-NV) or SEMS-V. All SEMS were successfully deployed. Similar proportion of patients in both arms improved from advanced dysphagia to moderate to no dysphagia [(SEMS-NV: 71%; SEMS-V 74%, CI 95%: 1.93 (-17.8, 21.7)]. The dysphagia scores were also similar across all follow-up time-points. Mean Gastroesophageal Reflux Disease Health-Related Quality of Life (GERD-HRQL) scores improved by  $7.4 \pm 10.2$  points in the SEMS-V arm as compared to  $5.2 \pm 8.3$  in the SEMS-NV group ( $p = 0.96$ ). The GERD-HRQL scores were similar across all follow-up time-points. Aspiration pneumonia occurred in 3.3% in the SEMS-NV arm and 6.9% in the SEMS-V arm ( $p = 0.61$ ). Stent migration rates were similar (SEMS-NV: 33%; SEMS-V: 48%;  $p=0.29$ ). Two SEMS-V stent spontaneously fractured. There was no perforation, food impaction or stent-related death in either group. In summary, the new sent with an anti-reflux valve was as effective as a standard stent in reliving dysphagia but not better than the standard stent in improving GERD-HRQL scores. Presence of the valve did not increase the risks of adverse events.

**Figure 1.** Standard self-expanding metal esophageal stent with no valve (A) and a modified self-expanding metal esophageal stent with a tricuspid anti-reflux valve (B).



**Figure 2.** Endoscopy view of the anti-reflux valve (A) The arrows indicates the stricture angulation with the anti-reflux valve positioned below the stricture. The angulated configuration of the stricture was also demonstrated by the expanded stent as observed on the fluoroscopy (B) Image C is a close-up view of the anti-reflux tricuspid valve.





**Stacey Lerret, PhD, RN,**

**CPNP-AC/PC, CCTC, FAAN**

Associate Professor

Pediatric Gastroenterology, Hepatology and Nutrition

Medical College of Wisconsin

Pediatric Nurse Practitioner, Liver Transplant Program

Children's Hospital of Wisconsin

I am an Associate Professor in the Department of Pediatric Gastroenterology, Hepatology and Nutrition and Pediatric Nurse Practitioner for the Liver Transplant Program. My program of research focuses on discharge transition processes and family self-management for complex chronic illness populations focusing on pediatric solid organ transplant patients and their families. My currently NIH funded study is evaluating the use of a smartphone application to improve family coping, family self-management behaviors for medication and medical follow-up and quality of life for family members of children that received a solid organ transplant.

**“A Clinical Description of Children with Solid Organ Transplants Who Present with Feeding Disorder”**

Lerret SM, Erato G, Goday PS, Silverman AH. *Pediatric Transplantation*. 2019;23:e13389.

Pediatric solid-organ transplant recipients have longstanding malnutrition concerns. This study described the severity of feeding disorder and parental stress in transplant patients compared to children followed in a feeding clinic and general community. 32 with transplant ages 2 months to 12 years and 32 matched control patients diagnosed with a feeding disorder without transplant were reviewed. Transplant patients who presented with a feeding problem had worse symptoms of feeding disorder than are found in the general community. These feeding problems disrupt mealtime behavior, caregiver and child relationship within a mealtime context, and may result in maladaptive feeding strategies used by families. When transplanted children present with feeding disorders, they are severe and have multiple effects on both the child and the feeding dynamic between the child and the child's caregivers.

**Table 1. Demographics of Cohort with Solid Organ Transplant**

Female, n (%)	21(32.8)
Race Ethnicity n, (%)	
White	19(29.7)
African American	7 (10.9)
Hispanic or Latino	1 (1.6)
Other	5 (15.6)
Solid Organ Transplant n, (%)	
Kidney	9 (28.1)
Liver	7 (21.9)
Lung	1 (3.1)
Heart	14(41.2)
Multivisceral	1 (3.1)

**Table 2. One Sample T-test Comparison of Transplant Population to Measure Normative Group**

	N	Mean	Standard Deviation	t	p
<b>Mealtime Behavior Questionnaire</b>					
Mealtime Aggression	28	10.14	4.97	1.65	0.11
Food Manipulation	28	13.96	5.07	5.15	< .001
Distraction/Avoidance	27	21.56	6.28	0.29	0.77
Choking, Gagging, Vomiting	28	8.00	3.61	6.20	< .001
Total	28	66.93	15.69	21.30	<0.001
<b>About Your Child's Eating</b>					
Positive Mealtime Environment	20	16.95	4.06	-1.76	0.09
Parent Aversion to Mealtime	20	8.65	3.51	1.58	0.13
Child Resistance to Eating	20	31.95	11.48	4.69	< .001
<b>Feeding Strategies Questionnaire</b>					
Child Control of Intake	31	9.87	3.75	-14.50	< .001
Schedule Structure	28	20.64	5.62	1.32	0.20
Setting Structure	31	17.81	3.65	9.157	< .001
Parent Control of Intake	27	7.70	2.83	-2.659	0.01
Laissez Faire	27	9.67	3.45	1.74	0.09
Coercive Interactions	26	10.42	3.65	3.22	< .001
<b>Parental Stress Index</b>					
Parental Distress	20	24.50	7.35	-1.16	0.26
Parent Child Dysfunctional Interactions	19	19.63	5.44	0.75	0.47
Difficult Child	18	24.72	6.89	-0.79	0.44
Defensive Responding	19	14.53	4.79	0.57	0.58



## Michael T. Zimmermann, PhD

Assistant Professor

Director, Bioinformatics Research and Development Lab

Genomic Sciences & Precision Medicine Center

Clinical & Translational Science Institute

Medical College of Wisconsin

My research focuses on interpreting data so that we can act on resulting knowledge. For example, as we gather genomic sequencing data we need methods to interpret the functional impact of variants. That impact can be at a molecular, cellular, or physiologic level, and the interplay between these resolutions is critical.

Therefore, my research starts from molecular modeling to see in 3D and over time how biomolecules achieve function and how genomic variants alter function.

Observations and simulations at this high-resolution inform cellular and physiologic models, so that we can predict how cells or systems will respond to those alterations. The long-term goal is to make each person's data relevant to their life – that we can learn from their data and tailor general knowledge to the individual, enabling Precision Medicine.

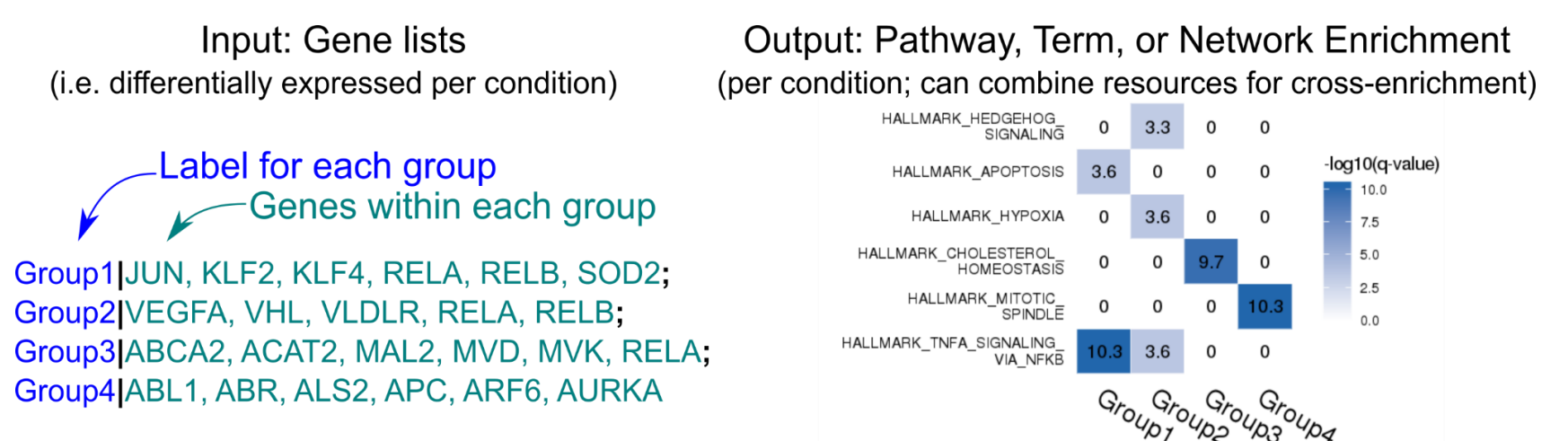
## “RITAN: Rapid Integration of Term Annotation and Network Resources”

Zimmermann, MT, Kabat B, Grill DE, Kennedy RB, Poland GA. *PeerJ*. 2019;7:e6994.

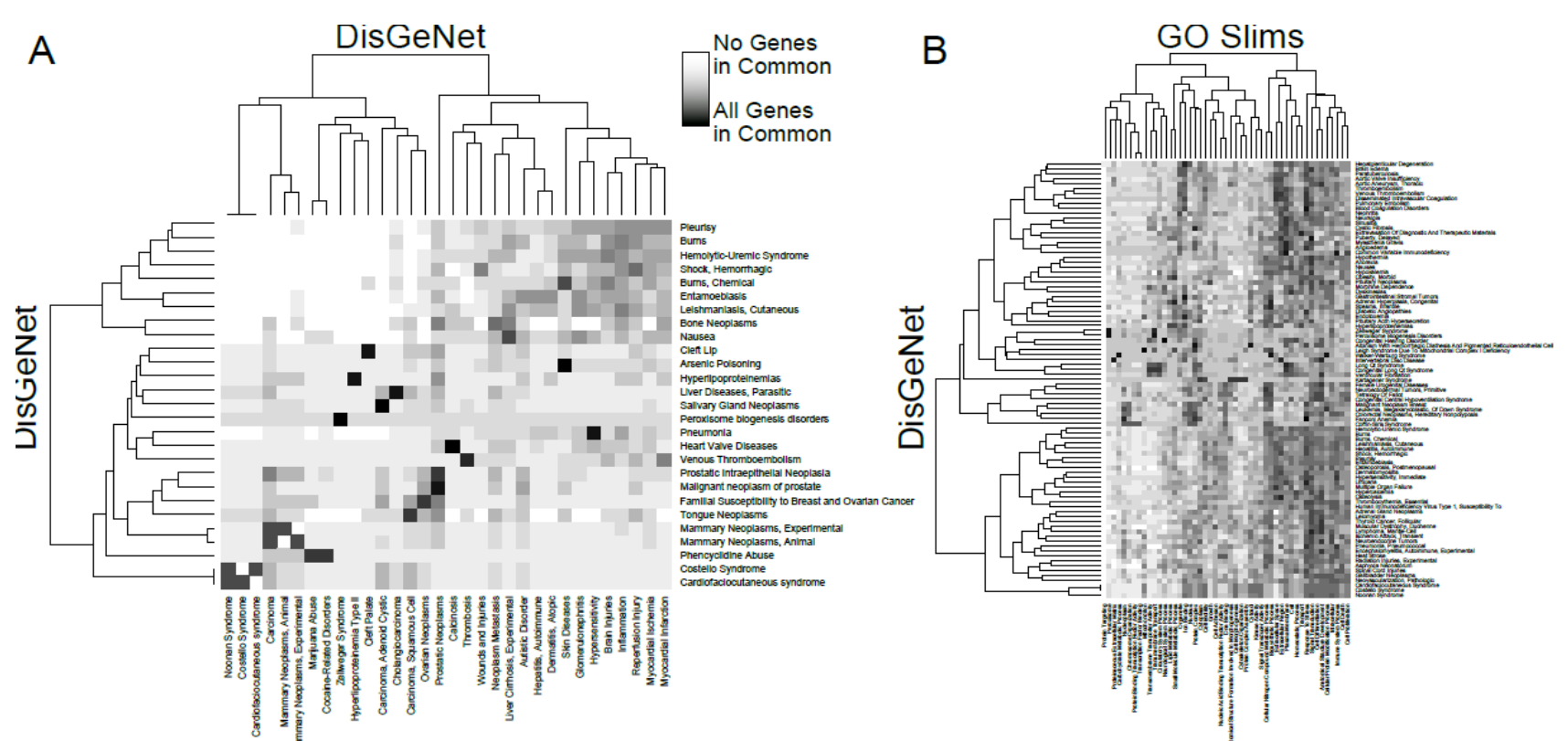
Identifying the biologic functions of groups of genes identified in high-throughput studies currently requires considerable time and/or bioinformatics experience. This is due in part to each resource housed within separate databases, requiring users to know about them, and integrate across them.

This is an increasingly common, time consuming, and often repeated task. Rapid integration of term annotation and network resources (RITAN), can be used to augment genes from your study with neighbors in pathway or network resources and run enrichment on the combination. RITAN has a set of methods for comparing gene lists, for example pathways from two different resources, and making redundancy-reduced combinations. We believe RITAN fills the important niche of bridging the results of high-throughput experiments with the ever-growing corpus of functional annotations and network biology resources.

**Figure 1.**



**Figure 2.**





## Hesham Soliman, MD, MS

Assistant Professor  
Director, Spinal Oncology Program  
Associate Director, Spine Fellowship Program  
Department of Neurosurgery  
Medical College of Wisconsin

I am an Assistant Professor in the Department of Neurosurgery at the Medical College of Wisconsin, Director of Spine Oncology, Associate Director of the Spine Fellowship program. My research is focused on tumors affecting the spine, 3D Navigation technology and Minimally Invasive techniques in spine surgery.

## “Minimally Invasive, Far Lateral Lumbar Microdiscectomy with Intraoperative Computed Tomography Navigational Assistance and Electrophysiological Monitoring”

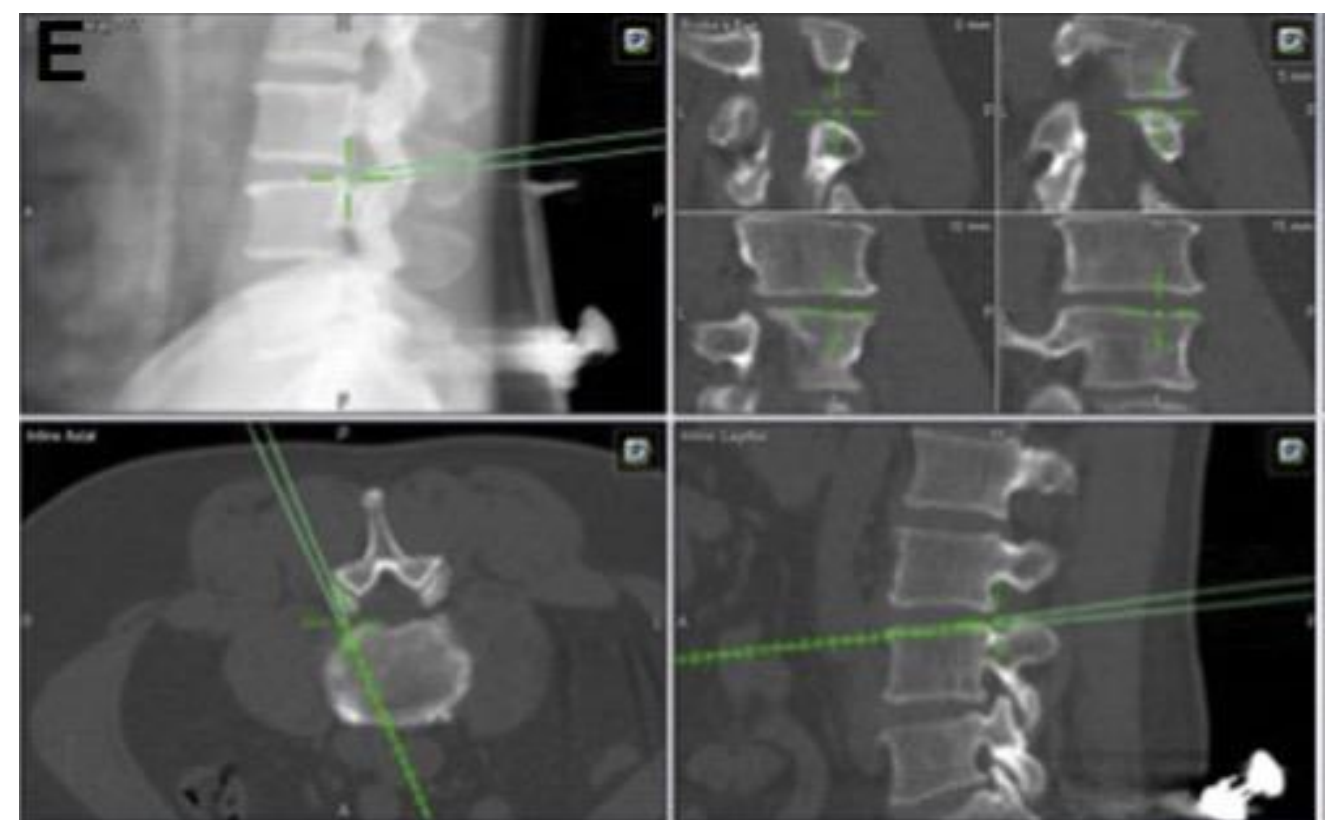
Soliman H, Fridley J, Telfian A, et al. *World Neurosurgery*. 2019;122:e1228-e1239.

Background: Patients with far lateral disc herniation (FLDH) experience more severe pain and sensory symptoms compared with those with paracentral disc herniation. In addition, surgical intervention has both been more challenging and resulted in poorer outcomes. Methods: We report our experience with intraoperative computed tomography (iCT) navigation-assisted minimally invasive tubular microdiscectomy via a paramedian approach with electrophysiological monitoring for precise 3-dimensional anatomical localization and early electrophysiological identification of the exiting nerve. Results: Five patients presenting with weakness and pain refractory to conservative management underwent iCT navigation surgery for lumbar FLDH with electrophysiological monitoring. The mean decrease in the visual analog scale pain score was -7.1 and the modified MacNab criteria outcomes were good in 1 patient and excellent in 4 patients. Conclusions: These results from a small group of patients suggest this is a safe approach with the potential for improved outcomes in the surgical treatment of FLDH.

**Figure 1.**  
Skin Incision



**Figure 2.**  
Navigation capture of left sided L3-4 far lateral discectomy



## “Assessment of Citations of the Retracted Article by Wakefield et al With Fraudulent Claims of an Association Between Vaccination and Autism”

Suelzer EM, Deal J, Hanus KL, Ruggeri B, Sieracki R, Witkowski E. *JAMA Network Open*. 2019;2(11):e1915552.

We analyzed scholarly publications that cited the 1998 retracted article by Wakefield that purported to show a link between MMR vaccines and autism. In reviewing the context of the citations we found that most authors cited the Wakefield article in a negative manner, but many failed to cite the retracted status of the article. As citation counts play a role in determining the significance of an article (for better or worse), even negative citations cause an article to get a higher rank in databases when results are sorted by citation count. Failing to properly cite a retracted article can give the perception that the work is valid.

**Elizabeth Suelzer, MLIS, AHIP**  
User Education & Reference Librarian  
Office of Research



**Linda Reis, MS, CGC**  
Program Manager  
Department of Pediatrics



**Elena Sorokina**  
Research Scientist  
Department of Pediatrics

## “De Novo Missense Variants in WDR37 Cause a Severe Multisystemic Syndrome”

Reis LM, Sorokina EA, Thompson S, et al. *American Journal of Human Genetics*. 2019;105(2):425-433.

Using exome sequencing and matchmaker databases, we identified de novo missense variants in WDR37 as a new cause of a human syndrome showing overlap with Peters plus and Walker-Warburg syndrome. Since the function of WDR37 is unknown, we used CRISPR-Cas9-mediated genome editing to generate zebrafish mutants with missense and frameshift alleles, including one that replicated a human variant. Zebrafish carrying heterozygous missense variants demonstrated larval lethality, while heterozygotes with frameshift alleles survived to adulthood, suggesting a potential dominant-negative mechanism. RNA-seq analysis of zebrafish embryos detected significant upregulation of cholesterol biosynthesis pathways, providing the first insight in possible molecular functions.



## “Cutaneous Metastases of Papillary Renal Cell Carcinoma: A Case Report and Review of the Literature”

Cardwell LA, Bender NR, Sokumbi O. *Journal of Cutaneous Pathology*. 2019;46(12):960-964.

Papillary renal cell carcinoma is an uncommon subtype of renal cell carcinoma. Histopathology shows well-defined papillary architecture with tumor cells lining fibrovascular cores and can be further subdivided into type 1 and type 2 tumors based on cytology and genetic basis. Type 1 tumors have a single layer of basophilic cells and low nuclear atypia, while type 2 tumors have a pseudostratified layer of eosinophilic cells and high nuclear atypia. We present a unique case of cutaneous metastases of papillary renal cell carcinoma with typical papillary architecture in the dermis and review the literature on this rare entity.

### Leah A. Cardwell, MD

PGY-3 Dermatology Resident  
Department of Dermatology



### Poojitha Sitaram, PhD

Research Associate II  
Department of Surgery

## “Beyond the Cell Surface: Targeting Intracellular Negative Regulators to Enhance T cell Anti-Tumor Activity”

Sitaram P, Uyemura B, Malarkannan S, Riese MJ. *International Journal of Molecular Sciences*. 2019;20(23):E5821.

Checkpoint therapy is a major focus of cancer immunotherapy today, and it primarily targets inhibitory cell surface receptors (ICRs) on T cells such as PD-1 and CTLA-4. While single and combination therapies targeting ICRs have demonstrated impressive responses in many instances, most patients remain unresponsive, relapse frequently occurs, and vigilance for induction of autoimmunity is required. Recently there is growing interest in targeting intracellular checkpoint inhibitors (ICPs) of T cells as potentially superior targets to ICRs since they can simultaneously confer insensitivity to multiple inhibitory cell surface receptors. In this review we provide a summary of currently known ICPs, their modes of action and anti-tumor activities.

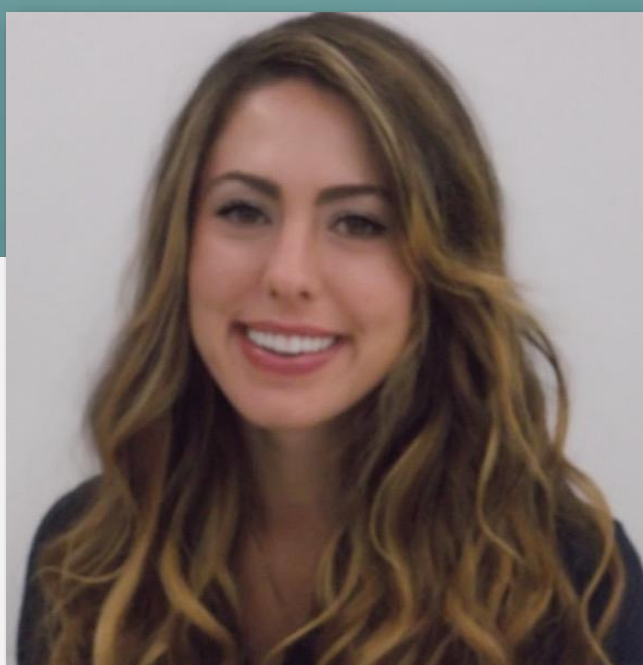
## “Surgery in the Older Patient with Breast Cancer”

Frebault J, Bergom C, Kong AL. *Current Oncology Reports*. 2019;21:69.  
<https://doi.org/10.1007/s11912-019-0822-2>

Women 70 and over represent nearly 50% of breast cancer deaths, yet no clear treatment guidelines exist for this population. This review covers trends in surgical and non-surgical management of older breast cancer patients. Surgery remains a principal component of breast cancer treatment in this population, though differences exist compared with younger women, including higher mastectomy rates and evidence-based support of omission of post-lumpectomy radiation or axillary dissection in subsets of patients. Proper treatment plan is best chosen after geriatric assessment of patients, which can help to identify patients best suited for non-surgical therapy or enrollment in hospice care.

### Julia Frebault

Medical Student, Class of 2021  
Department of Surgery



### Hailey Hayes, MS

Medical Student  
Department of Surgery

## “Sleeve Gastrectomy in Obese Wistar Rats Improves Diastolic Function and Promotes Cardiac Recovery Independent of Weight Loss”

Hayes H, Patz J, Corbett J, Afzal MZ, Strande J, Kindel TL. *Surgery for obesity and related diseases: Official journal of the American Society for Bariatric Surgery*. 2019;15(6):837-842.

Heart failure with preserved ejection fraction (HFpEF) is the most common cause of heart failure, and is characterized by impaired diastolic relaxation. Bariatric surgery improves diastolic relaxation, but a mechanism beyond weight loss remains unknown. In this study we used a rat model of obesity-induced heart failure to determine the weight-loss independent effects of a sleeve gastrectomy (SG) on cardiac function. We found that a SG improves diastolic function and induces beneficial alterations in cardiac gene expression of SERCA2a, IGFBP3, CCL-12, and SFRP1. Our data suggests that a SG may lead to weight-loss independent entero-cardiac axis-induced changes that reverse diastolic dysfunction and could translate to extending metabolic surgery to patients with HFpEF independent of obesity status.

