researchsummit2022

THURSDAY, JANUARY 13, 2022 | VIRTUAL

CONVERGENCE

Program Book

UNIVERSITY OF WISCONSIN · DEPARTMENT OF SURGERY

Welcome

Welcome to the 13th Annual University of Wisconsin Department of Surgery Research Summit!

For the last 12 years, we have gathered as members of the Department of Surgery to create an opportunity for learning and celebration, to share current research, and to imagine its future. Beginning in March 2020, the COVID-19 pandemic created profound disruptions to our research endeavors, clinical practices, and every aspect of our lives. We are no longer bound by physical proximity in the steady ways we were before. However, almost two years into that adjustment - both as a society and as a department - it is clear that we have created new ways to come together.

"**Convergence"** is therefore the theme of the 2022 Department of Surgery Research Summit.

Convergence is the integration of expertise from different disciplines that catalyzes discovery and innovation. Our vision for this summit is to highlight the surgery advancements and research collaborations in our department. We know that the size of our 11-division department presents the risk of becoming isolated in one's division or research program. Our literal "divisions" of expertise in surgery have been compounded by the separations necessitated by the pandemic. Thus, our goal this year has been to bring the entire department together to showcase the outstanding collaborative research being carried out in unique conditions and to spark new possibilities for the convergence that emerges when we bring shared motivations and diverse minds and methods together.

We also wish to emphasize that the collaborative work of *everyone* on the Department of Surgery team - students, residents, fellows, administrative and research staff, postdocs, researchers, and scientists - is a truly remarkable, daily convergence that can often escape our notice. The convergence of expertise across domains of work and distinct skillsets, and the generosity and inventiveness it takes to work toward a common cause, is what makes excellent research and true healing happen.

Fitting with our focus on convergence, this year's summit will feature keynote speaker Dr. Jayme Locke, Professor of Surgery and Arnold G. Diethelm MD Endowed Chair in Transplantation Surgery at the University of Alabama at Birmingham, Director of the Comprehensive Transplant Institute, and Chief of the Division of Abdominal Transplant Surgery. Dr. Locke will be addressing the convergence of surgery, science, and advocacy as we push to eradicate health disparities. The summit will also feature two panels: "Advancements in Surgery Research and Team Science" and "Perspectives from Faculty Research Collaborations and Clinical Trials."

The speakers for today's event have a wide array of expertise - from epidemiology to complex statistical analysis and modeling of surgical outcomes, to wound healing, genomics, otolaryngology, biomedical engineering, swine research, and more. Moreover, they lead a diverse range of programs across the university and community. May today show us the many ways in which we converge, both small and large.

We are so very glad to "see" you!

KEYNOTE SPEAKER

Jayme Locke, MD, MPH, FACS, FAST

Dr. Jayme Locke is a professor of Surgery and the Arnold G. Diethelm MD Endowed Chair in Transplantation Surgery at the University of Alabama at Birmingham and currently serves as the Director of the

Comprehensive Transplant Institute and Chief of the Division of Abdominal Transplant Surgery. She specializes in innovative strategies for the transplantation of incompatible organs, disparities in access to and outcomes after solid organ transplantation, and transplantation of HIV-infected end-stage patients. Dr. Locke completed an undergraduate degree in biology and chemistry at Duke University and her medical degree at East Carolina University prior to matriculating to Johns Hopkins Hospital where she received training in general surgery and multi-visceral abdominal transplantation. She completed her Master of Public Health degree with an emphasis in biostatistics and epidemiology at the Johns Hopkins Bloomberg School of Public Health.

Dr. Locke's research interests include complex statistical analysis and modeling of transplant outcomes and behavioral research focused on health disparities. She has authored more than 130 articles in peer-reviewed journals and 20 book chapters, and is an NIH R01-funded investigator. In addition, Dr. Locke is a Deputy Editor for the *American Journal of Transplantation,* and is an editorial board member for *Annals of Surgery.* Dr. Locke is the recipient of numerous honors, most recently the American College of Surgeons Traveling Fellow 2018, Association for Clinical & Translational Science (ACTS) Distinguished Investigator Award: Translation into Public Benefit and Policy (2018), and the AST Clinical Science Faculty Award 2020.

PANELISTS

Dawn M. Elfenbein, MD, MPH, FACS

Dr. Dawn Elfenbein graduated medical school from Johns Hopkins and received her Master's of Public Health from the University of North Carolina while she was a resident at Duke University. She completed her Endocrine Surgery fellowship in 2015 from the University of Wisconsin Hospital and Clinics. Dr. Elfenbein is an endocrine surgeon and surgical educator. She is the director of medical student education in the department, and her research focuses on teaching effectiveness and program evaluation, with particular interests in optimizing the learning environment, wellness and mindfulness, and self-efficacy. She has earned multiple faculty awards in teaching excellence in the Department of Surgery.

Amy Fiedler, MD

Dr. Amy Fielder graduated from The George Washington University School of Medicine and completed her General Surgery Residency as well as Cardiothoracic Surgery Fellowship at Massachusetts General Hospital. Dr. Fiedler's research interests focus on developing novel surgical treatments for heart failure, evaluating the utility of expanded donor criteria with respect to thoracic organ transplantation, ex-vivo perfusion for heart and lung transplantation, and surgical education. Her research endeavors have included the creation of a surgical, non-transplant option for the treatment of heart failure and the development of a novel model of right heart failure in sheep. Dr. Fiedler specializes in the care of patients with end stage heart failure, including mechanical assistance and heart transplantation. She has broad experience with all aspects of adult cardiothoracic surgery, including coronary artery bypass grafting, valve repair and replacement, endocarditis, and the treatment of thoracic aortic aneurysms.

Angela Gibson, MD, PhD

Dr. Angela Gibson graduated from the Medical Scientist Training Program in 2009 from the University of Wisconsin School of Medicine and Public Health, where she also completed her surgical residency in 2014. Subsequently, she completed a visiting Burn Surgery fellowship at the University of California, Davis, and a fellowship in Surgical Critical Care at the University of Wisconsin. Certified by the American Board of Surgery

in General Surgery and Surgical Critical Care, Dr. Gibson specializes in burn, trauma, emergency surgery and surgical critical care and treats complex wounds. She is the Medical Director of Wound Healing Services at UW Health, a program that she developed. Her research interests focus on epithelial regeneration in burn injury, evaluation of advanced tissue products, human skin model development for wound healing, and understanding the burn wound microenvironment. Dr. Gibson leads a basic and translational science laboratory studying wound healing and clinical trials involving her burn patients.

David Andrew Harris, MD

Dr. David Andrew Harris is an Assistant Professor in the Division of Minimally Invasive Surgery at the University of Wisconsin-Madison. Dr. Harris completed his fellowship in advanced GI and bariatric surgery at Brigham and Women's Hospital & Harvard Medical School, where he also completed his general surgery residency. Before Harvard, he completed his MD at the University of Virginia in Charlottesville. His research focuses on the intersection of metabolic surgery, metabolism, and aging. His recent publications helped define the mechanisms by which sleeve gastrectomy leads to improved glucose regulation. This work led to multiple publications, awards, and three provisional patent applications.

Sarah Jung, PhD

Dr. Sarah Jung obtained her PhD in Educational Psychology in 2014. She is an Assistant Professor in Education Research and Development in the Department of Surgery at the University of Wisconsin-Madison. She is an expert in educational psychology with a focus in Learning Science, the study of how people learn in different contexts. She has studied the incorporation and impact of digital technologies in multiple learning environments. She is currently involved in numerous studies in the areas of undergraduate, graduate, and continuing surgical education. Her background allows her to apply theories of learning to understand how people become expert physicians and how we can support this process to facilitate quality patient care. Her training in assessment as well as quantitative and qualitative research methods allows her to conduct and consult on a variety of research projects in surgical and medical education.

Elise Lawson, MD, MSHS, FACS

Dr. Elise Lawson graduated from Stanford University School of Medicine in 2007 and went onto complete her general surgery residency training and a Master's of Science in Health Services at the University of California, Los Angeles in 2015 and 2011, respectively. Subsequently, she finished her colorectal surgery fellowship at Lahey Clinic in 2016. Certified by the American Board of Surgery in General Surgery and the American Board of Colon and Rectal Surgery, Dr. Lawson specializes in the surgical treatment of colon cancer, rectal cancer, inflammatory bowel disease, diverticulitis, and other benign conditions. She is the Director of the Surgical Collaborative of Wisconsin, established in 2011 with the goal of creating a community of surgeons across the state committed to improving the quality of surgical care. Dr. Lawson also serves on the executive council of the Wisconsin Surgical Society and as the interim chair of the Division of Colorectal Surgery at the University of Wisconsin.

Hau D. Le, MD, FACS, FAAP

Dr. Hau Le is currently the Director of Pediatric Surgical Oncology at the American Family Children's Hospital. Dr. Le performs all types of general and thoracic pediatric surgeries. Clinically, he focuses on thoracic surgeries such as congenital diaphragmatic hernia, lung surgery, and esophageal surgery. He also has a

strong interest in pediatric surgical oncology. Dr. Le's research interests are parallel with his clinical interests as he is investigating lung growth and regeneration, especially in neonates with severe congenital diaphragmatic hernia. He also studies the effect of downstream products of essential fatty acids on tumor growth such as neuroblastoma. Dr. Le is certified by the American Board of Surgery in General Surgery and board eligible in Pediatric Surgery.

Bo Liu, PhD

Dr. Bo Liu completed her graduate study in the Department of Biochemistry at the State University of New York, Downstate Medical Center. She is now a Professor in the Department of Surgery and the Department of Cell and Regenerative Biology at the University of Wisconsin-Madison. She devotes her efforts to reducing cardiovascular disease through research and education. Dr. Liu is a passionate mentor who is committed to training the next generation of cardiovascular investigators. She has built a laboratory that fosters innovation, independence, and collaboration. Dr. Liu and her group have published on the topics of cell death, inflammation, aortic aneurysm, intimal hyperplasia, and gene therapy. Dr. Liu's research is funded by multiple grants from National Institutes of Health and the American Heart Association.

Muhammed Murtaza, MBBS, PhD

Dr. Muhammed Murtaza graduated with a Bachelor of Medicine and Bachelor of Surgery from Aga Khan University Medical College in Karachi, Pakistan, and a PhD in Medical Science from the Cancer Research UK Cambridge Institute at the University of Cambridge. Previously, Dr. Murtaza served as an Assistant Professor of Medicine at Mayo Clinic in Scottsdale, Arizona, and faculty member and co-director of the Center for Noninvasive Diagnostics in the Translational Genomics Research Institute in Phoenix. He is currently the Associate Director of the UW Center for Human Genomics and Precision Medicine, and an Associate Professor in the Department of Surgery. As a researcher, Dr. Murtaza has long-standing interests in pushing the boundaries of personalized cancer medicine using liquid biopsies.

Samuel O. Poore, MD, PhD

Dr. Samuel Poore received his medical training and doctorate from Brown University in Providence, Rhode Island, and completed his residency in Plastic and Reconstructive Surgery at the University of Wisconsin-Madison. He then completed a fellowship in microsurgery and research at the Bernard O'Brien Institute of Microsurgery in Melbourne, Australia. Dr. Poore specializes in microvascular surgery with an emphasis on breast reconstruction, upper and lower extremity reconstruction, and head and neck reconstruction. He is currently a tenured Associate Professor at the University of Wisconsin, the Section Chief of Plastic Surgery at the William S. Middleton Veterans Administration Hospital in Madison, Wisconsin and has a joint appointment in the Department of Biomedical Engineering. In addition, Dr. Poore directs the University of Wisconsin Microsurgical Training Laboratory with a focus on developing novel microsurgical simulators and leads the multi-institutional Annual UW Microsurgery Training Course.

Dhanansayan (Dhanu) Shanmuganayagam, PhD

Dr. Dhanu Shanmuganayagam is Co-Director of the UW Center for Biomedical Swine Research and Innovation, and currently leads genetic engineering of swine at UW. His research focuses on the development and utilization of pigs as homologous models to close the translational gap in human disease research, taking advantage of the similarities between pigs and humans in terms of genetics, anatomy, physiology, and

immunology. His team has created numerous genetic porcine models, including ones for the study of xenotransplantation, and pediatric cancer predisposition disorders such as neurofibromatosis type 1 (NF1). Broadly, Dr. Shanmuganayagam's program has numerous collaborations within and outside of UW in which swine models are used to drive research in other biomedical fields such as wound infections, heart disease, liver cirrhosis, metabolic disorders, imaging-guided radiotherapy systems, tumor ablation and resection devices, and ultrasound technologies.

Nathan V. Welham, PhD, CCC-SLP

Dr. Nathan Welham, PhD, is an Associate Professor in the Division of Otolaryngology-Head & Neck Surgery. He earned his degrees from the University of Canterbury, Whare Wānanga o Waitaha and the University of Wisconsin-Madison. Dr. Welham is also certified in speech language pathology by the American Speech Language Hearing Association. He specializes in the assessment and treatment of patients with organic, neurological, and functional voice disorders, resonance disorders, and upper airway disorders such as paradoxical vocal fold motion. He also treats patients with occupational voice problems. His research interests include vocal fold mucosal biology; extracellular matrix-focused proteomics; and vitamin A transport, storage and function.

Program

UNIVERSITY OF WISCONSIN DEPARTMENT OF SURGERY
13th Annual Research Summit: *Convergence*
Thursday, January 13, 2022
Virtual

Join Webinar HERE or <https://uwmadison.zoom.us/j/91073422584>

Passcode: 2022

AM

8:00 Welcome & Opening Remarks

Cynthia Kelm-Nelson, PhD, Program Co-Chair
Sudha Pavuluri Quamme, MD, MS, Program Co-Chair

8:05 "Advancements in Surgery Research and Team Science" Panel
Moderator: Susan Thibeault, PhD

- Nathan Welham, PhD
- Angela Gibson, MD, PhD
- Sarah Jung, PhD
- David Harris, MD
- Bo Liu, PhD
- Dhanu Shanmuganayagam, PhD

9:05 "Surgery, Science & Advocacy: Mitigating Health Disparities in Transplantation"
Moderator: David Foley, MD

Keynote Speaker
Jayme Locke, MD, MPH
Professor, University of Alabama at Birmingham
Arnold G. Diethelm Endowed Chair in Transplantation Surgery

10:00 Break

10:15 Abstract Oral Presentations *(see detailed schedule on pages 8,9 and 10)*

Please note: at 10:15 am, we will transition from the Zoom webinar to Zoom meeting breakout rooms. Breakout rooms will run simultaneously and attendees may choose which room to attend. Each breakout room is linked below.

- **Bascom Breakout**
  Moderator: Rebecca Sippel, MD
  Technical Support: Sarah Pavao

- **Badger Breakout**
  Moderator: John Rectenwald, MD, MS
  Technical Support: Kaitlin Dorst

- **Babcock Breakout**
  Moderator: Corrine Voils, PhD
  Technical Support: Danielle French

11:45 Lunch

PM

12:30 Welcome Back

Voting ends for Visual Abstracts and Surgery Science Image Contest at 1 PM

12:35 "Perspectives from Faculty Research Collaborations and Clinical Trials" Panel
Moderator: Nicole Smialek, MBA

- Amy Fiedler, MD
- Samuel Poore, MD, PhD
- Dawn Elfenbein, MD, MPH
- Hau Le, MD
- Elise Lawson, MD, MSHS
- Muhammed Murtaza, MBBS, PhD

1:35 Research Update

Rebecca Minter, MD
A.R. Curreri Distinguished Chair, Department of Surgery

2:10 Awards & Closing Remarks

Top Abstract Oral Presentations - Breakout Rooms 10:15AM - 11:45AM

Breakout rooms will run simultaneously. Attendees can select their preferred breakout room to attend.

Bascom Breakout – Join Bascom Breakout Room HERE

Judges: Muhammed Murtaza, MBBS, PhD; Sean Ronnekleiv-Kelly, MD; Rebecca Sippel, MD

Louis C. Bernhardt, MD Best Oral Presentation Award

- **10:15AM-10:25AM** Hillary Johnson
  - *"The Use of Protease Inhibitors to Treat Anal Cancer Spheroids Derived from HPV Transgenic Mice"*
  - Authors: H. Johnson; T. Moyer; L. Gunder; S. Park; N. Sherer; E. Carchman

- **10:25AM-10:35AM** Taylor Aiken
  - *"Peritoneal Recurrence after Resection for Stage 1-3 Colorectal Cancer - A Population Analysis"*
  - Authors: Taylor J. Aiken; Chung-Yuan Hu; Beth Helmink; Christopher P. Scally; Brian K. Bednarski; Keith F. Fournier; George J Chang; Syed Nabeel Zafar

- **10:35AM-10:45AM** Kristy Wendt
  - *"Co-expression Network Analysis of the Changing Transcriptome in Embryonic Mouse Esophagus, Trachea, and Larynx"*
  - Authors: Kristy Wendt; Jared Brown; Vlasta Lungova; Vidisha Mohad; Christina Kendziorski; Susan Thibeault

- **10:45AM-10:55AM** Tudor Borza
  - *"Assessment of Baseline Surgical Opioid Overprescribing in Wisconsin Stateline Area to Inform Surgeon Directed Opioid Stewardship"*
  - Authors: Neel Karne; Sudha Pavuluri Quamme; Jessica Schumacher; Joanne Peters; Randi Cartmill; Manasa Venkatesh; Dou-Yan Yang; Jeanette May; Elise Lawson; Tudor Borza

- **10:55AM-11:15AM** Courtney Broadfoot
  - *"Effects of Social Condition on Vocal Communication, Anxiety, Depression, Cognition, and Neurobiology in the Pink1-/- Rat Model of Parkinson Disease"*
  - Authors: Courtney K. Broadfoot; Charles Lenell; Cynthia A. Kelm-Nelson; Michelle R. Ciucci

- **11:15AM-11:25AM** Diana Gutierrez-Meza
  - *"Provider Perspectives on Challenges during Emergency General Surgery Transfer Calls: Importance of Surgeon-to-Surgeon Communication"*
  - Authors: Diana Gutierrez-Meza; Megan Saucke; Esra Alagoz; Angela Ingraham

- **11:25AM-11:35AM** Miraf Molla
  - *"Burn Pit-derived Particulate Matter Exposure Increases Disease Severity in a Murine Autoimmunity Model"*
  - Authors: M. Molla; Z.R. Sink; R.H. Daley; J.H. Fechner; J.J. Schauer; J.D. Mezrich

- **11:35AM-11:45AM** Allison Seitz
  - *"The Relationship between Neuropsychiatric Diagnoses and Revision Surgery Following Breast Reconstruction"*
  - Authors: Allison J. Seitz; Armin Edalatpour; Pradeep K. Attaluri; Kasey L. Wood; Zeeda H. Nkana; Brett M. Michelotti; Samuel O. Poore

Badger Breakout – Join Badger Breakout Room HERE
Judges: David Francis, MD, MS; John Rectenwald, MD, MS; Susan Thibeault, PhD;
K. Craig Kent, MD Best Oral Presentation Award

- **10:15AM-10:25AM** Laura Krecko
  - *"Validation of the Breast Cancer AJCC 8th Edition Pathologic Prognostic Stage vs. Anatomic Stage in Legacy Alliance Trials"*
  - Authors: Laura K. Krecko; Jessica Schumacher; Caprice C. Greenberg; Lee G. Wilke; Bret Hanlon; Heather Neuman

- **10:25AM-10:35AM** Patrick Schwartz
  - *"Circadian Dysregulation Accelerates Pancreatic Cancer Progression"*
  - Authors: Patrick B Schwartz; Manabu Nukaya; Mark Berres; Clifford D Rubinstein; Sean M Ronnekleiv-Kelly

- **10:35AM-10:45AM** Jacqueline Murtha
  - *"Association between Neighborhood Food Environment and Bariatric Surgery Outcomes"*
  - Authors: Jacqueline Murtha; Manasa Venkatesh; Natalie Liu; Jen Birstler; Bret M. Hanlon; Lawrence P. Hanrahan; Luke M. Funk

- **10:45AM-10:55AM** Linda Rowe
  - *"Effects of Thickened Liquids: A Translational Pilot of Chronic Use"*
  - Authors: Linda M. Rowe; John A. Russell; Michelle R. Ciucci; Nadine P. Connor

- **10:55AM-11:15AM** Colin Reisenauer
  - *"Incidence and Severity of Postoperative Delirium among Older Surgical Patients: A Descriptive Analysis"*
  - Authors: Colin R. Reisenauer; Courtney E. Morgan; Randi S. Cartmill; Alexis M. Eastman; Manish N. Shah; Julia R. Berian

- **11:15AM-11:25AM** Andi Donnelly
  - *"A Retrospective Case Study on the Valuation of a Full-Time Microsurgeon Educator in Training Highly Skilled Surgical Residents at Academic Centers"*
  - Authors: Marina I. Adrianzen Fonseca; Weifeng Zhang; Peter Nicksic; Aaron M. Dingle; Samuel O. Poore

- **11:25AM-11:35AM** Cristina Paz
  - *"Mesenchymal Stromal Cells for Treatment of Radiation Induced Xerostomia"*
  - Authors: Cristina Paz; Grace Blitzer; Annemarie Glassey; Jayeeta Giri; Andrea Pennati; Olga Ganz; Steven Schreiber; Kwangok P Nickel; Cynthia A. Kelm-Nelson; Vanessa L. Cannaday; Robert Pohlman; Tiffany Glazer; Ted Lunga; Daniel Robbins; Ryan Mattison; Tomy Varghese; Susan Thibeault; Nicole Rogus-Pulia; Jacques Galipeau; Randall J. Kimple

- **11:35AM-11:45AM** Andreas de Biasi
  - *"Impact of Illicit Drug Use on Outcomes Following Acute Type-A Aortic Dissection Repair: An Analysis of the STS ACSD"*
  - Authors: Andreas R. de Biasi; Entela Lushaj; Satoru Osaki; Jason Smith; Amy Fiedler; Malcolm M. DeCamp

Babcock Breakout – Join Babcock Breakout Room HERE
Judges: David Foley, MD; Rebecca Minter, MD; Corrine Voils, PhD
Layton F. Rikkers, MD Best Oral Presentation Award

- **10:15AM-10:25AM** Sarah Lechner
  - *"Gene Expression Alterations in Whole Blood as Potential Biomarkers for Early-stage Parkinson Disease"*
  - Authors: Sarah A. Lechner; Jacob M. Welsch; Stephen C. Gammie; and Cynthia A. Kelm-Nelson

- **10:25AM-10:35AM** David Hall
  - *"Reduction in Opioid Prescribing Following Lung Transplantation Utilizing Intercostal Nerve Cryoablation"*
  - Authors: David J Hall; Erin M Lowery; Hanna L Kleiboeker; Mary S Hayney; Malcolm M DeCamp; Daniel P McCarthy

- **10:35AM-10:45AM** Christopher Little
  - *"PD-1 Upregulation on Host CD8+ T Cells is Associated with Mixed Chimerism in Kidney Transplant Tolerance Induction"*
  - Authors: Christopher J Little; Steven C Kim; John Fechner; Jennifer Post; Dixon B Kaufman

- **10:45AM-10:55AM** Natalia Arroyo
  - "*Prevalence of Subclinical Papillary Thyroid Cancer by Age: Meta-analysis of Autopsy Studies"*
  - Authors: Natalia Arroyo; Katy J. L. Bell; Vivian Hsiao; Sara Fernandes-Taylor; Oguzhan Alagoz; Yichi Zhang; David O. Francis; Louise Davies

- **10:55AM-11:15AM** Nicole Schaen-Heacock
  - *"Assessment of Swallow Function in a Translational Rat Model of Chemoradiation and Lingual Exercise"*
  - Authors: Nicole Schaen-Heacock; Courtney Broadfoot; John Russell

- **11:15AM-11:25AM** Jessica Schumacher
  - *"A Statewide Approach to Reducing Re-excision Rates for Women with Breast Conserving Surgery"*
  - Authors: Joseph Weber; Amanda Kong; Jeanette May; Elise Lawson; Nicholas Marka; Bret Hanlon; Manasa Venkatesh; Randi Cartmill; Caprice Greenberg;Jessica Schumacher

- **11:25AM-11:35AM** Patricia Filippsen Favaro
  - *"Circulating Tumor DNA Analysis in Dogs with Sarcomas"*
  - Authors: Patricia Filippsen Favaro; Bradon R. McDonald; Max Schermacher; Deependra K. Singh; Nathaniel Van Asselt; Xuan Pan; Muhammed Murtaza

- **11:35AM-11:45AM** Peter Nichol
  - *"Quantifying the Cost of Surgical Instrument Errors in the OR in a Two-hospital Facility"*
  - Authors: M.J. Saari, N. Navas, N. Villegas, D. Aguilar, M. Jabbou, A. Hitzeman, S. Garcha, M. Leyden, J. Caceres, J. Philavong, A. McGrain, O. O'Brien, L. Qianyun, M. Chen, R. Bliesner, G. Hackinson, E. Ghawas, M. Kurth, S. Walsh, A. Jentsch, P. Brunner, M. Fischer, S. Wisdor, A. VanDommelen, G. Nytes, P.F. Nichol

Acknowledgements

We would like to thank the following individuals who served on the **2022 Research Summit Committee** and made invaluable contributions to the planning of this event:

Cynthia Kelm-Nelson, PhD; *Co-Chair*
Sudha Pavuluri Quamme, MD, MS; *Co-Chair*
Collin Brown
Kaitlin Dorst
Danielle French
Nicole Jennings, MA
Karen Lynch
Rebekah Olson
Sarah Pavao
Nicole Smialek, MBA
Susan Thibeault, PhD
Lee Wilke, MD

We also wish to recognize the **abstract reviewers** who served on our Program Committee. The following individuals generously donated their time to review the 76 abstracts that were submitted:

David Al-Adra, MD, PhD
Karan Budhraja, MD
Randi Cartmill, MS
Aaron Dingle, PhD
Lindsey Eierman, MPH
Patricia Filippsen Favaro, DVM, PhD, MSc
Kara Gavin, PhD, MPH
Rachel Anne Godbout, MS
Kirsten Gunderson, MD
Luis Hidalgo, PhD
Sarah Jung, PhD
Cynthia Kelm-Nelson, PhD
Elise Lawson, MD, MSHS
Hau Le, MD
Aiping Liu, PhD
Heather Neuman, MD, MS
Alex Nisbet
Sydney Leavitt Olson, BS
Annalise Panthofer, BS
Sudha Pavuluri Quamme, MD, MS
Samuel Poore, MD, PhD
Joseph Roche, MD
Jessica Schumacher, PhD
Susan Thibeault, PhD
Lee Wilke, MD
Jocelyn Zajac, MD

Finally, we would like to acknowledge the **abstract oral presentation judges and moderators** who worked to determine the winners of the Bernhardt, Kent, and Rikkers awards.

David Foley, MD
David Francis, MD, MS
Rebecca Minter, MD
Muhammed Murtaza, MBBS, PhD
John Rectenwald, MD, MS
Sean Ronnekleiv-Kelly, MD
Rebecca Sippel, MD
Susan Thibeault, PhD
Corrine Voils, PhD

List of Abstracts

Research Summit Oral Abstracts

Alphabetized by PI/Lab within each group.

To jump to the Abstract, "Ctrl" and click abstract title.

GROUP ONE: Basic Science and Translational Research

BROWN

Establishment of a Translational Rhesus-Primatized Mouse Model Using Transgenic Immunodeficient Mice; *Christopher J Little, W. John Haynes, Liupei Huang, Cross Daffada, Bryce B Wolfe, Elizabeth Perrin, John A Simpson, Jenna A Kropp Schmidt, Hayly M Hinkle, Logan T Keding, Dixon B Kaufman, James A Thomson, Thaddeus G Golos, Matthew Brown*

CARCHMAN

The Use of Protease Inhibitors to Treat Anal Cancer Spheroids Derived from HPV Transgenic Mice; *H. Johnson, T. Moyer, L. Gunder, S. Park, N. Sherer, E. Carchman*

CIUCCI

Positron Emission Tomography Neuroimaging of FDG Uptake in PINK1-/- Rats: Glucose Metabolism in a Parkinson Disease Model; *Alexander K. Converse, Maxim S. Slesarev, Alex F. Nisbet, John C. Szot, Michelle R. Ciucci*

Effects of Social Condition on Vocal Communication, Anxiety, Depression, Cognition, and Neurobiology in The Pink1-/- Rat Model of Parkinson Disease; *Courtney K. Broadfoot, Charles Lenell, Cynthia A. Kelm-Nelson, Michelle R. Ciucci*

Social Isolation Results in Disrupted Vocal Acoustics and Increased Dopamine and Serotonin in the Ventral Tegmental Area; *Courtney K. Broadfoot, Charles Lenell, Cynthia A. Kelm-Nelson, Michelle R. Ciucci*

The Pink1-/- Rat Demonstrates Oromotor and Gastrointestinal Dysfunction in the Early Stage of Parkinson Disease; *Maryann N. Krasko, Cynthia A. Kelm-Nelson, Michelle R. Ciucci*

CIUCCI, RUSSELL

Assessment of Swallow Function in a Translational Rat Model of Chemoradiation and Lingual Exercise; *Nicole Schaen-Heacock, Courtney Broadfoot, John Russell*

CONNOR

Effects of Thickened Liquids: A Translational Pilot of Chronic Use; *Linda M. Rowe; John A. Russell; Michelle R. Ciucci, Nadine P. Connor*

Motor Neuron Loss in the Contralesional Hypoglossal Nucleus is Associated with Reduced Tongue Force after Unilateral Stroke; *Miranda Cullins, Nadine Connor*

DINGLE

Application of the Novel Free Radical Scavenger PrC-210 to UW Organ Preservation Solution for Prolongation of Rat Hind Limb Static Cold Storage as a Vascularized Composite Allograft Model: A Pilot Study; *Weifeng Zeng, Zeeda H. Nkana, Maya M. C. Gitter, Samuel O. Poore, William E. Fahl, Aaron M. Dingle*

Building the Pre-clinical Rationale to Elevate the Osseointegrated Neural Interface to a Clinical Level; *Lucas Sears, Alison Karczewski, Aaron Dingle, Samuel Poore*

DINGLE, POORE

Ovine Peripheral Nerve Mapping to Facilitate Development of an Osseointegrated Neural interface; *Grant R. Seils, Kirsten A. Gunderson, Scott K. Odorico, Zeeda H. Nkana, Rashea L. Minor, Samuel O. Poore, Aaron M. Dingle*

GIBSON

Chlorhexidine Delays Wound Healing in Human Skin; *Sameeha E Hassan, Collin Tran, Aiping Liu, Angela L F Gibson*

Indocyanine Green: Harnessing Novel Methods to Identify Burn Wound Healing Potential; *Jocelyn C Zajac, Aiping Liu, Sameeha E Hassan, Angela L F Gibson*

KAUFMAN

PD-1 Upregulation on Host CD8+ T Cells is Associated with Mixed Chimerism in Kidney Transplant Tolerance Induction; *Christopher J Little, Steven C Kim, John Fechner, Jennifer Post, Dixon B Kaufman*

KELM-NELSON

Gene Expression Alterations in Whole Blood as Potential Biomarkers for Early-Stage Parkinson Disease; *Sarah A. Lechner, Jacob M. Welsch, Stephen C. Gammie, Cynthia A. Kelm-Nelson*

Nucleus Ambiguus Inflammation and Cell Loss May be Linked to Vocalization Dysfunction in Pink1-/- Rats; *Sarah A. Lechner, Jacob M. Welsch, Abby J. Haglin, Taylor A.R. Kaldenberg, Danielle R. Rosenblum, Amy Regenbaum, Elizabeth Hoeppner, Peyton E. Vogt, David G.S. Barnett, Cynthia A. Kelm-Nelson*

KIMPLE

Mesenchymal Stromal Cells (MSC) for the Treatment Of Radiation-Induced Xerostomia; *Cristina Paz, Grace Blitzer, Annemarie Glassey, Jayeeta Giri, Andrea Pennati, Olga Ganz, Steven Schreiber, Kwangok P Nickel, Cynthia A. Kelm-Nelson, Vanessa L. Cannaday, Robert Pohlman, Tiffany Glazer, Ted Lunga, Daniel Robbins, Ryan Mattison, Tomy Varghese, Susan Thibeault, Nicole Rogus-Pulia, Jacques Galipeau, Randall J. Kimple*

LE

Effect of Cold Atmospheric Plasma on Viability of Human-Derived Neuroblastoma Cells; *Bindu A. Nair, Ha Nguyen, Juan Favela, Leon Shohet, Hau Le*

MCCULLOCH

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ORAL ABSTRACTS: GROUP ONE

Basic Science and Translational Research

Establishment of a Translational Rhesus-Primatized Mouse Model Using Transgenic Immunodeficient Mice

Christopher J Little, MD; W. John Haynes, PhD; Liupei Huang, MD; Cross Daffada, BS; Bryce B Wolfe, PhD; Elizabeth Perrin, BS; John A Simpson, BS; Jenna A Kropp Schmidt, PhD; Hayly M Hinkle, BS; Logan T Keding, BS; Dixon B Kaufman, MD, PhD; James A Thomson, VMD, PhD; Thaddeus G Golos, PhD; Matthew Brown, PhD

Introduction: Non-human primates (NHPs) represent an important model for a wide variety of pre-clinical studies involving novel biomedical and surgical interventions. However, in contrast to small animal models, widespread utilization of NHPs is restricted by cost, logistics, and availability. We therefore sought to develop a translational primatized mouse model, akin to humanized mice, to allow for high-throughput *in vivo* experimentation. Such a model could be leveraged as an efficient, cost-effective mechanism to inform implementation of novel therapeutic or diagnostic NHP studies, thus minimizing the risk and logistical burden of large animal models.

Methods: Strains of immunodeficient mice crossbred with (NOG-EXL, NSG-SGM3) and without (NBSGW) human (rhesus cross-reactive) cytokine transgenes were intravenously infused with $1x10^5$-$1x10^6$ bead-separated CD34+ rhesus cells. Thymic implantation was performed using cryopreserved autologous rhesus thymus fragments surgically placed within the mouse kidney capsule. Rhesus cross-reactive α-CD2 was administered for passenger leukocyte depletion to mitigate risk of graft-versus-host disease. Flow cytometric analyses were used for chimerism testing and immunoprofiling. Mixed lymphocyte reactions were employed as *in vitro* functional assays.

Results: Adult rhesus macaque mobilized blood (AMb) CD34+ enriched hematopoietic stem and progenitor cells (HSPCs) engrafted at low but persistent levels in immune-deficient mice harboring transgenes for human (rhesus cross-reactive) GM-CSF and IL-3 but failed to achieve engraftment in mice with wild-type murine cytokines. To enhance level and durability of chimerism, fetal liver-derived HSPCs were subsequently selected as the infusion product based on an increased fraction of CD34(hi) cells, which is known to encompass HSPCs with the greatest lymphohematopoietic potential. Additionally, based on established humanized mouse models, co-transplantation of rhesus fetal thymic fragments were performed to allow for *de novo* T cell development. Together, these protocol adjustments yielded robust, multilineage lymphohematopoietic engraftment in the cytokine-transgenic mice (Figure 1). The resulting emergent immune system recapitulated that of the HSPC source, with similar relative frequencies of lymphocyte, granulocyte, and monocyte subsets within the thymic, secondary lymphoid, and peripheral compartments. Importantly, despite exhibiting a predominantly naïve phenotype, *in vitro* functional assays demonstrated robust cellular activation in response to non-specific and allogenic stimuli.

Conclusions: We have developed a durable primatized mouse model, characterized by robust multilineage engraftment yielding a functional, recapitulated NHP immune system. This model is

well-poised for multiple applications within the fields of stem cell biology, developmental immunology, virology, and transplant immunology, all of which currently rely on NHP models.

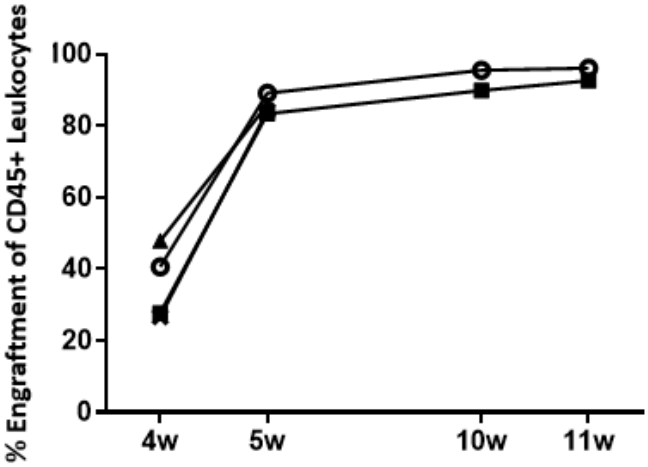

Figure 1. Total lymphocyte chimerism of NOG-EXL recipients of CD34+ enriched fetal liver-derived rhesus HSPCs and thymic fragment implantation

The Use of Protease Inhibitors to Treat Anal Cancer Spheroids Derived from HPV Transgenic Mice

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1. University of Wisconsin, Department of Surgery
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Introduction: Anal cancer is a disease of increasing incidence in the United States and globally. Anal cancer and anal dysplasia, precancerous anal lesions, are associated with infection with high-risk strains of human papillomavirus (HPV). Current treatments for anal dysplasia, to prevent anal cancer development, have a significant side effect profile and are associated with high recurrence rates. We have seen that certain protease inhibitors (PI), previously used in human immunodeficiency virus (HIV) treatment, are a well-tolerated and effective treatment in the setting of HPV-induced cervical dysplasia. We hypothesize that topical PI therapy will be an effective treatment for anogenital dysplasia, with the capacity to selectively target HPV positive tissue, leading to regression of anal dysplasia and prevention of anal cancer development.

Methods: Anal tumors were harvested from five transgenic mice *K14E6/E7*, who express E6 and E7 (HPV oncoproteins) in their epithelium. Tumors were excised and digested. Their cells were plated in Matrigel per standard protocols and allowed to grow for 24 hours before treatment. The tumor cells formed 3D multicellular aggregates, also known as spheroids, that were imaged prior to treatment. Spheroids were then placed in the following treatment groups: no treatment, vehicle (dimethyl sulfoxide (DMSO)), and Saquinavir 15μM, a protease inhibitor. At 24 hours post-treatment, spheroids were re-imaged. All images were taken using a Nikon Eclipse T*i*-S scope and spheroid diameters were measured using ImageJ. Data was analyzed using SPSS via one-way ANOVA.

Results: No treatment (n=119) and vehicle (n=126) groups demonstrated an increase in spheroid size over the 24-hour treatment period. In contrast, spheroids treated with Saquinavir (n=150), demonstrated a statistically significant percent reduction when compared to no treatment (p value < 0.01) and vehicle (p value < 0.01) groups.

Conclusions: Use of the protease inhibitor, Saquinavir, leads to a statistically significant percent reduction in mice anal tumor spheroid growth ex-vivo when compared to no treatment and vehicle. Protease inhibitor therapy may be an effective treatment or adjuvant therapy to the Nigro protocol to promote anal cancer tumor regression.

Positron emission tomography neuroimaging of FDG uptake in PINK1-/- rats: glucose metabolism in a Parkinson Disease model

Alexander K. Converse, PhD[a]*, Maxim S. Slesarev, BS[a], Alex F. Nisbet, BS[b], John C. Szot, BS[b], Michelle R. Ciucci, PhD[bc]

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Introduction: Degeneration of central noradrenergic and dopaminergic systems is observed in Parkinson Disease (PD), leading to vocal communication deficits. We seek to test the central hypothesis that brainstem norepinephrine and dopamine are altered in response to behavioral and pharmacologic treatments aimed at improving vocal communication using the *Pink1*-/- rat model of PD. In addition to behavioral and histological measures, we will use positron emission tomography (PET), which permits within-subject longitudinal imaging. This enhances sensitivity to treatment response and may inform the design of human neuroimaging studies, which are lacking in translational voice research. Here we describe preliminary studies using the glucose metabolism radiotracer [^{18}F]fluorodeoxyglucose (FDG).

Methods: Adult male wild type and *Pink1-/-* Long Evans rats were imaged four at a time with high resolution PET under isoflurane anesthesia. Following acquisition of a ^{57}Co transmission scan, data were acquired in event mode for 90 minutes with 0.87±0.09 microCi/g FDG injected 1-4 minutes after scan start. List mode data were framed at 90 x 1 minute and reconstructed to produce quantitative 4D radioactivity concentration images (Bq/mL). Images were aligned to a template space. Time-activity curves were determined for 80 regions of interest and scaled to injected dose / body weight (standardized uptake value, SUV) to account for differences in radiotracer administration and distribution. 30-60 minute average uptake values were further normalized to whole brain to account for individual differences in metabolism, excretion, and delivery to brain (SUVr).

Results: Preliminary analysis of SUVr measures from four wild type subjects (Figure 1) indicates a mean coefficient of variation between subjects, averaged over the 80 regions of interest, of CV = 0.041 +/- 0.025. In regions of particular interest for examination of noradrenergic effects, the CVs were medial prefrontal cortex (62 uL): 0.07, thalamus (also 62 uL): 0.02, and locus coeruleus (96 uL): 0.03.

Conclusions: These preliminary results show this method is feasible, and suggest that within-subject baseline and follow-up measures of treatment response will be sensitive to relatively small changes in this index of glucose metabolism in brain regions associated with vocal control. Analysis is ongoing to examine metabolic differences between wild type and *Pink1*-/- subjects. In future PET work with this rodent PD model, we will measure binding of the norepinephrine transporter ligand [^{18}F]NS12137 to determine its response to treatment and its association with vocal communication outcomes.

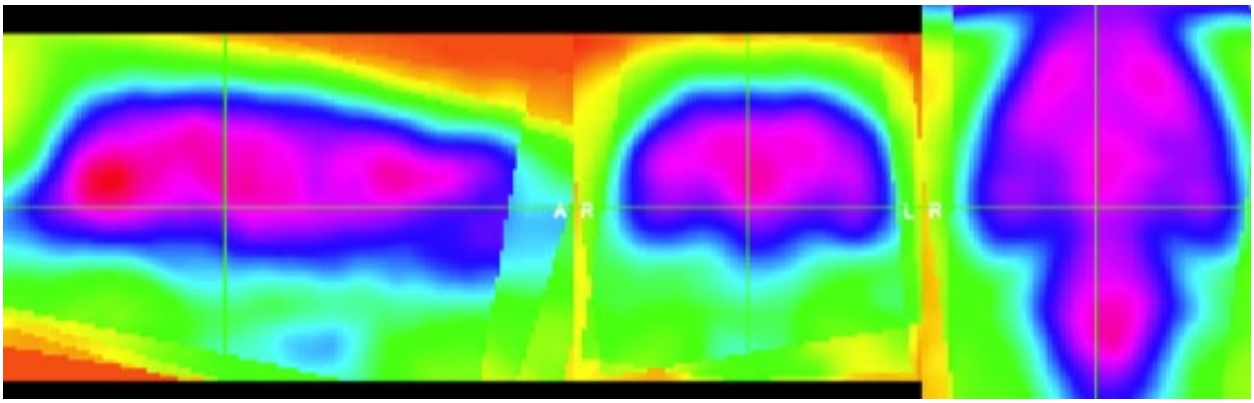

Figure 1. Average aligned brain radioactivity image of four wild type subjects (0-90 minutes p.i. FDG).

Effects of social condition on vocal communication, anxiety, depression, cognition, and neurobiology in the *Pink1-/-* rat model of Parkinson Disease

Courtney K. Broadfoot[1,2], Charles Lenell[1], Cynthia A. Kelm-Nelson[1], and Michelle R. Ciucci[1,2,3]
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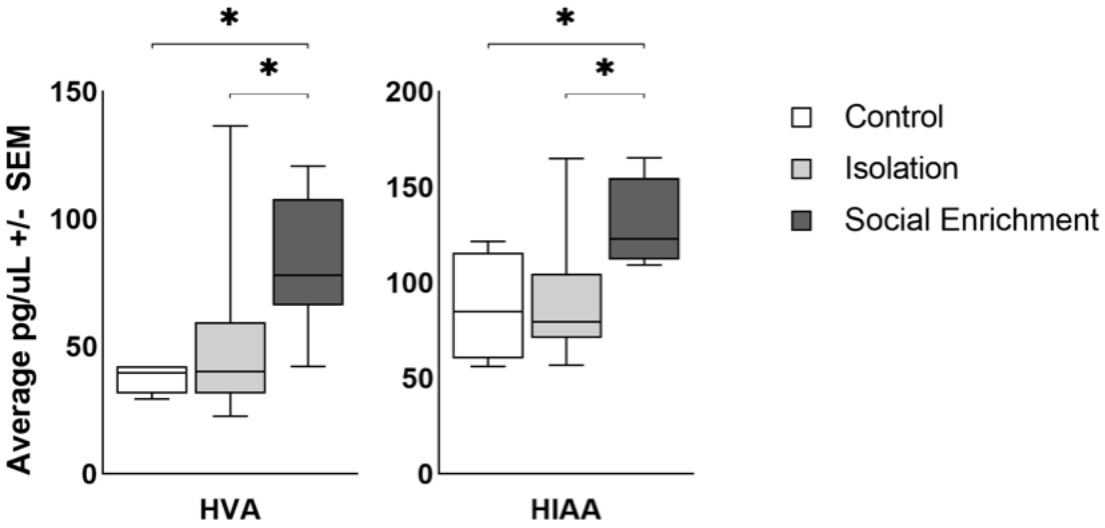
[3]Neuroscience Training Program

Introduction: Social interactions are negatively impacted by communication deficits, anxiety, depression, and cognitive decline in Parkinson Disease (PD). The influence of social condition (isolation or enrichment) on the progression of these deficits, however, is unknown. Further, the underlying neurobiology that modulates vocal and non-motor outcomes (anxiety, depression, cognition) in PD is not well understood, which prevents treatment optimization. The ventral tegmental area (VTA), a region associated with reward-like social processing, is distrupted by stressful stimuli (i.e., isolation) and is impacted by PD. Humans with PD display variability in age, phenotype, social situation, medication, and motivation, thus our lab uses the *Pink1-/-* rat model of PD, which displays early and progressive sensorimotor dysfunction paralleling disease progression in humans. The central hypotheses for this study were that social condition would alter vocal function, anxiety, anhedonia (depression), and cognition; specifically, that isolation would degrade these functions and that social enrichment would enhance them. Further, we hypothesized that social isolation would reduce dopaminergic (DA) and serotoninergic (5HT) systems in the VTA and that social enrichment would result in increases in these systems.

Methods: Twenty-four *Pink1-/-* rats were randomized into 3 social conditions: 1) control: housed in pairs, 2) isolation: housed individually, and 3) social enrichment: housed in pairs and underwent social enrichment, which involved grouping rat pairs for 1 hour, 5x per week to promote socially-driven vocalizations. Rat vocalizations (USVs), anxiety (elevated-plus maze), anhedonia (sucrose preference test), and cognitive function (novel object task) were assessed and compared at 2, 4, 6, 8, and 10 months of age. High-performance liquid chromatography (HPLC) was used to assay catecholamine concentrations in micro punches of the VTA.

Results: Repeated measures ANOVAs with factors of timepoint (2, 4, 6, 8, and 10 months) and social condition (control, isolation, social enrichment) found no differences in USV acoustics. The social enrichment group displayed reduced anhedonia compared to the isolated ($p<0.001$) and control groups ($p<0.05$). The remaining cognitive and anxiety assay results will be presented. Illustrated in Figure 1., one-way ANOVAs with the factor of social condition show increased HVA (a dopamine metabolite) in the social enriched group compared to the isolated ($p<0.05$) and control groups ($p<0.05$). Additionally, HIAA (a serotonin metabolite) was elevated in the socially-enriched group compared to the isolated ($p<0.05$) and control groups ($p<0.05$).
Conclusions: Our results confirmed aspects of our hypotheses; specifically, that social enrichment reduced anhedonia (depression) and resulted in increased DA and 5HT turnover in the VTA of *Pink1-/-* rats. This work will guide future clinical studies to explore how social interactions may affect functional communication outcomes in PD.

Figure 1. Catecholamine Concentration in the VTA. HPLC results revealed HVA (a dopamine metabolite) in the VTA was significantly increased in the socially enriched group compared to the isolated ($p<0.05$) and control groups ($p<0.05$). Additionally, HIAA (a serotonin metabolite) in the VTA was significantly elevated in the socially enriched group compared to the isolated ($p<0.05$) and control groups ($p<0.05$). N=24 ($n=8$ per group) $* p <0.05$



Social isolation results in disrupted vocal acoustics and increased dopamine and serotonin in the ventral tegmental area

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Introduction: Vocal communication plays an important role in health and wellness. The effects of social isolation on vocal communication, anxiety, depression, and cognition are not well understood. Futher, the usefulness of a social enrichment intervention to treat these aspects of dysfunction is unknown and the underlying mechanisms govenerning these complex behaviors are not well-defined. As a crucial first step, we studied socially-motivated ultrasonic vocalizations (USVs) in wild-type (*i.e*. healthy) rats. The catecholaminergic systems of the ventral tegmental area (VTA) are associated with social and reward processing and ultrasonic vocalizations and are suseptible to changes in social stress (isolation). The central hypotheses for this study were that 1) *social isolation* would alter rodent behavior by decreasing USV acoustics (i.e. loudness), increasing anxiety and anhedonia (depression), and reducing cognition and that 2) *social enrichment* would increase vocal communication, reduce anxiety and anhedonia, and increase cognitive function.

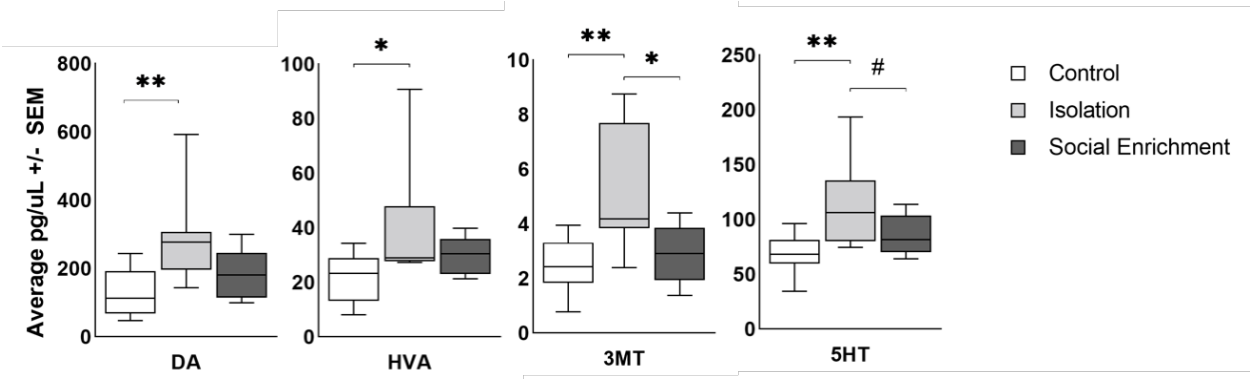
Methods: Twenty-four male WT rats were randomized into 3 groups: 1) control, housed with a cage-mate, 2) isolated, housed individually, and 3) socially-enriched, housed with a cage-mate and underwent social enrichment, which involved grouping rats in a larger ‘socialization’ cage with another pair of cage mates 5x per week. USVs were recorded at 2 (baseline-prior to randomization), 4, 6, 8, and 10 months of age (timepoints). At each timepoint, rats were also assessed for anxiety (elevated-plus maze), anhedonia (sucrose preference test), and cognitive function (novel object recognition test). Micro punches of the VTA were assayed for levels of dopamine, norepinephrine, and serotonin and associated metabolites using high-performance liquid chromatography.

Results: To investigate our first hypothesis regarding the impact of social isolation, a repeated measures ANOVA with factors of housing condition (pair housed, isolation) and timepoint (2, 4, 6, 8, and 10-months) was used. We found that the isolated group produced vocalizations of reduced tonality (loudness) ($p<0.05$). Trends revealed the isolated group demonstrated reduced anxiety and reduced cognitive function compared to the group house in pairs. Regarding our second hypothesis, the impact of social enrichment, results revealed that the social enrichment group had increased cognitive function compared to the control group. HPLC results revealed that the isolation group had significant increases in levels of dopamine ($p<0.01$), HVA ($p<0.05$), and 3MT ($p<0.01$) as well as 5HT ($p<0.05$) compared to the groups housed in pairs. There were no effects of social enrichment on VTA outcomes (Figure 1).

Conclusions: This study suggests that chronic social isolation in adulthood adversely impacts

socially-mediated vocal communication and results in increased dopaminergic and serotonergic systems in the VTA of otherwise healthy rats.

Figure 1. Average concentration (pg/uL) (+/- SEM) of dopamine (DA), HVA, and 3MT and serotonin (5HT) in micro punches of the VTA (Bregma -4.80). Rats in the isolation group had significant increases in levels of DA (p<0.01), HVA (p<0.05), and 3MT (p<0.01) as well as 5HT (p<0.05) compared to the control group (housed in pairs) and increased 3MT (p<0.05) compared to the social enrichment group. When comparing the social enrichment group to the control group, there were no effects of social enrichment on VTA outcomes. N=24 (n=8 per group) $*$ p <0.05, $**$ p < 0.01, $***$ p < 0.001, # p < 0.10



The *Pink1-/-* rat demonstrates oromotor and gastrointestinal dysfunction in the early stage of Parkinson disease

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Introduction: Parkinson disease (PD) is a degenerative disorder most-commonly known for hallmark motor signs at the time of diagnosis. Other signs, including swallowing and gastrointestinal (GI) dysfunction, however, manifest decades prior to a formal diagnosis, appear as non-specific, and go unreported. This makes the identification, treatment, and the study of swallowing and GI dysfunction in the early stages difficult. The *Pink1*-/- rat, a model of early PD, demonstrates salient early PD signs including vocal, chewing, and limb dysfunction; however, swallowing and GI deficits have not been evaluated. We hypothesized that adult *Pink1-/-* rats would show early and progressive oropharyngeal dysphagia, delayed gastric emptying, and signs of constipation.

Methods: Thirty male rats were tested at 4 (*Pink1-/-* = 15, wildtype (WT) controls = 15) and 6 (*Pink1-/-* = 7, WT = 6) months of age. Videofluoroscopic images of rats ingesting a peanut-butter-barium mixture were taken at 30 frames/second. Mastication rate (cycles/second), oropharyngeal bolus velocity (mm/s), and pharyngoesophageal bolus velocity (mm/s) were measured. Videofluoroscopic images of rats post-oral gavage of 2 mL of liquid barium were obtained to track barium contents at the stomach, small intestine, caecum, and colon at hours 0-6. Number of fecal emissions and average weight (grams) of fecal emissions over a 24-hour period were also collected. Two- and three-way mixed model ANOVAs were performed for swallowing and GI data, respectively ($\alpha<0.05$).

Results: Compared to WT controls, *Pink1-/-* rats showed slower rates of mastication ($p<0.001$) and had increased pharyngoesophageal bolus velocities ($p<0.01$) at both 4 and 6 months of age. No differences were noted for oropharyngeal bolus velocity. At 2 hours post-gavage, *Pink1-/-* demonstrated faster gastric emptying ($p<0.05$). Two, four, five, and six hours post-barium gavage, *Pink1-/-* rats showed fewer contents in the colon compared to WT controls ($p<0.01$). *Pink1-/-* rats (per cage unit) also had a lower fecal pellet count and higher fecal pellet weight after 24 hours at 6 months of age ($p<0.01$).

Conclusions: Our data suggest that the *Pink1-/-* rat has aerodigestive and GI functional deficits. *Pink1-/-* rats exhibit signs of oropharyngeal dysfunction as early as 4 months of age (younger than previously reported). This study is the first to report delayed content transit to the colon and constipation-like signs. These early deficits in *Pink1-/-* rats are analogous to those observed in human PD and suggests that this model of PD may be useful for future work studying mechanisms underlying Parkinsonian GI pathology.

Assessment of swallow function in a translational rat model of chemoradiation and lingual exercise

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Introduction: Radiation and chemotherapy combined with radiation treatment (chemoradiation) can lead to impaired swallow function (dysphagia), which has significant health and quality of life implications for patients diagnosed with head and neck cancer both acutely and long-term. Lingual exercise may be beneficial in reducing swallow deficits, yet research is limited. In this study, we assessed the effects of chemoradiation, radiation, radiation + lingual exercise, and chemoradiation + lingual exercise on bolus dynamics in a rat model. We hypothesized: 1) both treatments would impact bolus dynamics, and 2) exercise would affect bolus dynamics, leading to improved swallow outcomes compared to treatment alone.

Methods: 32 Sprague-Dawley rats were divided into 4 groups: radiation, chemoradiation, radiation + lingual exercise, and chemoradiation + lingual exercise. Rats underwent a baseline videofluoroscopic swallow study (VFSS), the gold standard for functional swallow assessment, prior to treatment (+/- exercise) and 3 months' post-treatment, and therefore served as their own controls. Radiation treatment consisted of 10 fractions of 4.5 Gy/day (SAARP) at an 8 mm X 12 mm area of the tongue base. Rats in the chemoradiation group were given a dose of Cisplatin (3mg/kg) prior to radiation. Following treatment administration and standard recovery time, rats in the exercise groups completed a progressive resistance tongue training paradigm. Kinematic analysis was conducted via ImageJ on VFSS data to analyze differences in bolus velocity (speed), bolus area (mm2), and mastication rate between the 4 groups. We used a two-way repeated-measures ANOVA and post hoc Bonferroni correction. A p-value < 0.05 was used to determine significance. Three swallows and five mastication cycles were analyzed and averaged per rat.

Results: There were significant decreases in bolus speed ($p<0.001$), bolus area ($p=0.002$), and increase in mastication rate (cycles/second, $p=0.021$) pre- to post-treatment overall. Chemoradiation rats had significantly faster mastication rate compared to chemoradiation + lingual exercise ($p=0.027$), who maintained rates similar to baseline measurement. This indicates a potential issue with musculature/mandibular range of motion (ROM) post-treatment; jaw aperture and breathing patterns will be further explored.

Conclusions: Kinematic analysis demonstrated deficits in functional swallow measures post-treatment. Further, there is a potential benefit of lingual exercise in maintaining mandibular ROM. These analyses provide helpful information regarding the impacts of treatment on swallow function and potential benefits of lingual-based intervention on bolus dynamics and subsequent swallow outcomes.

Effects of Thickened Liquids: A Translational Pilot of Chronic Use

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Introduction: Thickened liquids are a common clinical intervention for dysphagia across a wide range of etiologies. However, it is not well-understood how chronic use of thickened liquids affects the swallowing system and underlying biology. Clinical studies are limited by low patient adherence to thickener recommendations, broad outcome measures, and the invasive measures needed for studying underlying biology. The goal of this pilot study was to determine if a rat model represents a feasible and valid method for studying the effects of chronic use of thickened liquids on functional swallowing outcomes and kinematics.

Methods: Across 7 weeks, 12 young adult male Sprague-Dawley rats received *ad libitum* access to International Dysphagia Diet Standardization Initiative (IDDSI) level 2 mildly-thick liquids or IDDSI level 3 moderately-thick liquids for 12 hours per day and food for 24 hours per day. Rats underwent videofluoroscopic swallow study (VFSS) of the assigned texture at baseline and after 7 weeks of thickened liquids. Variables examined were: respiratory-swallow pattern, apnea duration, percentage of swallows with pharyngeal residue, and percentage of daily fluid intake consumed relative to recommended fluid intake normalized by body weight.

Results: All rats completed the study, and no rats exhibited significant (≥15%) loss of body weight from baseline. Relative to veterinary-recommended volume of fluid intake (10-12mL/100g body weight), the mildly-thick and moderately-thick groups consumed suboptimal volumes following 7 weeks of thickened liquids: 70.1% (6.5%) and 59.9% (9%), respectively. Sufficient data for analysis of VFSS were obtained for 9 rats (n=4 mildly thick groups; n=5 moderately thick). Both groups demonstrated an increase in percent of swallows with pharyngeal residue (mildly thick: +38%, moderately thick: +10%), and a modest increase in an aberrant post-swallow inhale pattern (mildly thick: +5%, moderately thick: +6%) compared to baseline swallows of assigned viscosity.

Conclusion: Use of thickened liquids reduces liquid consumption, increases the presence of residue after the swallow, and alters respiratory-swallow coordination analogously for rats and humans, indicating validity of this model for addressing translational clinical questions regarding effects of chronic use of thickened liquids. Understanding effects of chronic thickened liquid use would facilitate clinical decision-making in balancing patient risk of thin liquid aspiration, versus overall health, quality of life, and deleterious effects associated with thickened liquid use. Future studies building on this work will interrogate biological mechanisms underlying these changes in swallow function, first in healthy rats, and in models of aging and neurologic disease.

Motor neuron loss in the contralesional hypoglossal nucleus is associated with reduced tongue force after unilateral stroke

Miranda Cullins, PhD and Nadine Connor, PhD

Introduction: Lingual weakness commonly occurs after stroke, yet the neuromuscular changes that underlie this phenomenon are not well understood. The motor neurons that activate the tongue muscles are located in the left and right hypoglossal nuclei. Our previous studies in a rat stroke model found evidence of tongue muscle fiber remodeling on the side opposite the damaged cerebral hemisphere (contralesional). Our hypothesis is that cerebral ischemia results in the loss of motor neurons in the contralateral hypoglossal nucleus.

Methods: Rats underwent either unilateral middle cerebral artery occlusion to induce cerebral ischemia or a sham-control surgery (N = 7 stroke, 6 sham). Brainstems were collected 8 weeks after surgery and sectioned by cryostat. The middle regions of the hypoglossal nuclei were sampled using five 50μm sections of the brainstem, spaced 300μm apart and centered at the formation of the central canal. Alpha motor neurons within each hemisphere's hypoglossal nucleus were identified by fluorescent staining and counted using a customized ImageJ macro. The average number of motor neurons per 50μm section are reported. In a subset of the rats (N = 5 stroke, 4 sham), maximum volitional tongue force was measured at baseline and 8 weeks after surgery; the 8-week maximum force was normalized to baseline.

Results: The number of motor neurons in the hypoglossal nucleus contralateral to the damaged hemisphere was significantly less in the stroke group compared to the sham group (Stroke = 49.5 ± 10.9, Sham = 62.2 ± 14.4; $p = 0.049$). Motor neuron reductions in the nucleus on the stroke side were not significant (Stroke = 56.1±14.7, Sham = 63.4±12.3; $p = 0.18$). Within the stroke group, there were significantly fewer motor neurons in the contralesional nucleus as compared to the nucleus on the side of the cerebral damage (Contralesional = 49.5±10.9, Ipsilesional = 56.1±14.6; $p = 0.039$). The number of motor neurons in the contralesional hemisphere was moderately correlated with tongue force (Pearson's $r = 0.64$).

Conclusion: Motor neuron loss in the brainstem hypoglossal nuclei occurs after cerebral ischemia, predominantly on the side opposite the damaged hemisphere. This motor neuron loss is associated with lingual weakness.

Application of the Novel Free Radical Scavenger PrC-210 to UW Organ Preservation Solution for Prolongation of Rat Hind Limb Static Cold Storage as a Vascularized Composite Allograft Model: A Pilot Study

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Introduction: Vascularized composite allotransplantation (VCA) represents a superior solution to autologous free tissue transfer and prostheses, yet a major factor limiting widespread success is the irreversible tissue damage caused by ischemia reperfusion. Current organ preservation solutions, such as University of Wisconsin (UW) solution, have transformed the field of transplantation but do not demonstrate extensive efficacy in terms of scavenging the reactive oxygen species (ROS) that lead to apoptosis and necrosis. PrC-210 currently the most efficient ROS scavenger in existence, demonstrating efficacy in several studies. The present study aims to determine if the addition of PrC-210 to UW solution can increase the preservation time of a rat hind limb VCA graft model.

Methods: Lewis rats (male, 295-450g) were anesthetized using 5% isoflurane before receiving full body cardiac perfusion of room temperature UW solution with or without PrC-210 (0, 10, 20, 30, and 40 mM). Following transfemoral amputation of both hind limbs, the limbs are stored independently at 4°C in UW solution with the same PrC-210 concentration as the perfusate for 48h. Two punch biopsies per-time point (0, 4, 8, 24 and 48 hours) were taken for enzymatic and histological examination of apoptotic cell death marker, cleaved caspase.

Results: PrC-210 significantly reduced apoptotic cell death over 48h of cold storage: Enzymatic assays of caspase activity in amputates stored at 4°C in UW solution (control) indicates a peak apoptotic response at 8h post amputation, followed by a rapid decline out to 48h in control tissue. Additional statistical analysis on the peak apoptotic time (8h) indicates a significant increase in apoptosis for control samples compared to baseline and a significant decrease in caspase activity for all concentrations of PrC-210. Additionally, all concentrations of PrC-210 demonstrate significantly lower levels of apoptosis at all-time points, including the experimental end point of 48h. Histology showed that while injury was observed to some degree in all samples, and qualitatively appears to increase as a product of time, the injury to cells treated with PrC-210 appears to occur at a lesser rate than the control tissue without PrC-210. This was best demonstrated at 8h, with all groups being comparably damaged at 24h.

Conclusions: The addition of PrC-210; a newly invented ROS scavenger, to UW solution can substantially reduce the incidence of irreversible tissue damage in cold preservation. Work to determine the optimal concentration and preservation of donor VCA limbs remains ongoing and will inform future transplantations in rats.

Building the Pre-clinical Rationale to Elevate the Osseointegrated Neural Interface to a Clinical Level

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Introduction: New-age prosthetics must confront the challenge of restoring functionality and sensation through the establishment of a bidirectional closed-loop interface with the nervous system. Noninvasive approaches such as electromyography demonstrate stability but lack the necessary selectivity; the more invasive percutaneous methods employing implantable electrodes exhibit great selectivity but suffer the chronic instability of dynamic soft tissue environments. In conjunction with their inability to provide sensory feedback, the current Peripheral Nerve Interfaces (PNIs) have failed to confront the seemingly contradictory need for chronic stability and selectivity demanded by neuroprosthetics. The osseointegrated neural interface (ONI) was developed to transcend this central paradox through the combination of osseointegration and nerve regeneration, intending to exploit the protection and stem cell-rich environment provided by the medullary canal of long bones. The objective of this study was to explore requirements and surgical approaches for establishing an ONI in humans for future clinical application.

Methods: Three upper and three lower limb cadavers underwent dissection for anatomical examination of the major peripheral nerves and CT imaging of the medullary canal of select long bones. Measurements of peripheral nerve circumference, length, and depth were taken. CT imaging of the ulna, radius, tibia, and fibula enabled the measurement of bone length, medullary cavity diameter, and medullary cavity volume.

Results: Measurements were conducted on six limbs (5 male, 1 female) with an average cadaver age of 67.3 ±9.1. The medullary cavity volume of the ulna and radius exhibited means 11.15 ± 1.70 and 13.30 ± 3.84 mL, respectively. The mean medullary cavity volume of the tibia and fibula was 180.92 ± 13.45 and 23.29 ± 12.44 mL. The average midpoint circumference of all major nerves was 10.94 ± 0.84 mm in the upper extremities and 7.37 ± 3.70 mm in the lower limbs.

Conclusion: The anatomical information obtained in this study will inform the future surgical integration of an ONI in humans. Measurements of nerve morphology and medullary cavity enable prospective decision-making regarding electrode selection and placement within the intramedullary space, accompanied by an osseointegrated prosthetic abutment. These measurements will be vital in the clinical application of an ONI. The ONI seeks to transcend the limitations of modern PNIs through the microsurgical establishment of bi-directional interface within the protected space of the medullary canal capable of balancing the need for chronic stability and selectivity, synthesizing a more holistic solution to improving the quality of life for millions of amputees.

Ovine Peripheral Nerve Mapping to Facilitate Development of an Osseointegrated Neural interface

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Introduction: Large animals are commonly used as preclinical models in medical research, yet their usage in the field of neural prosthetic control is scarce. Osseointegrated prosthesis research is currently being conducted on ovine models, but research of the neuronal control of advanced prostheses will require further development of the model. Technological innovations in neural interfacing, such as the osseointegrated neural interface (ONI), require a model that is capable of determining the validity of these cutting-edge technologies. Generalized topographical maps of the ovine nerves do exist, but specific information regarding the nerves distal to the carpal and tarsal joints is inadequate. This study aims to examine the major nerves of ovine thoracic and pelvic limbs distal to the carpal and tarsal joints to create an anatomical map to assist the development of a chronic ONI for prosthesis control with clinical translatability to humans.

Methods: Six thoracic and four pelvic cadaveric limbs were obtained from mature, non-lactating female sheep of mixed breeds for anatomical study. Radiographic analysis of each limb was performed and measurements of bone length, intermedullary space, and cortical bone thickness were obtained. Microsurgical dissection was utilized to explore the topography of the prominent nerves of the thoracic and pelvic limbs along the metacarpus and metatarsus. The branch points of each nerve were also noted. Additionally, the circumference of the proximal, mid, and end points of each nerve along the metacarpus or metatarsus were recorded. From this data, illustrations of the variations in nerve branching were created. Finally, histological analysis was performed to determine fascicular number and epineural thickness

Results: Three ventral and one dorsal thoracic limb nerves were identified with a mean midpoint circumference of 5.032 mm and 5.611 mm, respectively. Two ventral and one dorsal pelvic limb nerves were identified with a mean midpoint circumference of 7.074 mm and 5.313 mm, respectively. The mean diameter of the intermedullary canal in the limbs was 9.461 mm at the midpoint. The mean cortical bone thickness of the limbs was 3.685 mm at the midpoint. Measurements of the bone indicate an average metacarpal length of 15.0 cm and an average metatarsal length of 19.5 cm

Conclusions: There is a paucity of clinically translatable chronic large animal models to determine the validity of neural prosthetic control technologies. This study mapped ovine pelvic and thoracic limb nerve topography to assist in the design and integration of an ONI suitable for chronic testing.

Chlorhexidine Delays Wound Healing in Human Skin

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Introduction: Chlorhexidine (CHG) is ubiquitous in surgical perioperative care. *In vivo* studies of CHG cytotoxicity on human skin are lacking. Given the use of CHG for daily wound cares and as a presurgical scrub, including donor site preparation, we sought to identify if CHG cytotoxicity would persist in a clinically relevant *in vivo* human skin xenograft model.

Methods: Human skin tissues were obtained from elective surgeries. Partial thickness wounds were created *ex vivo* in human skin using a 4 mm punch biopsy. 2% CHG (treatment) or PBS (control) was applied to the wounds for 30 minutes followed by rinsing the tissue +/- mechanical disruptive irrigation. Tissues were cultured at the air-liquid interface for 24 hours in culture media after treatment and tissue viability was performed using an MTT assay. For *in vivo* studies, athymic mice (n=4) were grafted on bilateral flanks with human skin. Eight weeks after engraftment and normalization of skin architecture, 4 mm partial thickness wounds were created on each xenograft (2 per mouse – treatment and control). 2% CHG was applied daily for 2 minutes followed by irrigation with PBS in the treatment wound. The control wound received PBS application and irrigation. The xenografts received treatment daily for 14 days to mimic daily wound cares, and digital images were obtained to document presence of infection and gross wound healing. On day 14, the xenografts were harvested and stained for lactate dehydrogenase and H&E to assess cell viability and wound re-epithelization, respectively.

Results: An MTT assay on *ex vivo* human skin wounds showed that CHG treated groups (irrigation or non-irrigation) had lower cell viability compared to the PBS treated group, however irrigation mitigates the cytotoxicity of CHG on human skin. In the *in vivo* xenograft study, no signs of infection were identified in either PBS or CHG treated wounds throughout the study. The wound size appeared larger on gross inspection in the CHG treated group compared to the PBS group as early as day 2. Microscopically, the PBS treated wounds were fully re-epithelialized (n=2) or had significantly more re-epithelialization (n=2) than the CHG treated wounds (n=4) after 14 days of treatment. The PBS-treated wounds were viable throughout the tissue, indicating the irrigation procedure was not harmful to the cells. In the CHG-treated wounds, nonviable cells were observed in the dermis beneath the wound that was directly in contact with CHG suggesting penetration of CHG contributes to cytotoxicity in acute wounds.

Conclusions: Daily CHG use is cytotoxic to human skin and impedes wound healing. Use of CHG for cleansing acute wounds should be avoided. Perioperative use of CHG baths, where the CHG is allowed to persist without rinsing, should be further evaluated for impact on wound healing including on donor site preparation for autograft harvest.

Indocyanine Green: Harnessing Novel Methods to Identify Burn Wound Healing Potential

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Introduction: Objective determination of burn wound healing potential remains elusive and significantly impacts decision making for surgery, the extent of tissue excised intraoperatively and the use of donor site-sparing alternative tissue therapies. Indocyanine green angiography (ICGA) has promise as an adjunct to evaluate healing potential, but feasibility has limited adoption in clinical practice. Delayed fluorescence imaging of indocyanine green (ICG), in a method called second-window ICG (SWIG), is a new technique used intraoperatively to guide tumor resection via increased peritumoral endothelial permeability. The objective of this study is to examine ICGA and SWIG fluorescence in burns requiring excision and grafting, and to correlate SWIG fluorescence to microscopic localization of inflamed and necrotic tissue.

Methods: Deep partial thickness, indeterminate depth or full thickness burns were identified in adult patients scheduled for excision and grafting. 24 hours prior to surgery, baseline bright light and fluorescence images were obtained before the administration of up to 5 mg/kg ICG intravenously. ICGA was performed within 5 minutes of infusion initiation. On the day of surgery, bright light and SWIG fluorescence images were obtained before and after burn excision. The excised tissue was imaged *ex-vivo* to determine the presence of fluorescence in the tissue compared to that remaining within the wound bed. Excised tissue was processed for histologic analysis of cellular architecture, viability, inflammation and necrosis. Macroscopic ICGA and SWIG fluorescence images were compared to the associated microscopic tissue sections to determine the presence of inflammatory infiltrate, localization of non-viable tissue, and co-localization of ICG fluorescence.

Results: ICGA imaging performed preoperatively demonstrated variable fluorescence throughout the burns without a clear cutoff value to delineate deep partial versus full thickness burns. SWIG imaging revealed a speckled fluorescence pattern prior to burn excision that became diffuse after excision suggesting a potential utility of SWIG to intraoperatively identify excision completion. ICGA and SWIG fluorescence demonstrated an inverse relationship, and SWIG fluorescence was associated with non-viable tissue.

Conclusions: ICGA imaging alone was unreliable to delineate the need for surgical intervention. SWIG imaging of burn injuries may represent a valuable tool to guide the extent of excision intraoperatively and reduce unnecessary excision of viable tissue. Further studies are needed to understand SWIG fluorescence at the inflammation-necrosis border and how ICGA fluorescence along with SWIG can synergistically improve detection of healing potential in burn patients.

Applicability of Research to Practice: This study addresses the gap in knowledge regarding

objective determination of burn wound healing potential and lays a foundation for novel technology development.

PD-1 Upregulation on Host CD8+ T Cells is Associated with Mixed Chimerism in Kidney Transplant Tolerance Induction

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Introduction: Transplant tolerance obviates the need for lifelong immunosuppression. A promising strategy to achieve tolerance involves establishment of immunologic chimerism in recipients via infusion of donor-derived hematopoietic cells (HC). The underlying peripheral mechanisms of mixed chimerism-based tolerance induction is poorly understood, thus restricting novel therapeutic strategies. PD-1 is a T cell co-inhibitory molecule involved in T cell exhaustion and antigen specific hypo-reactivity. PD-1 signaling has a known role in the development and maintenance of self-tolerance, with its dysfunction having been implicated in multiple autoimmune pathologies. Based on these foundations, we sought to elucidate its contribution to engraftment and mixed chimerism-based operational tolerance in the rhesus macaque model.

Methods: A non-myeloablative, helical tomotherapy-based total lymphoid irradiation and anti-lymphocyte globulin conditioning regimen was applied to a 3-5 MHC antigen mismatched rhesus macaque kidney + HC transplant model. Peri-infusion Belatacept was utilized as T cell costimulatory blockade to reduce early donor-specific antibody production. Eight animals were included in this experimental cohort. Flow cytometry-based assays were utilized to perform cellular immunophenotyping and PD-1 analyses.

Results: The tolerance induction protocol coupled with Belatacept therapy yielded a 50% (4/8) rate of transient mixed chimerism induction after donor HC infusion. None of the four chimeric animals developed evidence of alloreactivity, as evident by negative flow cross match and clean allograft histology. In contrast, three of the four non-chimeric animals succumbed to acute antibody- and cellular-mediated rejection by one year. As shown in Figure 1, there was an upregulation of PD-1 expression on the surface of emerging host CD8+ T cells in chimeric animals, as evident by a 4.5-fold increase in percentage of PD-1(hi) cells compared to non-chimeric recipients at 30 days post-infusion ($P<0.05$). Importantly, CD8+ T cells were the predominant phenotype among the recovering immune system in both groups. Conversely, CD4+ T cells, which represented the minority of circulating T cells, exhibited a similar relative frequency of PD-1(hi) expression irrespective of engraftment. Preliminary data additionally revealed a 9-fold decrease in PD-1(hi) expression among CD8+ T cells during development of acute allograft rejection.

Conclusions: Post-transplant non-myeloablative conditioning coupled with T cell costimulatory blockade is sufficient for the establishment of mixed chimerism in MHC-disparate recipients, which is protective against allograft rejection. Furthermore, these findings suggest that PD-1 expression by CD8+ T cells could play an important role in controlling alloreactivity during engraftment and homeostatic recovery, thus serving as a potential target for therapeutic

augmentation.

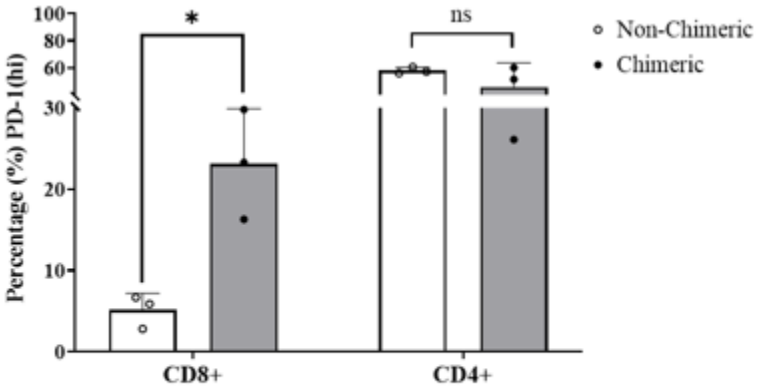

Figure 1. PD-1(hi) expression on CD8+ and CD4+ T cells at 30d post-infusion among recipients of immediate post-transplant tolerance induction (* P<0.05)

Gene Expression Alterations in Whole Blood as Potential Biomarkers for Early-stage Parkinson Disease.

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Introduction: The molecular pathology of early-stage Parkinson disease (PD) is poorly understood; as such, there are no specific predictive or non-invasive diagnostic tests. To address this gap in knowledge, our work uses the *Pink1*-/- rat model of early-onset and progressive PD. Male *Pink1-/-* rats demonstrate progressive motor deficits by mid-to-late adulthood (8 months (mo) of age) as well as brainstem and muscle pathophysiology including markers of inflammation. The purpose of this work is to identify dysregulated gene pathways within the blood of young *Pink1-/-* rats (2-4mo of age) that appear *prior* to the onset of limb motor signs. We tested the hypothesis that loss of *Pink1* alters inflammation gene expression in the blood resulting in the upregulation of gene pathways that begin early, progress with age, and may predict limb motor deficits.

Methods: Limb sensorimotor testing (open field) was performed, immediately followed by the collection of whole blood from: *Pink1-/-* rats (young, n=16; old, n=16) and wildtype (WT) controls (young, n=16; old, n=16). The Illumina® Total RNA-Seq TruSeq platform was used to profile differential expression of genes (DGE) in the whole blood between genotypes and ages. Statistically significant DGE were identified, values were sorted by fold change and false discovery rate adjusted *p*-value. ENRICHR gene enrichment was used to identify the top up-regulated biological pathways (WikiPathways Human 2021). Based on these data, the top inflammatory candidates were quantified with western blots for serum proteins (TNF-α and CRP). A two-way analysis of variance was used to analyze protein changes between genotypes and age. Fisher's Least Significant Difference was used for post-hoc comparisons. Pearson correlations were used to test for linear relationships between motor behavior and protein concentrations.

Results: Young rats had few up-regulated genes (*n*=19) but included interleukins and RAS protein activators. Older rats had an extensive list of up-regulated genes (*n*=553) and enriched biological pathways including cytokine-cytokine receptor interaction, TNF signaling pathway, MAPK signaling pathway as well as necroptosis. Data showed that *Pink1-/-* rats have increased circulating levels of both CRP and TNF-α compared to WT controls that increase with age (**Fig 1A, B**). Within *Pink1-/-* rats, protein levels were significantly negatively correlated to total distance traveled in the open field (**Fig 1C**).

Conclusions: Data suggest that early-stage inflammation may predict limb motor dysfunction in the *Pink1*-/- rat. Moreover, these findings parallel what is observed in human subjects and will be used in future work as candidates for drug-repurposing studies.

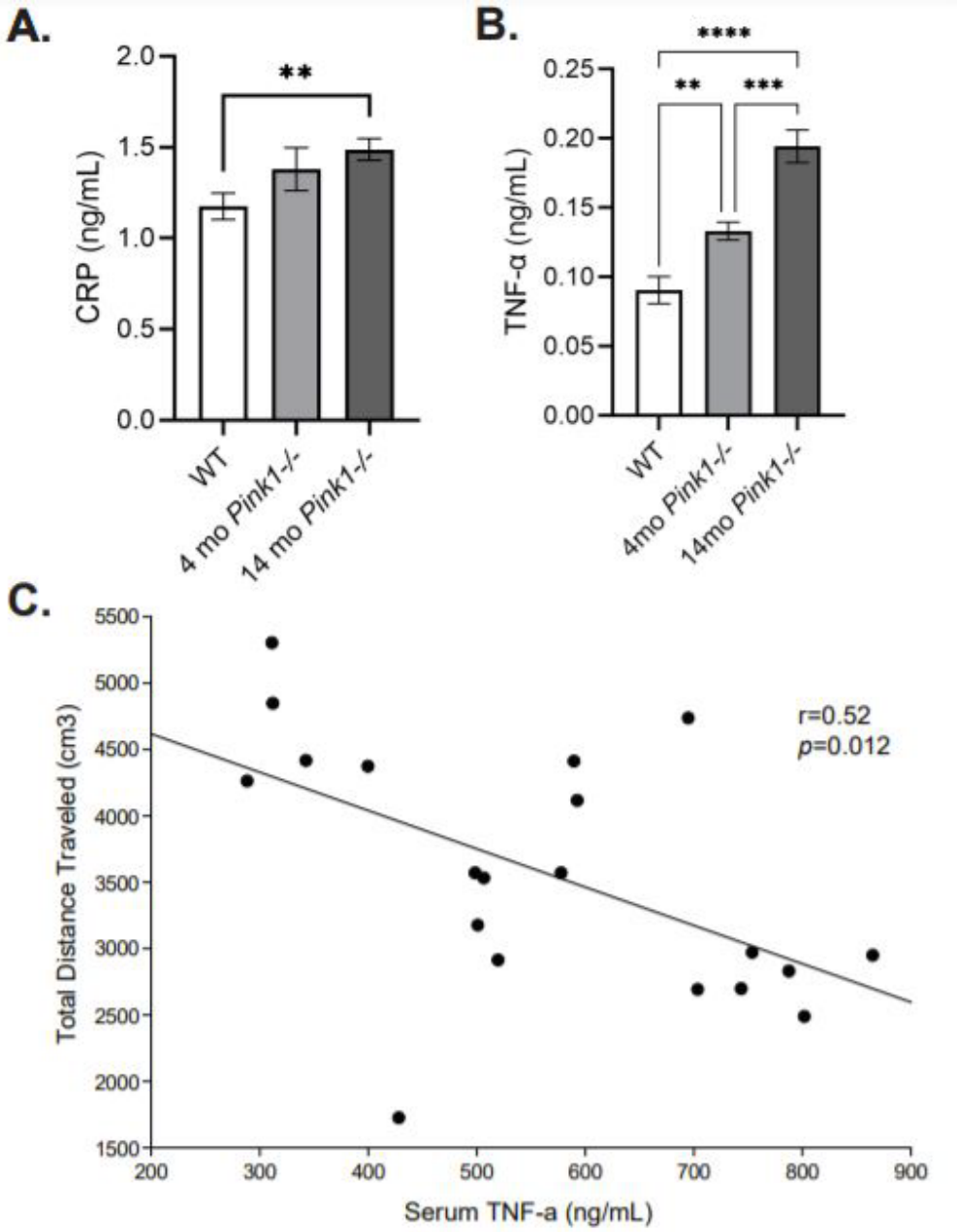

Figure 1. Inflammatory protein concentrations in blood serum are negatively correlated to movement. Average (**A**) CRP and (**B**) TNF-α protein concentrations (ng/mL) +/- standard error of the mean (SEM). Concentration on the y-axis and genotype/age on the x-axis (white bar = wildtype (WT control), light gray = 4-month (mo) *Pink1-/-*, dark gray = 14mo *Pink1-/-*). Statistical significance between groups indicated by bar and ****p<0.0001, ***p<0.001, **p<0.01. Pearson correlation (**C**) between serum TNF-α concentrations and open field total distance traveled (cm^3) in *Pink1-/-* rats.

Nucleus ambiguus inflammation and cell loss may be linked to vocalization dysfunction in *Pink1-/-* rats.

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Introduction: Pathology underlying vocal motor dysfunction for degenerative disorders including Parkinson disease (PD) is poorly understood and understudied. In both humans and rats, the brainstem nucleus ambiguus and larynx are mechanistically responsible for vocal motor functions. Our previous work has shown that male *Pink1-/-* rats, a rat model of early and progressive PD, develop deficits including reductions in ultrasonic vocalization acoustics that affect their functional communication, as well as protein alterations within the nucleus ambiguus and larynx muscle. Here, we tested the specific hypothesis that loss of *Pink1* **(A)** reduces cell density that affects ultrasonic vocalization acoustics, and **(B)** increases inflammation-related gene expression within the nucleus ambiguus of *Pink1*-/- rats.

Methods: In **Experiment A**, male *Pink1-/-* rats (*n*=11) were tested for vocalization acoustics including duration, bandwidth, peak frequency, and intensity. Under anesthesia, rat vocal fold muscle was unilaterally injected with the retrograde tracer Fluorogold. Immunohistochemistry and unbiased stereology were used to count Fluorogold-positive motor neuron cell bodies in the nucleus ambiguus. Relationships were statistically assessed with Pearson correlations. In **Experiment B**, Illumina® Total RNA-Seq TruSeq platform was used to profile differential expression of genes (DGE) in the nucleus ambiguus of male *Pink1-/-* rats (*n*=4) compared to wildtype controls (*n*=4). DGE were identified, values were sorted by fold change, and a false discovery rate adjusted *p*-value. ENRICHR gene enrichment was used to identify the top up-regulated biological pathways and key genes.

Results: There was a significant positive correlation between cell number in the nucleus ambiguus and ultrasonic call duration. Additionally, there were trends for negative correlations between cell number and call bandwidth and peak frequency. An extensive list of differentially expressed genes in the nucleus ambiguus was identified; *n*=513 up-regulated; *n*=327 down-regulated genes. Using the ENRICHR tool, the top up-regulated biological pathways included inflammatory pathways such as interleukin (IL) activation of NF-kappa β, IL-1, IL-5, and IL-6 signaling pathways as well as apoptosis signaling pathways.

Conclusions: These data are the first to suggest that reduced motor neuron number in the nucleus ambiguus may compromise vocalization acoustics, including duration, and inflammation and apoptosis gene upregulation may underlie pathological mechanisms. While all behavioral and cell density data in this study were from *Pink1-/-* male rats, we are currently collecting data on wildtype controls. This will allow us to continue to test the hypothesis that *Pink1-/-* rats will have progressive reduction in motor neuron cell density compared to wildtype controls.

Mesenchymal stromal cells (MSC) for the treatment of radiation-induced xerostomia

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Introduction: Radiation induced xerostomia (RIX) is a condition of subjective dry mouth caused by radiation therapy to the head and neck resulting in hyposalivation and altered sialochemistry. There is a **critical need** for a treatment that will safely and effectively alleviate RIX. To determine if IFN-ɣ stimulated marrow-derived mesenchymal stromal cells (MSC(M)) from HNC patients could function as a source of autologous cells for treatment of RIX we performed a pilot clinical study and associated preclinical investigations.

Methods: Bone marrow aspirates from HNC patients previously treated with chemoradiation were obtained (IRB #2019-0497, NCT 04007081). MSC(M)s were isolated from bone marrow, expanded in culture, their identity confirmed via flow cytometry, stimulated with IFN-ɣ, and cryopreserved. Thawed MSC(M)s were profiled to evaluate their functionality after cryopreservation. MSC(M)s were tested for their ability to stimulate salivary production in a murine model of RIX by injecting $1x10^6$ cells into the submandibular gland (SMG) one week after delivery of a 15 Gy dose of radiation. Efficacy was evaluated by histology and saliva production.

Results: MSC(M)s from six patients were expanded to $>20x10^6$ cells (median 15.5, range of 8-20 days). Cultured cells showed an MSC(M) phenotype, positive for CD73, CD90, and CD105 and negative for CD14, CD20, CD34, or CD45. IFN-ɣ stimulated MSC(M)s had immunomodulatory potential based on increased expression of IDO, ICAM-1, PD-L1, MHC I and MHC II expression compared with non-stimulated MSC(M)s (391%, 263%, 114%, 70% and 196% percent increase respectively). Post-thaw cultures demonstrated robust growth, with a median doubling time 3.1 days. In a murine model of RIX, delivery of a single 15 Gy dose resulted in structural changes in the SMG evidenced by decreased acinar size, increased fibrosis, and immune cell infiltration. Saliva production decreased 1 month after injection. Injection of MSC(M)s to the SMG following radiation resulted in a reduction in fibrosis and an increase in the size and density of acini within the tissue compared to control.

Conclusions: These data strongly support the feasibility of a first-in-human clinical trial of autologous IFN-ɣ stimulated MSC(M)s to treat RIX and the potential of using human derived MSC(M)s in future murine studies of RIX.

Effect of Cold Atmospheric Plasma on Viability of Human-Derived Neuroblastoma Cells

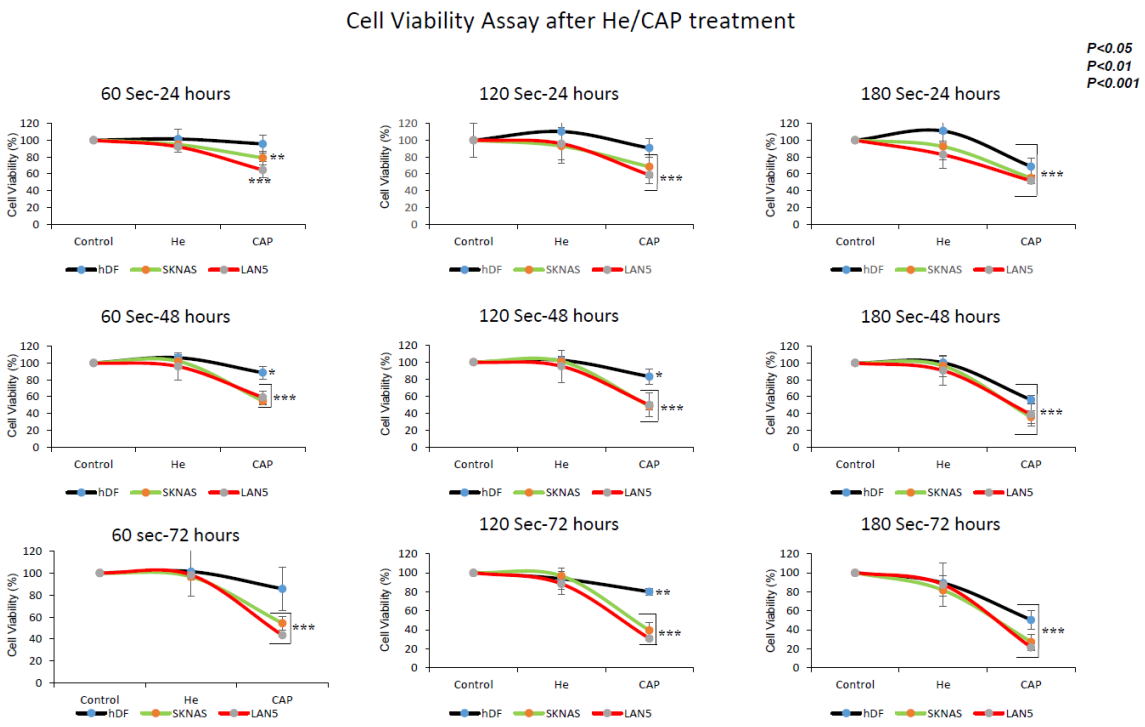
Bindu A. Nair, PhD, Ha Nguyen, Juan Favela, MD, Leon Shohet, PhD, Hau Le, MD
(Wisconsin Institutes for Medical Research and University of Wisconsin Department of Pediatric Surgery)

Introduction: Our project explores the ability of Cold Atmospheric Plasma (CAP) as a dose-dependent treatment for Neuroblastoma (NB). We hypothesize that the amount of radical species produced by CAP varies in a time-dependent fashion and, therefore, cancer cells and normal control cells exposed to CAP will also exhibit a time-dependent response to this treatment[1].

Methods: A Helium-based, plasma jet device was custom-built to operate at flow rate of 2 standard liters per minute, voltage amplitude of 4 kV with a frequency of 4 kHz. Hydroxyl radicals were used as a surrogate for all radicals and quantitatively measured using a terephthalic acid (TA) in phosphate buffer solution treated with CAP for 60s, 120s and 180s. TA reacts with OH- radicals to yield hydroxyterephthalic acid (HTA). Human-derived neuroblastoma cell lines SK-N-AS and LAN5 were used for in vitro experiments. Primary human dermal fibroblasts (hDF) served as control. Cells were treated with CAP for 60s, 120s and 180s. Cell viability for each of these cell lines was then assessed at 24h, 48h, and 72h post-exposure.

Results: There was a linear correlation between the level of hydroxyl radicals produced and the time of exposure to CAP. For SK-N-AS and LAN5, the number of live cells decreased after CAP treatment as a function of duration of treatment from 60s to 180s. CAP had minimal effect on hDF at 60s and 120s but began to show a cytocidal effect at 180s (Fig 1).

Conclusions: CAP can be fine-tuned to produce varying amounts of radicals such as hydroxyl radicals. The selectivity of CAP’s effect on tumor cells vs normal cells could be dependent on the amount radicals generated, such as hydroxyl radicals, which is a function of duration of treatment.


Cell Viability Assay after He/CAP treatment
P<0.05
P<0.01
P<0.001
60 Sec-24 hours
120 Sec-24 hours
180 Sec-24 hours
60 Sec-48 hours
120 Sec-48 hours
180 Sec-48 hours
60 sec-72 hours
120 Sec-72 hours
180 Sec-72 hours
Cell Viability (%)
Control
He
CAP
hDF
SKNAS
LAN5

The Natural Swallow: Factors Affecting Subject Choice of Bolus Volume and Pharyngeal Swallow Parameters in a Self-Selected Swallow

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Introduction: Predetermined volumes are used extensively throughout clinical assessment of swallowing physiology, but bolus volumes selected by an individual in their natural swallow can vary greatly from those used in structured assessment. This study aims to identify factors influencing self-selected volume and how the mechanics of self-selected volume swallows differ from predetermined volume swallows.

Methods: We used pharyngeal high-resolution manometry (HRM) with simultaneous videofluoroscopy to measure swallowing pressures in the velopharynx (VP), tongue base (TB), hypopharynx (HP), and upper esophageal sphincter (UES). Data were collected from 95 healthy adults during thin liquid swallows of 10 mL and a self-selected comfortable volume. An intraclass correlation coefficient (ICC) was calculated to analyze within-subjects self-selected volume reliability. Linear mixed effects regression models were used to examine the association of subject characteristics with self-selected swallow volume and of self-selected volumes on pharyngeal swallowing pressures and timing events.

Results: Mean self-selected volume was 16.66 ± 7.70 mL. Increased age (p=0.002), male sex (p=0.021), and increased pharyngeal hold area (p=0.007) were significantly associated with increase in self-selected bolus volume. There was good reliability between subjects' individual swallow volumes (ICC = 0.80). VP maximum pressure and pressure integral, TB duration and maximum pressure, UES pre- and post-swallow maximum pressure and overall pharyngeal contractile integral decreased significantly with self-selected boluses.

Conclusions: Self-selected swallow volume is associated with age, pharyngeal hold area and male sex. Individuals’ swallow volumes are highly correlated, suggesting that each individual has an intrinsic comfortable sip volume, potentially established at the level of the brainstem. Natural swallows were associated with lower maximum TB pressures, suggesting that natural swallows utilize more efficient dynamics than structured swallows. These findings contribute to a more robust understanding of natural swallow dynamics and how external factors contribute to motor control. Understanding a patient's natural swallow volume, and how their natural swallow functions, will be important for designing clinical evaluations that place stress on the patient’s

natural swallowing mechanics in order to assess for areas of dysfunction.

Burn Pit-derived Particulate Matter Exposure Increases Disease Severity in a Murine Autoimmunity Model

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Introduction: Air pollution has been increasingly implicated as a major contributor to mortality worldwide. Military personnel are exposed to sources of particulate matter (PM) that are specific to combat zones, such as burn pits, in addition to common sources of PM, like diesel exhaust. The risks of burn pit exposures are of interest to both the lay public and scientific community; these burn continuously and are utilized to dispose a large variety and quantity of waste at military bases, and concern has been raised that they lead to significant disease in our deployed troops. Exposure to PM has been implicated as an aggravator and predisposing factor for autoimmune diseases, which affect 24.5 million Americans.

Three major pathogenic mechanisms have been suggested for PM: genotoxicity, oxidative stress, and activation of the aryl hydrocarbon receptor (AHR). For impacts on clinical issues with a strong immune system component, the AHR is of interest as activation of this pathway can be both pro- and anti-inflammatory. Polycyclic aromatic hydrocarbons are AHR ligands that are generated by combustion of hydrocarbon-based fuels and adhere to PM. Upon activation, AHR translocates to the nucleus, where it acts as a transcription factor for several genes, including cytochrome P450 genes associated with toxin metabolism, immune inflammatory and immune regulatory pathways. Our lab has previously demonstrated that exposure of mice to diesel exhaust particles (DEP), whether intact PM or following extraction with an organic solvent, results in worsened clinical outcome in experimental autoimmune encephalomyelitis (EAE), a murine model of multiple sclerosis. The current study sought to assess whether the organic extract of a burn pit surrogate (BPS) PM sample also contains AHR activity and if it impacts EAE.

Methods: To determine AHR ligand activity contained in BPS, a cell-based luciferase assay was utilized. Based on this finding, a preliminary experiment was performed using dilution of BPS that gave equivalent AHR activity compared to DEP stock that has been previously shown to worsen EAE following intranasal exposure. Female C57BL/6 mice (n = 5 per group) were treated via intranasal route 8 times every 3 days with BPS or vehicle control diluted 1 to 2500. On the day of the 5th dose, EAE was induced, and mice were scored daily starting on day 7 of EAE induction on a 0 – 5 scale for disease symptoms.

Results: Compared to a 1 to 1000 dilution of DEP (10mg/ml), our standard stock concentration used to treat mice in previous EAE experiments, equivalent AHR activity from BPS was achieved when BPS was diluted 1 to 2.5 x 10^6 of 5 BPS treated mice showed incidence of disease, compared to 3 of 5 mice in the control group. BPS also had significantly greater ($p < 0.05$) mean +/- std dev cumulative score (12.5 +/- 3.2) compared to control (4.9 +/-4.5) after 18

days follow-up and trended towards getting disease earlier.

Conclusion: Preliminary data suggests that intranasal exposure to BPS can exacerbate symptoms in a standard EAE model. Further studies are ongoing.

Circulating tumor DNA analysis in dogs with sarcomas

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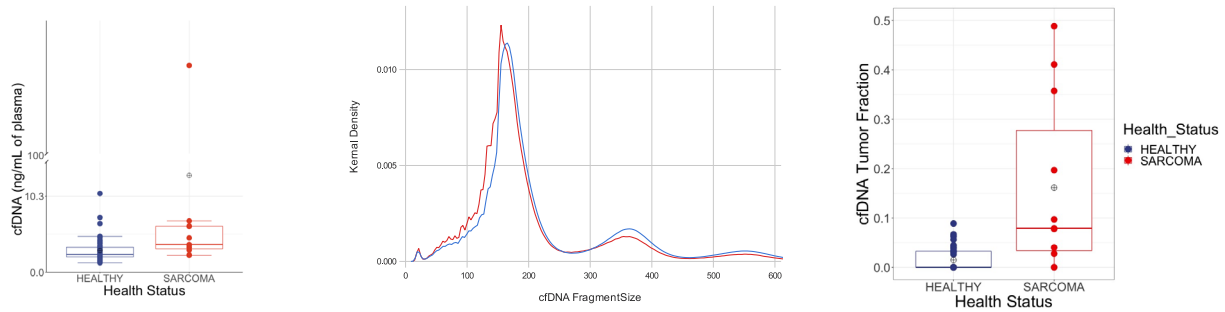
4. Wisconsin Blood Cancer Research Institute, Madison, WI, USA

Introduction: Dogs have an estimated 25% lifetime incidence of cancer. Comparative study of canine cancers can be informative for both, veterinary and human oncology. Naturally-occurring canine cancers such as osteosarcomas exhibit several similarities to human cancers including shared molecular alterations and tumor heterogeneity. Dogs who develop cancer are routinely treated with surgical resection and systemic therapy, but most cancers are detected at advanced stage and diagnostic tests for molecular stratification and treatment monitoring remain limited. In this study, we present preliminary experience with circulating tumor DNA analysis in dogs with naturally-occurring sarcomas.

Methods: We analyzed circulating tumor DNA (ctDNA) in pre-treatment plasma samples from 63 pet dogs including 11 dogs treated for naturally-occurring osteosarcoma and hemangiosarcoma, and 52 age-matched healthy dogs at the UW-School of Veterinary Medicine during a cancer vaccine trial. Blood samples were collected in Streck tubes (designed for cell-free DNA analysis), and processed within 24 hours of collection to isolate plasma. Plasma DNA was extracted and analyzed using shallow Whole Genome Sequencing (sWGS) to generate 1 million paired-end reads per sample. To detect and quantify ctDNA, we used an informatic approach based on characterization of copy number aberrations, adapted for the canine genome.

Results: At presentation, dogs with sarcomas presented higher mean plasma DNA concentration of 13.1 (sd 29.5) compared to healthy dogs (2.9 ng / mL, sd 1.7; two-sided Wilcoxon p = 0.002). Mean tumor fraction in plasma DNA was 16.1% (sd 17.6) in dogs with sarcoma, higher than healthy dogs (1.5%, sd 2.3; two-sided Wilcoxon p = 0.0001). Mode and median DNA fragment size in plasma from dogs with sarcomas (mode: 153 bp; median: 168 bp) were shorter than those observed in the healthy cohort (mode: 164 bp; median: 178 bp).

Figure 1. Comparisons between healthy dogs and dogs with sarcomas. (A) Plasma DNA concentration (ng / mL of plasma), (B) Plasma DNA fragment size (base pairs) cumulative frequency distribution and (C) Tumor fraction in plasma DNA.



Conclusions: These preliminary results demonstrate feasibility of circulating tumor DNA analysis in plasma from healthy dogs and dogs with naturally-occurring sarcomas. The study is currently enrolling canine patients diagnosed with sarcoma, and obtaining blood samples throughout treatment and disease course. Further analysis is planned to assess relationship between changes in ctDNA levels and tumor burden including minimal residual disease throughout treatment period.

Genomewide analysis of fragment ends in plasma DNA from patients with cancer

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Introduction: Analysis of plasma DNA is a promising approach for cancer detection and monitoring. Most current circulating tumor DNA tests rely on high depth targeted sequencing to analyze genome regions for mutations and methylation marks, resulting in high costs and sample volume requirements. Recent studies have shown that fragmentation patterns in cell-free DNA are not random. Due to differences in chromatin accessibility, when DNA from a cancer cell is shed into plasma, fragmentation sites may differ in genomic position relative to the majority of cell-free DNA in plasma that is derived from peripheral blood cells. In this study, we have developed a novel approach for Genomewide AnaLYsis of FRagment Ends (GALYFRE), to leverage differences in fragmentation breakpoints of tumor-derived DNA in plasma and detect presence of tumor DNA in blood.

Methods: Using whole genome sequencing of plasma DNA samples from 17 healthy individuals, we first inferred a genomewide map of regions recurrently protected from degradation. For each test sample, we quantified the fraction of aberrant fragments (FAF), defined as fragments whose ends fall within these recurrently protected regions. To further capture aggregate differences in genomic positioning of fragment ends, we calculated nucleotide frequencies observed at each position 10 bp upstream and downstream of each fragment end (based on the reference genome sequence), averaged across all fragments for each sample.

Results: FAF was higher in patients with cancer compared to healthy individuals ($p<0.01$). In patients with metastatic disease, FAF was correlated with tumor fraction (0.70, $p<0.001$). In patients with melanoma and glioblastoma, longitudinal changes in FAF were consistent with changes in tumor fraction during therapy. In 27 plasma samples with >20% tumor fraction, FAF was higher in copy number gain regions in the tumor genome, compared to neutral or loss

regions (p<0.05). In 2 deep sequenced plasma samples (>280x), FAF was higher for mutated DNA fragments compared to non-mutated ones (p<0.001 in both). Training a random forest classifier on FAF and nucleotide frequencies, we observed an area under the receiver operating characteristic curve (AUC) of 0.96 for detection of cancer. When this analysis was limited to patients with potentially curable Stage I-III disease, AUC value dropped marginally to 0.93. Our findings remained robust with as few as 1 million fragments analyzed per sample.

Conclusions: Our results suggest GALYFRE is a promising approach for blood-based cancer detection and monitoring that may be more cost-effective and require smaller amounts of plasma DNA compared to current methods.

Figures:

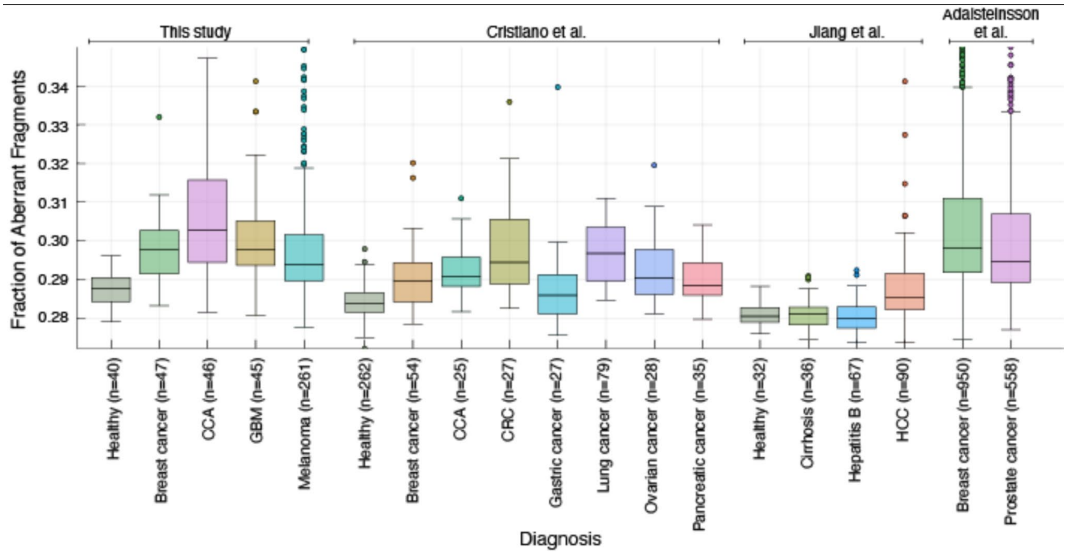

Figure 1: Fraction of aberrant fragments in >2700 plasma DNA samples including healthy individuals and patients with 11 different cancer types (including 2270 external datasets from 3 recent publications). FAF was higher in plasma samples from patients with cancer compared to healthy volunteers.

Central and Peripheral Nerve Stimulation on Functional Recovery of Mixed Nerve in Rat Forelimb Peripheral Nerve Injury Model

Simran Bedi[1], Peter J Nicksic[1], MD, D'Andrea Donnelly[1], BA, Aaron Dingle, PhD[1], Samuel O Poore, MD, PhD[1]

Introduction: Current treatment of peripheral nerve injury (PNI) is a tension-free coaptation of the injured nerve. This treatment yields inconsistent and suboptimal results, notable in older patients. Newer treatments include utilizing electrical stimulation of the peripheral and central nervous system to increase peripheral nerve regeneration. The trigeminal nerve is a promising alternative to the vagus nerve and brief electrical stimulation (BES) as it is more easily accessible and does not require a prolonged period of electrical stimulation intraoperatively. We aim to quantify the effects of trigeminal nerve stimulation (TNS) paired with rehabilitation and intra operative brief electrical stimulation (IO BES) at the site of PNI on functional recovery, peripheral regeneration, and central organization. We hypothesize that rats in a forelimb PNI model will recover function of a quantifiable reaching and grasping task quicker and more robustly with adjunctive trigeminal nerve stimulation (TNS).

Methods: During weeks 1-4, 48 rats will be trained using a MotoTrak system and will be fully trained when able to pull at 120 grams of force with the level 2 cm outside of the cage on 75% of their attempts in 10 consecutive sessions. At the end of week 4 we will randomize the rats into 4 groups as detailed in Table 1. At week 5 rats will undergo a PNI of the right forelimb and receive IO BES depending on the group. After 5 weeks of recovery at week 10, rats will undergo second surgery for placement of the TNS cuff in the left supraorbital nerve. After 1 week of recovery, during weeks 11-15 rats will return for rehabilitation of the previously learned task with the MotoTrak system. The active TNS group will receive stimulation with each successful task. At week 16 functional recovery will be assessed and later cortical mapping to determine size of the left-sided motor cortex and histomorphology to quantify nerve recovery.

Results: Animals are currently undergoing 5 weeks of training prior to intervention and that the first series of experimental data is expected to be completed by January 2022.

Conclusions: This study will provide useful data regarding ES benefits for PNI and will further indicate if the trigeminal nerve is a legitimate alternative to VNS and IO BES. If our hypothesis is correct, hopefully we can transfer this data onto large animals and guide future studies in finding clinically applicable ES stimulation for PNI in humans.

Group Name	n=	Injury	Intervention(s)
1. Positive Control	12	Sham PNI	Sham TNS and sham IO BES

2. Negative Control	12	PNI of medium and ulnar nerve 1cm proximal to elbow in right forelimb	Sham TNS and sham IO BES
3. IO BES Only	12	PNI of medium and ulnar nerve 1cm proximal to elbow in right forelimb	IO BES and sham TNS
4. TNS Only	12	PNI of medium and ulnar nerve 1cm proximal to elbow in right forelimb	TNS and sham IO BES.

Table 1. Groups will be randomly assigned at the end of week 4 after successful training. At week 5 they will receive peripheral nerve injury (PNI) or sham PNI- group 3 will receive intraoperative brief electrical stimulation (IO BES) during the surgery. At week 10 groups will undergo a second surgery where they will have a trigeminal nerve stimulation (TNS) cuff implanted in the left supraorbital nerve. Only group 4 will receive TNS during rehabilitation.

Electronic Bone Growth Stimulators in In Vitro and In Vivo Models

Peter J. Nicksic, D'Andrea Donnelly, Madison Hesse, Simran Bedi, Nishant Verma, Allison Seitz, Andrew J. Shoffstall, Kip A. Ludwig, Aaron Dingle, Samuel O. Poore*

Introduction: Since the piezoelectric quality of bone was discovered in 1957, scientists have applied exogenous electrical stimulation for the purpose of bone healing. Despite the efforts made over the past sixty years, electronic bone growth stimulators are not in common clinical use. Reasons for this include high cost and lack of faith in the efficacy of bone growth stimulators on behalf of clinicians. We sought to systematically examine the preclinical body of research supporting electrical stimulation for the purpose of bone healing, and elucidate gaps in clinical translation with an emphasis on device specifications and mechanisms of action.

Methods: The authors evaluated the limitations of capacitive coupling, pulsed electromagnetic field and direct current stimulation by examining radiographic, histomorphologic and biomechanical outcomes of 59 studies. The key words: “electrical stimulation”, “bone healing”, “in vitro”, “animal”, “direct current”, “pulsed electromagnetic field” and “capacitive coupling” were searched on PubMed. Each study was categorized into “In Vitro”, “Small Animal” and Large Animal”. We then compared injury and cell type, stimulation type, device specifications such as current, voltage, equipment type, magnetic field and magnetic field strength, protocol, and outcomes.

Results: Of the 59 studies that met our criteria, 17 were on In Vitro stimulation (28.81%), 29 on small animals (49.15%), and 13 on large animals (22.03%). When examining these studies, trends become apparent. In vitro, small animal studies are successful in inducing osteogenesis with all electrical stimulation modalities: direct current, pulsed magnetic field, and capacitive coupling. However, large animal studies are largely unsuccessful with the non-invasive modalities. This may be due to issues of scale, thickness of tissue planes with varying levels of resistivity, not present in small animal studies.

Conclusion: It is difficult to draw conclusions from studies due to the varying units of stimulation strength and stimulation protocols, as well as incomplete device specification reporting. To better understand the disconnect between the large and small animal, the authors recommend increasing scientific rigor for these studies and offer criteria for reporting a minimum set of parameters depending on the stimulation modality. Additionally, future work from our group will focus on DCES in clinically translatable animal models as that category had the smallest number of published studies, and large animal studies are imperative to clinical adoption.

Evaluating the Delivery of a Percutaneous Electrical Stimulus to Deep Cortical Bone Space Utilizing an Injectable Biopolymer in Human Cadaveric Tibias

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Introduction: The use of electrical stimulation to heal non-union fractures in cortical bone has been frequently considered. One of the current limitations of the technique's more ubiquitous use comes from the lack of experiments done to quantify the current that can reach deep bone from non-invasive stimulation methods. The invention of a novel polymer called the Injectrode can be injected into fracture sites to amplify an electrical stimulus from the surface of the skin, thereby improving the current and potential recovery benefit of electrical stimulation to that fracture. This experiment is the first to attempt to record percutaneous electrical stimulation in bone of a clinically relevant human cadaver model. Our objective was to quantify the electrical field delivered from a percutaneous electrical stimulus in the presence and absence of a novel injectable electrode (Injectrode).

Methods: We obtained five lower legs from human cadavers in which a 5.5-mm diameter circular defect was created in the tibia. We measured the electric field from a 5 mA pulse administered through a percutaneous electrical stimulus before and after filling the defect with Injectrode.

Results: Compared to the computational finite-element model analysis (10% gain), a difference of 8.4% gain was found in the cadaveric tibial models (18.4% gain, n = 5). The baseline voltage measured 2 mm deep to the tibial surface in a tibia with a 5.5-mm diameter defect was on average 63.5 mV (n = 5) without Injectrode and 70.0 mV (n = 5) with the defect filled with Injectrode. A paired t-test between a tibia with a defect without Injectrode versus with Injectrode was performed to determined statistical significance ($p = 0.068$), which warrants additional analysis. When stratified by overlaying tissue thickness (< 5 mm, 5-15 mm, > 15 mm), an average value of 108 mV (n = 4), 59 mV (n = 3), and 31 mV (n = 5) without Injectrode and 113 mV, 77 mV, and 32 mV with Injectrode were observed, respectively.

Conclusions: Our results show that administration of Injectrode to a tibial defect has potential to increase the delivery of an electric field to the bone. Clinically, this implies that administration of Injectrode could improve the efficacy of non-invasive electrical stimulation methods for promoting bone growth. Further testing in different models could help make the case that Injectrode use should be considered to improve healing through non-invasive electrical stimulus in the case of non-union fractures.

The Effect of Tension on Gene Expression in Primary Nerve Repair via the Epineural Suture Technique

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Introduction: The precise mechanism through which excessive tension confers poor outcomes in nerve gap repair is yet to be elucidated. Furthermore, the effect of tension on gene expression in regenerating nerves has not been characterized. This study investigated differential gene expression in transected nerves repaired under high and minimal tension.

Methods: Male Lewis rats underwent right sciatic nerve transection with either minimal- or high-tension repair. Fourteen weeks postoperatively, segments of the right sciatic nerves were harvested along with equal length segments from the contralateral, healthy nerve to serve as internal controls (naïve nerve). Differentially expressed genes (DEGs) and differentially regulated biochemical pathways between the samples were identified.

Results: Seventeen animals were studied. The gene expression profiles of naïve nerve and minimal-tension repair demonstrated minimal within-group variation, while that of high-tension repair demonstrated heterogeneity. Relative to naïve nerve, high-tension repair samples had 4,276 DEGs (1,941 upregulated; 2,335 downregulated) and minimal-tension repair samples had 3,305 DEGs (1,479 upregulated; 1,826 downregulated). High-tension repair samples had 360 DEGs relative to minimal-tension repair samples (68 upregulated; 292 downregulated). Upregulated biological pathways in all repaired nerves included steroid biosynthesis, ECM-receptor interaction, and ferroptosis. Finally, upregulated pathways in high-tension repair samples relative to minimal-tension repair samples included TNF signaling, IL-17 signaling, cytokine-cytokine receptor interaction, and MAPK signaling.

Conclusions: The improved outcomes achieved with minimal tension nerve repair may take root in a favorable gene expression profile. Additionally, the biological pathways implicated in inflammation and ferroptosis may be promising avenues for additional research geared toward eventual therapeutic intervention, as these physiologic processes play important roles in nerve regeneration following transection. The authors hope to inspire future elucidation of biochemical pathways in healthy nerve regeneration so as to optimize primary nerve repair outcomes.

Circadian Dysregulation Accelerates Pancreatic Cancer Progression

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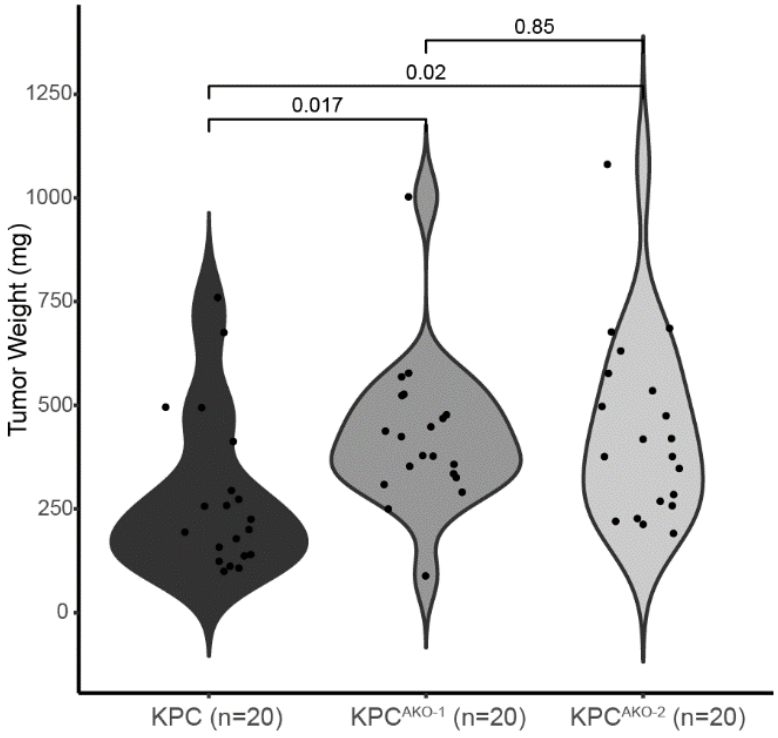
Introduction: The circadian clock is a cell-autonomous molecular feedback mechanism found in nearly every organ of the body that is designed to maintain homeostasis. Previous studies have suggested disruption of the clock in pancreatic ductal adenocarcinoma (PDAC) may portend worse outcomes for patients. We sought to further understand the ramifications of disrupting clock function on PDAC progression.

Methods: CRISPR/Cas9 was utilized to achieve knockout of the core circadian clock gene *Arntl* in cells derived from an aggressive PDAC mouse model (*Kras$^{G12D/+}$; Tp53$^{-/-}$; Pdx-1* Cre (KPC)). Two *Arntl* knockout clones (KPC^{AKO}) were validated with targeted sequencing and western blot analysis. To create tumors, 100,000 cells in 50 µL (1:1 Matrigel: DMEM) were injected into the flank of 6–8-week-old C57Bl/6J mice. Tumors were measured twice weekly for 28 days, and tumor weight was evaluated at the study endpoint. Besides growth, biological behavior was assessed by chemotherapeutic resistance. Cells were subjected to gemcitabine treatment and both cell survival and Caspase 3/7 activity were examined. Differential gene expression (KPC vs KPC^{AKO}) was evaluated with RNA sequencing (RNAseq) using edgeR and KEGG testing.

Results: DNA sequencing of both KPC^{AKO} clones indicated the presence of an identical frameshift mutation resulting in ARNTL protein loss (western blot). Heterotopic flank tumor experiments revealed accelerated tumor growth in both KPC^{AKO} clones resulting in larger tumor weight (Figure 1). To identify mechanisms of growth advantage, cell survival was compared following gemcitabine treatment, which demonstrated resistance of both KPC^{AKO} clones compared to wildtype (IC50 28 and 21 vs. 12 nM [p=0.03]). Increased survival of the KPC^{AKO} cells was found to be secondary to increased resistance to apoptosis with 25 nM-1 µM treatment (2.6-5.3-fold increased resistance; all $p<0.05$). DGE testing following RNAseq revealed an overrepresentation of the PI3K/AKT pathway in KPC^{AKO} compared to KPC cells.

Conclusions: The circadian gene *Arntl* is essential for maintaining clock functionality. Loss of ARNTL in a PDAC cell line led to a more aggressive cancer phenotype and conferred resistance to gemcitabine – a backbone of PDAC chemotherapy. Furthermore, KPC^{AKO} resistance appeared to be secondary to decreased apoptosis. RNAseq revealed an overrepresentation of the PI3K/AKT pathway in KPC^{AKO}, which has been shown to mediate the circadian-associated chemotherapeutic resistance seen in other cancers. Future experiments will investigate the role of the PI3K/AKT pathway in mediating chemotherapeutic resistance in KPC^{AKO} cells. Elucidation of this relationship may allow for new treatment paradigms and/or novel biomarker identification for patients with PDAC.

Figure 1:


0.85
0.02
0.017
1250
1000
750
500
250
0
Tumor Weight (mg)
KPC (n=20)
KPC^AKO-1 (n=20)
KPC^AKO-2 (n=20)

Novel Treatment Strategies for Fibrolamellar Carcinoma

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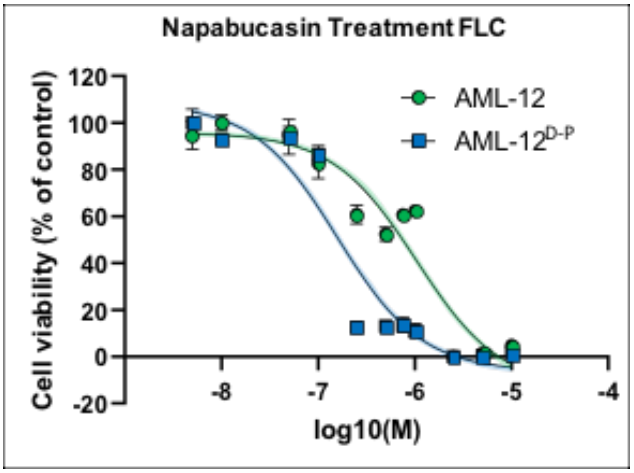
Introduction: Fibrolamellar carcinoma (FLC) is a rare but lethal liver cancer with an overall 5-year survival rate of 34%, for which there are no proven treatment options beyond surgical intervention. FLC primarily affects adolescents and young adults with no history of cirrhosis or liver disease. A segmental deletion resulting in *DNAJB1-PRKACA* gene fusion is now recognized as the singular genetic event of FLC. Unfortunately, FLC is intractable with standard chemotherapies and radiation, currently leaving surgical resection as the only promising treatment. We created an FLC cell line harboring the fusion oncogene in order to evaluate other treatments options.

Methods: The FLC cell line was generated from AML12 cells using CRISPR/Cas9 to express the *DNAJB1-PRKACA* chimera fusion protein (AML12-FLC). This was verified by genomic DNA analysis (*DNAJB1-PRKACA* gene fusion) followed by mRNA and oncoprotein analysis (DNAJ-PKAc). We then assessed known downstream targets of the fusion oncoprotein to validate the FLC cell line. Differences in cell growth between the AML12 cells and the AML12-FLC cells (CellTiterBlue) was performed. To assess for drug therapy, promising candidate drugs were evaluated, based on several published lines of evidence in FLC.

Results: Analysis of the genomic DNA from the AML12-FLC cell line demonstrated successful formation of the *DNAJB1-PRKACA* gene fusion, and mRNA and protein analysis confirmed DNAJ-PKAc expression. AML12-FLC cells demonstrated upregulation of known FLC upregulated genes including *Car12*. Following validation, we identified a significant growth advantage in AML12-FLC cells compared to AML12 cells, demonstrating transformation. Subsequently, promising high-yield therapies for FLC were examined, including cobimetinib (MAP kinase pathway), and KT5270, H89 and PKI-tide (PKA signaling). However, these therapies did not demonstrate a therapeutic window compared to parent cells. We then assessed a second group of promising candidates, including Napabucasin, FRAX597, JIB-04, UNC06646, Binimetinib, and 666-15, which yielded a strong therapeutic effect for Napabucasin (**Figure 1**).

Conclusion: Our validated cell line recapitulates previously established FLC cell lines and results seen in human cancer tissue. The therapies that were tested based on existing data revealed Napabucasin as an effective treatment for FLC, demonstrating efficacy and a therapeutic window. In future studies, we will use Napabucasin as a backbone drug and screen additional drugs in a combination drug screen to develop lethal multi-drug combinations. We will then proceed with orthotopic tumor implant studies to confirm therapeutic efficacy *in vivo*. Ultimately, we aim to develop a novel therapeutic strategy for a cancer that currently has no proven systemic therapies.

Figure 1. Napabucasin drug dose response curve in wild-type and FLC (AML12^{D-P}) cells.



Co-expression network analysis of the changing transcriptome in embryonic mouse esophagus, trachea, and larynx

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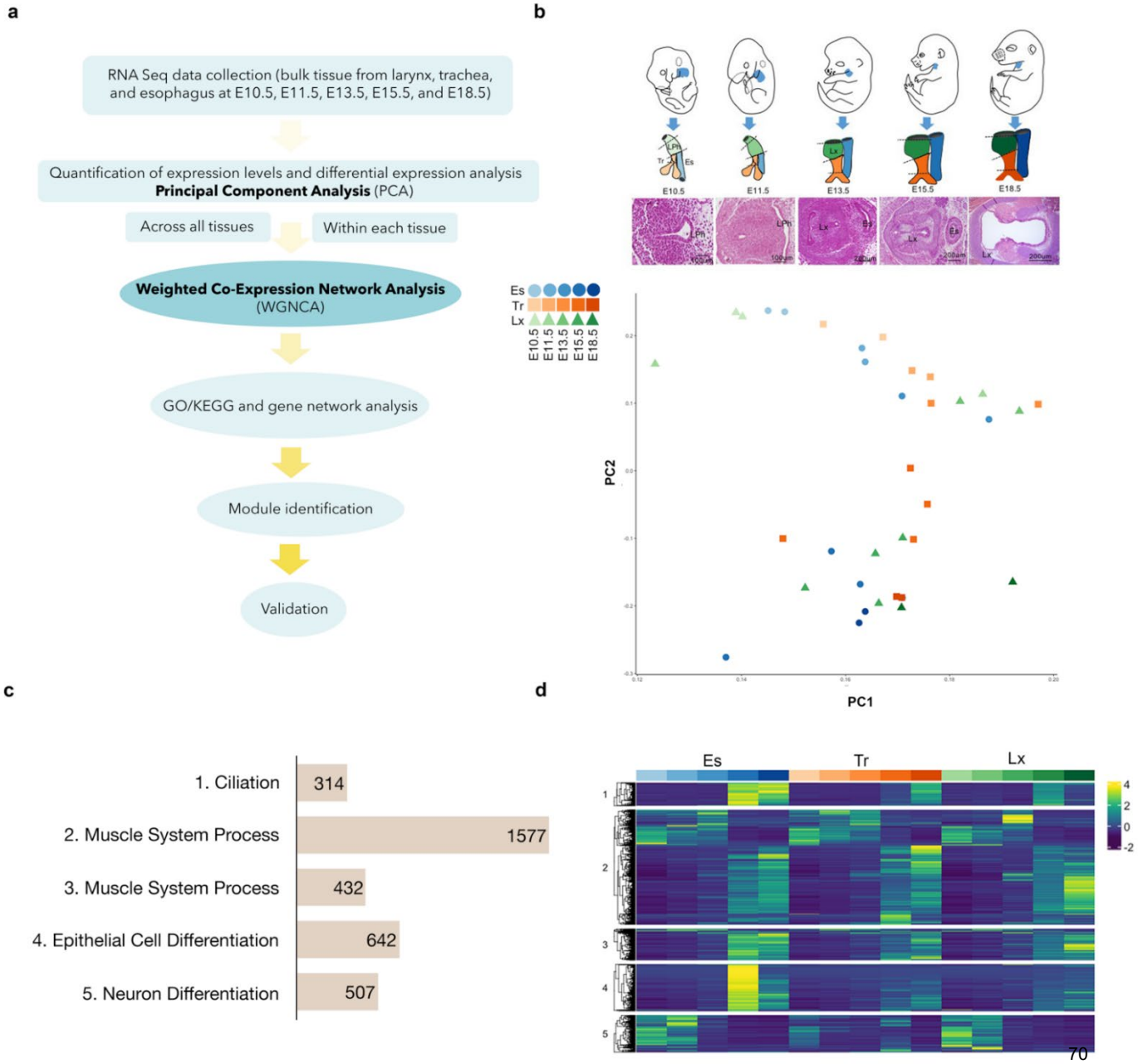
Introduction: The larynx, trachea, and esophagus share origin and proximity during embryonic development, with clinical and experimental evidence supporting the existence of neurophysiological, structural, and functional interdependencies before birth. This investigation provides the first comprehensive transcriptome profile of interrelated gene sets shared by all three organs during embryonic organogenesis, where differential gene expression gradually builds the identity and complexity of these proximal organs from a shared origin in the anterior foregut.

Methods: Transcriptional dynamics were characterized during embryonic development of the esophagus, trachea, and larynx by a time-series study of in-vivo gene expression generated from bulk tissue RNA sequencing. We used principal component analysis (PCA) as well as a statistical analysis pipeline informed by weighted correlation network analysis (WGCNA) to identify modules enriched for biological processes across developing embryonic mouse larynx, esophagus, and trachea through developmental time (Fig. 1a).

Results: The time course transcriptomes across esophagus, trachea, and larynx clustered according to their respective tissue identities by developmental time for the genes represented by the first two principal components in the x and y axis respectively, which comprise the most dramatic shifts in expression across the transcriptome (Fig. 1b) Co-expressed clusters enriched for key biological processes including ‘ciliation’, ‘muscle system process’, ‘epithelial cell differentiation’, and ‘neural differentiation’ (Fig. 1c, Fig. 1d)

Conclusions: The findings of this study provide new insights into interrelated gene sets governing organogenesis of this tripartite organ system within the aerodigestive tract, with relevance to multiple families of disorders contained by the cardiocraniofacial syndromes. We also further define and validate a ‘heart development’ gene module unique to the mammalian larynx that contains a subset of genes associated with cardiogenesis and cardiac valvulogenesis with upregulated activity at E13.5 concurrent with vocal fold realization during recanalization of the epithelial lamina within the developing larynx.

Figure 1 a, **Methods** Using bulk RNA sequencing and gene network analysis informed by weighted gene co-expression analysis (WGCNA), we identify differentially expressed genes (DE) within and across developing embryonic mouse larynx (Lx), esophagus (Es), and trachea (Tr) as co-expressed clusters enriched for key biological processes **b**, **Global transcriptome structure of Es, Tr, and Lx during embryonic development** Schematic of developing embryos shows the color key for organ identity and developmental stage across the timespan of the study above hematoxylin and eosin histological sections at the level of the developing vocal folds during each timepoint. PCA analysis demonstrates 2D representation of whole-tissue transcriptome principal components at each timepoint. **c**, **Gene numbers contained by key GO enrichment terms for each module across all tissue correspond to those in the heatmap d**, **Hierarchal clustering of shared gene modules during embryonic development across Es, Tr, and Lx.** Hierarchical clustering of differentially expressed genes (n = 3472) shown as a heat map for normalized log_2(FPKM) values across embryonic development of the Es, Tr, and Lx.



Laryngeal infection with *Mus musculus* papillomavirus

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Introduction: Recurrent respiratory papillomatosis (RRP), caused by laryngeal infection with low-risk human papillomaviruses, has devastating effects on communication and quality of life. Dysphonia is the most frequent symptom due to exophytic vocal fold epithelial lesions and scarring from repeated surgical excision. Research has been stalled by limited preclinical models due to papillomavirus species specificity. The only papillomavirus able to infect laboratory mice, *Mus musculus* papillomavirus (MmuPV1), induces disease in multiple tissues. We hypothesized that MmuPV1 could infect the larynx as a foundation for a preclinical model of RRP. Injury is required for MmuPV1 infection of other tissues. We further hypothesized that injury would enhance the ability of MmuPV1 to cause laryngeal disease.

Methods: Under laryngoscopy, 42 cages of 3-5 NOD-scid gamma mice per cage underwent 1 of 3 treatments: (1) vocal fold abrasion and MmuPV1 infection, (2) infection only, or (3) abrasion and saline mock infection. Two cages were sacrificed on days 1 and 3 and weeks 1, 2, 4, 8, and 12 post treatment. Mice were assessed for measures of viral infection and disease pathogenesis at the organism, tissue, and molecular level including animal health, pathology grading, and assays of viral DNA, RNA, and protein.

Results: Laryngeal disease emerged as early as week 1 post infection. Disease incidence and severity increased earlier in mice that underwent vocal fold injury in addition to infection. However, laryngeal disease was diagnosed in all infected mice by week 12, with or without injury. At late timepoints, lesions ranged from severe dysplasia to invasive squamous cell carcinoma. Endoscopically, lesions were flat, smooth, and pale, which is not consistent with RRP. Disease spread to trachea and bronchi, but not lungs. MmuPV1 capsid protein was produced in diseased hypopharynx but not larynx or trachea. MmuPV1 RNA was revealed in all diseased tissues, including larynx and vocal folds. Viral transcripts were also found in infected larynges with negative pathology as early as day 1 post infection.

Conclusions: MmuPV1 infects the larynx of immunocompromised mice. Injury enhances disease progression but is not necessary for laryngeal MmuPV1 infection or disease. Laryngeal lesions induced by MmuPV1 are dysplasias that do not grow exophytically as seen in RRP. These dysplastic lesions can progress to cancer, as occurs with MmuPV1-induced lesions at other tissue sites, but is not seen in RRP. Lateral spread of infection to trachea is also observed, as seen in RRP. We conclude that MmuPV1 infection of the mouse larynx provides a useful, if imperfect, preclinical model for RRP.

Role of mechanoreceptor *Piezo1* in vocal fold epithelial development and regeneration

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Introduction: Mechanoreceptors are implicated as functional afferents in laryngeal mucosa; mediators of vocal fold (VF) pathologies and laryngeal disease. However, biologic identity of receptors and upstream targets at the mucosa-airway interface remain ill defined, limiting treatment innovation. *Piezo1*, a mechanosensitive channel, has proved essential for various mechanically sensitive tissues; a likely candidate given its regulation of the epithelial life cycle. In this study, we developed of a novel mouse model for VF epithelial-specific injury and tested the hypothesis that *Piezo1* is a critical mechanoreceptor for development of VF stratified squamous epithelium and repair pathways for acute VF remodeling.

Methods: Epithelium-specific *Piezo1*CKO mice were generated to assess functional roles for developing VF epithelia. Histological and immunofluorescent analysis were performed on mutant and control samples for all developmental and adult timepoints. Adult 6wk mice additionally underwent Naphthalene-induced injury to elucidate *Piezo1*-mediated repair pathways for the regenerating VF epithelium. Analysis was performed at 1, 3, 7 and 14 days post-injury (dpi).

Results: Endogenous protein expression of PIEZO1 mechanoreceptor exhibited cell-selective expression to stratified squamous epithelia of the VF, hypopharynx and esophagus, while PIEZO2 expression was restricted to ciliated respiratory epithelial cells of supra- and subglottic regions. Surprisingly, *Piezo1* mutants did not show abnormal VF epithelial phenotypes across development and postnatal stages. *Piezo1* mutants, albeit, exhibited functional role in acute VF regeneration characterized by allele dose effect resulting in increased injury severity, nuclear YAP and ectopic Keratin17 expressivity.

Conclusions: These findings together demonstrate a role for *Piezo1* mechanoreceptor in VF regeneration, likely through regulating canonical differentiation programs for remodeling events and uncontrolled cell turnover via its downstream inhibition of *Yap* transcriptional targets.

Single-cell transcriptomics to explore laryngeal innate immunity regulated by commensal microbiota

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Introduction: The larynx lies at the crossroads of the upper respiratory and digestive tracts, with the vocal folds serving as a valving mechanism for voice production and airway protection during swallowing. It has unique bacterial profile and immunological architecture. Studies in other organs have demonstrated that mucosal immunity is essentially determined by the interaction between commensal bacteria, mucosa cells, and the immune cells in the epithelium and underlying lamina propria, while little is known in the larynx. We hypothesize that laryngeal immunity is regulated by the resident microbiota instead of distal gut microbiota.

Methods: To test our hypothesis, we characterized and compared the immune system in the larynx of conventionally raised (ConvR) and GF mice through single-cell transcriptomic analysis. Immunostaining of host proteins was performed to support the sequencing results. Laryngeal microbiota in the ConvR mice was characterized with 16S rRNA gene sequencing.

Results: A total of 13 cell types were recovered overlapping between the two mouse groups, of which 2 were macrophage and lymphocyte B cells. While no significant difference was observed in the cell type proportion or the total number of immune cells between ConvR and GF mice, epithelial cell numbers, subtypes, and developmental trajectories significantly differ across mouse groups, reinforcing the importance of airway epithelial barrier as the first line of defense against external assaults. The most meaningful DE genes were observed in various epithelial cells, including basal, suprabasal, secretory (goblet, serous, club cells), ciliated epithelial cells, which could be resulted from the colonization of the residential bacteria in the larynx. While the macrophage cell numbers were comparable between the mouse groups, enrichment analysis showed MHC II protein complex binding significantly increased in ConvR than that in GF mice. The well-known genes associated with antibacterial humoral response and defense towards gram-negative bacteria, such as Pglyrp1, Pigr, Cebpb, Ltf, Bpifa1, and Lyz1/2 were significantly enriched across cell types in ConvR mice. PERK mediated unfolded protein response, mainly induced by viral or bacterial infection, was also significantly increased in ConvR mice. Other biological processes and molecular functions, including cell junction and adhesion, desmosome assembly, epithelium development, and neutrophil mediated immunity were also significantly increased in ConvR mice.

Conclusions: Our results provided evidence to the role of commensal microbiota in shaping the laryngeal immunity through the regulation of both immune and non-immune response and laid the groundwork for the understanding of host-microbiota interactions in the mouse upper airway.

Wnt/beta-Catenin signaling triggers intense VF mucosal remodeling in response to the lipid-mediated injury caused by exposure to electronic cigarette vaping extract

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Introduction: Electronic cigarettes (e-cigs) are nicotine delivery systems that have been touted as safer alternatives to smoking. A recently reported case of epiglottitis revealed a connection between vaping and swollen laryngeal and vocal fold (VF) structures that can lead to acute life-threatening airway obstruction. The clinical course and biopsy revealed direct epithelial injury and subsequent inflammatory reaction[1]. Here we show that we were able to recapitulate this phenomenon in *in vitro* conditions.

Methods: We first differentiated human induced pluripotent stem cells (hiPSC) into VF basal epithelial progenitors and created engineered VF mucosae composed of hiPSC-derived VF epithelium and collagen gel seeded with VF fibroblasts as reported previously[2]. The differentiation protocol lasted 32 days. At day 32 VF mucosae were exposed for one week to 5% e-cig vaping extracts (ECVE) composed of propylene glycol (PG) and vegetable glycerin (VG) only – Group 1 (vehicle control), and to PG + VG + nicotine and flavor (Group 2). VF mucosae exposed to medium only were used as controls (Group 3). At Day 39 VF mucosae were harvested and analyzed by hematoxylin-eosin (H&E) to assess the morphology, to immunohistochemistry (IHC) and quantitative polymerase chain reaction (qPCR) to assess expression of genes involved lipid metabolism and immune cell responses. Next, we set up the similar experiment where engineered VF mucosae were exposed to 0.5% ECVE for one week, then the ECVE was removed from the system and VF mucosae were led to regenerate for 1, 3 and 7 days. At these timepoints VF mucosae were harvested and analyzed by H&E, IHC and qPCR. We were looking at expression of structural genes and signaling pathways responsible for mucosal remodeling.

Results: Exposure of engineered VF mucosae to 5% and 0.5% ECVE for one week induced cellular damage in VF luminal epithelial cells, disrupting mucosal homeostasis and mucosal innate immune responses. Epithelial erosion was likely caused by the accumulation of solvents and lipid particles, most likely medium chain fatty acids, in the cytosol and intercellular spaces, which altered lipid metabolism and plasma membrane properties. We next we investigated how the mucosal cells responded the damage of the epithelial protective barrier and whether this chemical injury can affect deeper epithelial cell layers. We withdrew the ECVE from the experimental system and led the VF mucosae to regenerate for 1, 3 and 7 days. Withdrawal of ECVE triggered intense epithelial remodeling likely mediated by Wnt/beta-Catenin signaling pathway. The reactive epithelial changes included increased cell proliferation and p63 (basal cell marker) expression (Days 1 and 3 post-exposure) and cytokeratin 14 and laminin alfa 5 deposition (Day 7 post-exposure) which may lead to epithelial hyperplasia and the basement membrane thickening.

Conclusions: In summary, vaping represents a threat to the VF mucosa health and airway protection, whereby raising further concerns over the safety of e-cig use.

ORAL ABSTRACTS: GROUP TWO

Clinical Science and Health Services Research

Migraine surgery affects measurable change in the brains of patients on neuroimaging

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Introduction: The value and efficacy of surgery to treat migraines has been shown in multiple studies from various institutions across the country. Patient reported outcomes measures, the staple of migraine surgery outcomes research, have demonstrated significant improvement in migraine symptoms and quality of life following surgery. These results have been criticized due their subjective nature; therefore this study was designed to provide objective evidence of the efficacy of migraine surgery via changes in neuroimaging.

Methods: All subjects enrolled in the study participate in a preoperative study visit and a postoperative study visit once their symptoms have plateaued. Each study visit consists of: 1) psychological tests assessing attention, focus and mood, 2) structural MRI, 3) fMRI at rest, and 4) fMRI while performing a task of executive function (verbal fluency). Pre- and postoperative results are compared to measure change.

Results: Chronic migraine patients score extremely high for depressive symptoms and demonstrate impairment in executive function in the form of poor focus/attention. Preliminary analysis of our completed postoperative study visits show a dramatic improvement in depressive symptoms and a trend toward improved executive function, specifically in the form of verbal fluency tasks. Most interestingly we are seeing potential changes in functional connectivity on fMRI that may correlate with this improvement in verbal fluency. Both pre- and postoperative images show responses in regions typically activated during this task, but the postoperative images show greater involvement of the right inferior frontal gyrus, in addition to the standard regions. The inferior frontal regions form part of the Broca's area that is typically involved in language production and fluency tasks. This suggests a more co-hemisphere pattern on this task postoperatively, compared to a left lateralized pattern before surgery.

Conclusions: While these are just preliminary data, we are hopeful to demonstrate the first ever objective changes in the brain following migraine surgery. Such data would provide strong, irrefutable evidence for the efficacy of migraine surgery and potentially shed light on the exact mechanism by which migraine surgery improves migraine symptoms.

Hypovitaminosis and Vitamin C Deficiency in Critically Ill Pediatric Patients Undergoing Cardiopulmonary Bypass

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Introduction: Vitamin C levels are known to be decreased in adult critical illness and associated with illness severity. Cardiopulmonary bypass (CPB) can lead to significant inflammation, endothelial dysfunction, and interruption of nutrition during the perioperative period. Combining these effects, children with congenital heart disease (CHD) and undergoing cardiac surgery might be at increased risk for low circulating vitamin C levels. This study aimed to investigate the risk of hypovitaminosis C (serum concentration < 23 µmol/L) and vitamin C deficiency (serum concentration < 11.4 µmol/L) in pediatric patients with congenital heart disease undergoing surgical repair using cardiopulmonary bypass.

Design/Methods: An ongoing prospective single-center observational study evaluating the perioperative time course of vitamin C levels in critically ill children (< 18 years of age) who are undergoing congenital heart surgery using CPB. Vitamin C serum levels were collected and recorded preoperatively (before CPB) and postoperatively (upon admission to the ICU, 24 hours, and 72 hours).

Results: Thirty-six patients with median age of 8.1 [IQR 2.5,68] months were consented and enrolled between October 2020 and July 2021. Median CPB duration was 117 [86,15] minutes, and hospital length of stay was 8 [4,13] days. Average vitamin C level decreased from 84.1 (sd=24.3) µmol/L before CPB to 55.8 (sd=22.4) µmol/L upon admission to the ICU, a reduction of 28.7 (95% CI: 19.9–37.5; p<0.001) µmol/L. Levels remained low on post-op days one and three compared to before CPB, averaging 25.3 (95% CI: 16.3–34.3; p<0.001) and 21.8 (95% CI: 12.8–30.8; p<0.001) µmol/L lower than before CPB. Three patients had hypovitaminosis C or vitamin C deficiency. Reduction in vitamin C serum levels was not associated with hospital length of stay (p=0.53).

Conclusions: Pediatric patients undergoing cardiac surgery with CPB showed decreased vitamin C levels during the postoperative period. The effects of hypovitaminosis C and vitamin C deficiency in this population remains unclear, and further investigation is needed to understand the potential effect of treatment with intravenous vitamin C.

Volume should not be used as the sole criterion in designing regionalization of care systems in Congenital Cardiac Surgery

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Introduction: Regionalization of care around larger volume programs has been proposed to optimize outcomes in Congenital Cardiac Surgery (CCS). However, the volume/outcomes relationship in CCS is far from clear. We hypothesized that hospital infrastructure/systems-of-care factors are also associated with outcomes in CCS and should be considered in regionalization efforts.

Methods: We used STS public reporting data (n=93 hospitals over 4 years) to obtain the ratio between risk-adjusted observed and expected mortality (O/E) using hospital-level CCS volumes. Two excluded hospitals were high outliers with an O/E ratio (>2 SD). Other candidate predictors (obtained from American Hospital Association, Children's Hospital Association and public websites) were hospital-level capacity/resources including pediatric surgical and non-surgical specialties, transplant programs, infrastructure, and trauma level. Linear regression models were used to estimate relationships between O/E mortality and volume only, then with hospital factors added. Separate models were run by procedure-specific STAT categories to account for case mix.

Results: We found wide variation in the volume of congenital cardiac surgeries performed (90-3,920) and a seven-fold difference between the highest- and lowest-performing hospitals by O/E mortality (0.3-2.1). Many pediatric specialties (anesthesiology, critical care medicine, gastroenterology, infectious disease, nephrology, neurology, pediatric surgery, otolaryngology, neurosurgery) and services (hemodialysis, nutritionists, respiratory therapy) were provided in nearly all hospitals studied. Univariate analysis of all cases combined (Table 1, Model 1) indicates that higher volume predicts a lower O/E mortality ratio, but univariate models stratified by category show that volume is only a significant predictor for STAT category 5, the highest risk procedures (Figure 1). In multivariate regression models, the effect of volume is attenuated and no longer statistically significant after accounting for hospital-level capacity and resources, both for all cases (β =-0.012, SE=0.009, p=0.165) and for category STAT 5 cases (β =-0.029, SE=0.044, p=0.514).

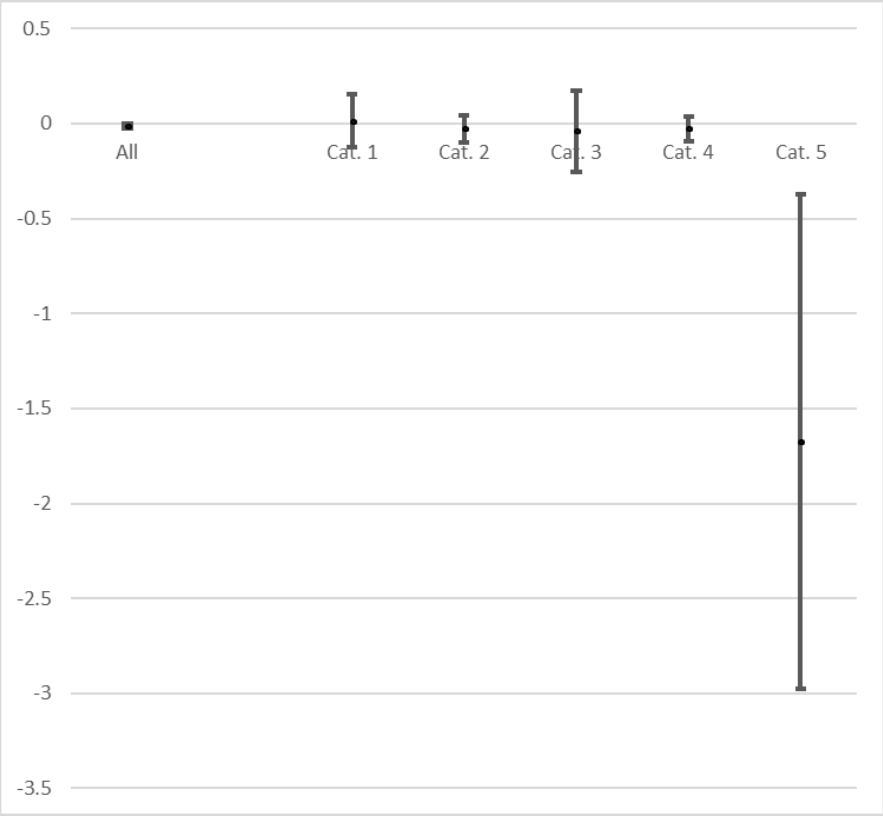
Conclusions: Volume should not be used as the sole criterion in designing regionalization of care systems in CCS. More granular analysis of larger clinical and administrative databases is needed to better define the necessary infrastructure and optimal model of care associated with best outcomes in CCS.

Table 1: Regression models predicting the observed-to-expected mortality ratio

	All congenital heart surgeries		STAT category 5 surgeries	
	Model 1	Model 2	Model 3	Model 4
	beta (SE) p	beta (SE) p	beta (SE) p	beta (SE) p
Intercept	1.192	1.237	2.265	4.858
Volume of congenital heart procedures, in hundreds	-0.014 (0.006) **0.03**	-0.012 (0.009) 0.165	-0.079 (0.035) **0.028**	-0.029 (0.044) 0.514
Heart transplants (1=yes, 0=no)		0.015 (0.114) 0.893		-0.544 (0.581) 0.352
Surgical NICU level 4 (1=yes, 0=no)		0.02 (0.158) 0.898		-0.838 (0.859) 0.333
Pediatric radiologist staffing per 100 beds		-0.013 (0.028) 0.648		-0.163 (0.145) 0.263
Pediatric trauma level 1 (1=yes, 0=no)		0.106 (0.1) 0.29		0.522 (0.518) 0.317
Have high-risk obstetrics and fetal medicine (1=yes, 0=no)		0.028 (0.091) 0.759		0.288 (0.466) 0.538
Have three specialties* for pediatric kidney and liver transplants (1=yes, 0=no)		-0.136 (0.115) 0.241		-0.28 (0.584) 0.633
Bone marrow transplants (1=yes, 0=no)		0.009 (0.113) 0.939		-1.455 (0.595) **0.017**
Percent of all beds in NICU		-0.003 (0.004) 0.476		-0.034 (0.022) 0.138
Adjusted R^2	0.041	-0.013	0.044	0.142

* The specialties are transplant nephrologists, transplant hepatologists and transplant surgeons

Figure 1: Univariate regression coefficients for volume as a predictor of observed-to-expected mortality ratio for all cases and by STAT risk-based categories of procedures (1 lowest to 5 highest), with 95% confidence interval



Effect of early biopsy-proven rejection on liver transplant outcomes

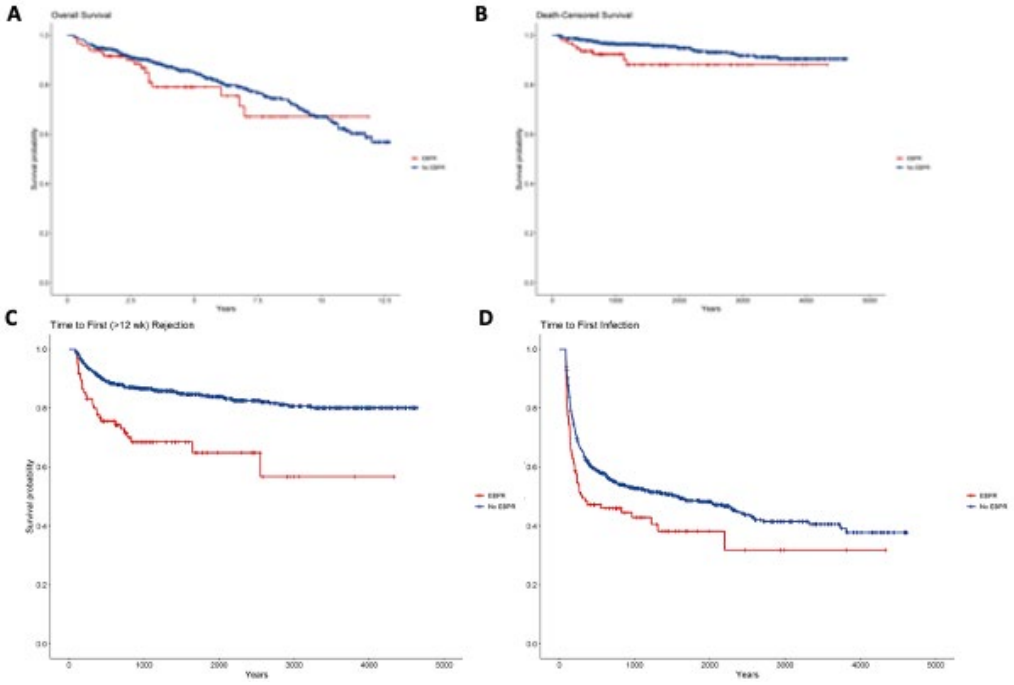
David D Aufhauser MD, Glen Leverson PhD, Nicholas Marka MS, Lily Stalter, David Al-Adra MD PhD, and David P. Foley MD

Introduction: Existing literature offers conflicting conclusions about whether early acute cellular rejection (ACR) influences long-term outcomes in liver transplantation. Several older studies report no long-term detrimental consequence of ACR but a recent study of living donor liver recipients demonstrated a significant association between early ACR and graft loss.

Methods: We retrospectively collected donor and recipient data on all adult, first-time liver transplants performed at a single center between 2009 and 2020. We divided this population into two cohorts based on the presence of early biopsy-proven acute cellular rejection (EBPR) within the first 12 weeks post-transplant and compared outcomes between the groups.

Results: There were 898 liver transplants that met inclusion criteria with 112 cases (13%) of EBPR. Donor and recipient characteristics did not differ between patients with and without EBPR. Recipients with EBPR had similar overall survival compared to patients without EBPR ($p=0.29$, Fig 1A) but had inferior graft ($p<0.05$) and death-censured graft survival ($p<0.01$, Fig 1B). EBPR was also associated with decreased time to first episode of late (>12 weeks post-transplant) rejection ($p<0.0001$, Fig 1C). Recipients with EBPR had increased vulnerability to bacterial and viral infection ($p<0.05$, Fig 1D).

Conclusions: EBPR after liver transplanted is associated with inferior death-censured graft survival, increased susceptibility to late rejections, and increased vulnerability to infection. This finding conflicts with older published experiences and may reflect changes in liver donors and recipients.


A
Overall Survival
Survival probability
Years
B
Death-Censored Survival
Survival probability
Years
C
Time to First (>12 wk) Rejection
Survival probability
Years
D
Time to First Infection
Years

Incidence and Severity of Postoperative Delirium Among Older Surgical Patients: A Descriptive Analysis

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Introduction: Postoperative delirium (POD) is a common complication among older adults, estimated to cost Medicare $32.9 billion annually. Poorly tracked, POD varies in the literature from 3.3% to 77%. Our institution initiated a preoperative comprehensive geriatric assessment (pCGA) to identify high-risk, frail surgical patients. In this retrospective chart review, we aim to (1) define the incidence of POD in this cohort as a baseline for future intervention and (2) to characterize the severity of these episodes.

Methods: We performed a retrospective chart review of pCGA patients (March 2019-June 2021). Eligible patients were 60 years or older with vision/hearing loss, cognitive concerns, poor nutrition, or more than 2 comorbidities. Included patients completed pCGA, surgical intervention and 30-day recovery. The pCGA included cognitive, mood, functional, nutrition, polypharmacy tests and comorbidity risk stratification. Data collected were demographics, comorbidities, pCGA data, operation, 30-day morbidity and all mortality outcomes. The primary outcome was incidence of POD; secondary was severity as defined by duration and use of restraints. Chart-abstraction of delirium was performed using a previously validated strategy with specific keywords.

Results: Of 64 pCGA patients, 25 were excluded (non-operative), with 39 in the final cohort. Mean age was 72.8 years (+/- 8.5y), 21 (53.8%) were female, and mean Charlson Score was 4. Preoperative cognitive impairment was present in 27 (69.2%) by Montreal Cognitive Assessment. Ten (25.6%) patients were frail and 10 (25.6%) pre-frail. Nine (23.7%) patients had a high-risk anticholinergic burden score. There were 10 cases of POD, with an unadjusted rate of 25.6%. Episodes lasted median 2 days (range 1-3), with one case requiring the use of chemical restraints (quetiapine) and no cases required physical restraints. Among patients with preoperative cognitive impairment, delirium occurred in 8 of 27 (29.6%) compared to 2 of 12 with no preoperative cognitive deficits (18.2%), p=0.69. Mean length of stay for cohort was 7.9 days (+/- 6.2), with 37 (94.9%) patients discharged home and 2 to skilled nursing. Seven (17.9%) patients died.

Conclusion: Postoperative delirium rates were high in this frail population. Pre-existing cognitive impairment increases risks, underscoring the value of preoperative cognitive screening. Limitations for this study include a small sample size, retrospective nature, and the potential for surveillance bias among a frail population undergoing pCGA. Given strong

evidence for delirium prevention, establishing baseline incidence is a critical first step to improve this geriatric syndrome.

Assessment of baseline surgical opioid overprescribing in Wisconsin Stateline area to inform surgeon directed opioid stewardship

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Introduction: The US is experiencing a well-recognized opioid epidemic. In Wisconsin, opioid overdose deaths have been increasing since formal measurement began at the state level in 2014 despite national, regional, and local mitigation efforts. Overdose and mortality rates have been highest in the Stateline area, with Rock and Green counties among the most affected. Surgical overprescribing of opioids has been described in multiple clinical scenarios, but the degree to which this may be contributing to the opioid epidemic in Rock and Green counties has not been quantified. We herein seek to quantify opioid prescribing patterns following common general surgery procedures and use this data to inform a directed intervention aimed at optimizing opioid stewardship among surgical prescribers.

Methods: This study retrospectively analyzed secondary administrative data provided by the Wisconsin Health Information Organization (WHIO), an all-payer claims database covering 75% of Wisconsin's population. Eligible adults (≥18 years old) included patients who underwent laparoscopic cholecystectomy, inguinal hernia repair, and appendectomy in the Wisconsin Stateline area (Green and Rock counties) between January 1 and December 31, 2017. Patients were excluded if they filled an opioid medication in the 6 months prior to surgery, or if they did not have continuous health insurance coverage in the 6 months before through 1 month after their surgical index procedure. Opioid prescriptions filled within 7 days of discharge were identified as well as the median morphine milligram equivalents (MME), duration and opioid type of the initial prescription.

Results: 291 patients undergoing the procedures of interest (106 laparoscopic cholecystectomy, 90 inguinal hernia repair, 95 appendectomy) were identified in one of 5 hospitals in the Stateline region. Overall, 55.6% of patients filled an opioid prescription. Fill rates were similar for appendectomy and inguinal hernia repair (69.5% and 64.4%, respectively) but lower for laparoscopic cholecystectomy (48.1%). Hydromorphone was the most common opioid prescribed. The median MME prescribed was 200, the equivalent of 40 tablets of hydromorphone (IQR = 150-225). This is substantially higher than reported patient use, which typically is <10 tablets, resulting in an estimated 8,730 unused tablets. The median duration of the initial prescription was 3 days (IQR = 3-5).

Conclusions: High levels of opioid overprescribing was observed. This quantifies the role of the surgical prescriber in the regional opioid epidemic as these excess unused tablets serve as a reservoir for diversion to illicit use. These baseline data are being used to inform the development of an intervention aimed at improving opioid stewardship within the surgical setting. The intervention consists of targeted surgical prescriber engagement, local surgeon champions, educational interventions that meet the state opioid CME requirement, and individualized prescribing data to allow for longitudinal measurement of prescribing patterns.

Passive Opioid Stewardship Initiatives Associated With Significant Changes in Opioid Prescribing Following Urologic Surgery

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Introduction: Post-operative overprescribing contributes to the ongoing opioid epidemic by (i) leading to persistent use in a significant subset of patients and (ii) increasing the supply of opioids available for non-medical use. We evaluate the impact of passive stewardship initiatives, where no direct urologist engagement occurred (e.g., Prescription Drug Monitoring Plan (PDMP), continuing medical education, emergence of guidelines) implemented since 2017 on statewide prescribing patterns following common urologic procedures.

Methods: We used Wisconsin Health Information Organization data, an all-payer claims database covering 75% of Wisconsin's population, to identify patients undergoing office (vasectomy), stone (ureteroscopy, ESWL), endoscopic (TURP, TURBT) and major (prostatectomy, nephrectomy) surgeries in the one year periods prior to June 30, 2018 and 2020. We captured filled opioid prescriptions within 14 days of a discharge and identified dose (median morphine milligram equivalents, MME) and duration (median days) for the initial prescription. We compared prescribing between 2018 and 2020 to assess for change in practice patterns.

Results: We identified 4,234 patients (1238 vasectomy, 1143 ureteroscopy, 361 ESWL, 432 TURP, 550 TURBT, 292 prostatectomy, 218 nephrectomy) in 2018 and 5,095 patients (1542 vasectomy, 1575 ureteroscopy, 394 ESWL, 482 TURP, 518 TURBT, 357 prostatectomy, 227 nephrectomy) in 2020. Overall, 40.2% and 26.9% ($p<0.0001$) of patients filled an opioid prescription. Of patients with an opioid fill, the median MME was 100 (IQR 75-180) and 90 (IQR 60-150) in 2018 and 2020, respectively ($p<0.0001$). Largest changes patient fills occurred after vasectomy followed by stone, endoscopic and major procedures (25.2, 10.5, 9.0, 4.7 percentage points, respectively). For filled prescriptions, the MME and number of tablets prescribed exceeded recommended levels for all procedures by 50 to >100%.

Conclusions: Multiple passive stewardship initiatives led to significant decreases in opioid prescribing in Wisconsin. This was driven primarily by decreased fill rates, which capture a combination of decreased prescribing and patients choosing not to fill. Despite the decrease, prescribing remains well above recommended levels. Active interventions focused on direct urologist engagement may lead to further improvement in opioid stewardship.

Figure 1. A) Fill rate and B) Dose (median total morphine milligram equivalents, MME) for the initial prescription following urologic surgery. Bar graphs with each procedure on x axis with two bars for the individual years. Text box with p-value above bars.

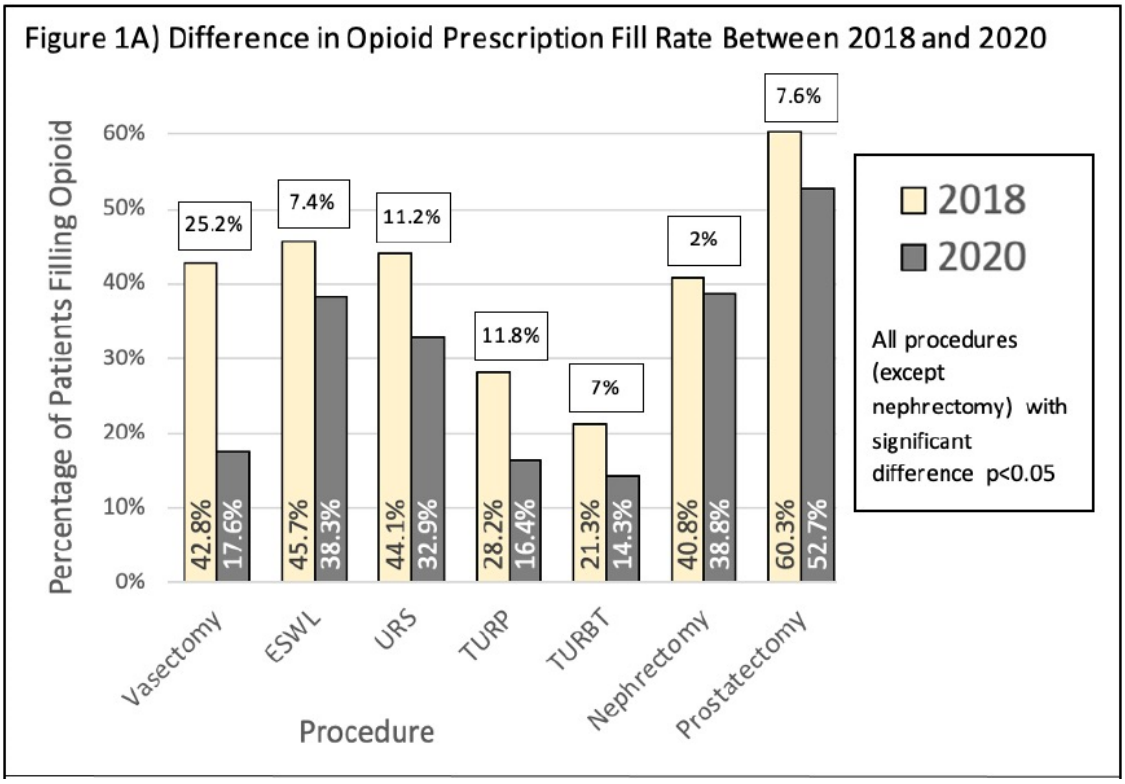
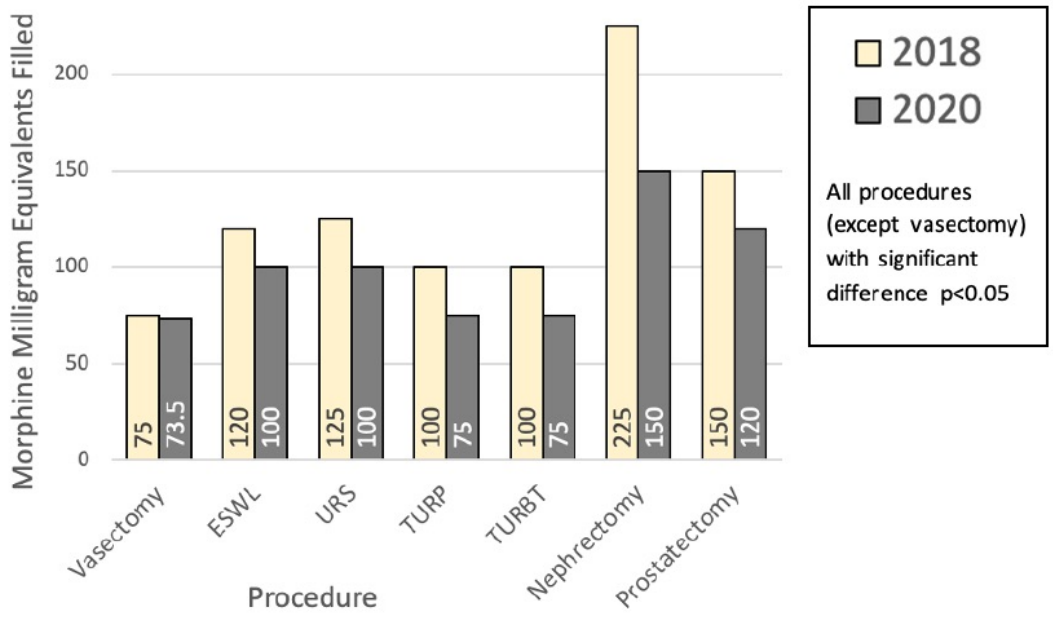


Figure 1B) Difference in Initial Post-operative Opioid Prescription Dose (MME) Between 2018 and 2020



Burden of synkinesis in patients with facial nerve paralysis: a qualitative investigation prior to treatment

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Introduction: Synkinesis causes hypertonicity and involuntary facial movements in patients within complete recovery after peripheral facial nerve injury. To date, no study has investigated the social, emotional, and functional burden of patients with synkinesis using qualitative research methods. This study aims to demonstrate the impact of synkinesis using qualitative analyses of patient interview data prior to treatment.

Methods: Eligible patients were recruited and enrolled from the Facial Nerve Clinic at the University of Wisconsin Hospital at their initial clinic visit. They simultaneously participated in a randomized clinical trial comparing treatment order of neuromuscular retraining therapy versus chemodenervation before receiving dual modalities. Prior to treatment, patient-reported instruments were collected, and semi-structured interviews were performed.

Results: Participants (n=15) had a mean age of 50 years (range 22-71) and were 80% female. Facial Clinimetric Evaluation scores at presentation had a median of 47.5 (IQR 69.2,25.8). The majority had paralysis from Bell’s Palsy. Primary themes derived from patient interviews included embarrassment, self-consciousness, and avoidance of social situations such as taking pictures or public eating. Patients also reported distress related to waiting for specialist referral, need for self-advocacy, and perceived lack of provider knowledge.

Conclusions: Patients who presented to our facial nerve clinic described the significant psychosocial burden of synkinesis on their own quality of life. Many patients expressed feelings of frustration with reduced self-esteem and reported modified social behaviors because of their disease. Understanding the patient experience through this qualitative investigation will help clinicians better support and treat patients with synkinesis.

Impact of Illicit Drug Use on Outcomes Following Acute Type-A Aortic Dissection Repair: An Analysis of the STS ACSD

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Introduction: Acute type-A aortic dissections (ATAADs) are life-threatening surgical emergencies. Despite the evolving drug crisis in the United States, the impact that illicit drug use (IDU) has on ATAAD outcomes is not well-described in the contemporary literature. We therefore queried the STS ACSD to examine the impact of IDU on ATAADs.

Methods: All patients ≥ 18 years in the STS ACSD who underwent ATAAD surgery between July 2010 and July 2020 were stratified into those with ("IDU+") and without ("IDU-") concomitant IDU. Demographics, preoperative factors, operative characteristics, and short-term outcomes were described. Continuous variables were compared using ANOVA with multivariable analysis of covariance models used to adjust for other factors. When not normally distributed continuous variables were presented as medians (IQR) and compared using Mann-Whitney test. The impact of IDU on categorical variables was evaluated with logistic regression; where necessary, values were adjusted for age, hypertension, and cigarette smoking. P-values less than 0.05 (two-sided) were considered statistically significant.

Results: 11% of ATAAD patients (4,218/38,053) had concomitant IDU at presentation; IDU+ patients were younger (51±11 years vs. 62±14, $p<0.001$), more likely to be male (80% (3,366/4,218) vs. 64% (21,810/33,835), $p<0.001$), consume ≥8 drinks/week (21% (872/4,218) vs. 7% (2,490/33,835), $p<0.001$), and have liver disease (10% (437/4,218) vs. 3% (993/33,835), $p<0.001$) than IDU- patients. No clinically significant differences in operative characteristics were observed between IDU+ and IDU- patients (Table). IDU was associated with longer length-of-stay (15±14 days vs 14±13, $p<0.001$) and a greater proportion of IDU+ patients were discharged home (61% (2,559/4,218) vs. 50% (17,055/33,835), $p<0.001$) (Table). Although IDU did not affect in-hospital morality, 30-day mortality was lower among IDU+ patients (13% (531/4,218) vs. 16% (5,484/33,835), $p<0.001$) (Table); however, adjusted short-term outcomes were clinically equivocal.

Conclusions: IDU does not deleteriously impact short-term outcomes following ATAAD surgery. This should not be misinterpreted as a tacit endorsement of IDU but highlights an opportunity for intervention among those IDU+ patients fortunate enough to survive their ATAADs. Leveraging such an impactful life-event for positive behavioral change warrants further investigation.

Table:

Variable	Overall (n=38053)	IDU+ (n=4218; 11%)	IDU- (n=33835; 89%)	*P* Value
CPB time (min)	197 ± 84	199 ± 82	197 ± 84	<0.001
Cross-clamp time (min)	115 ± 60	118 ± 61	115 ± 60	<0.001
Circulatory arrest time (min)	14 ± 19	13 ± 19	14 ± 19	<0.001
Arterial cannulation				
Axillary	12505 (33%)	1393 (33%)	11112 (33%)	0.811
Central	9939 (26%)	1097 (26%)	8842 (26%)	0.862
Femoral	12934 (34%)	1347 (32%)	11587 (34%)	0.003
Cerebral perfusion				
Antegrade	12759 (34%)	1517 (36%)	11242 (33%)	<0.001
Retrogade	6084 (16%)	633 (15%)	5451 (16%)	0.110
None	19261 (51%)	2068 (49%)	17193 (51%)	0.029
Coldest temperature (°C)	23 ± 6	23 ± 6	23 ± 6	<0.001
Surgery				
Supra-coronary ascending + hemi-arch replacement	11223 (29%)	1357 (32%)	9866 (29%)	<0.001
Supra-coronary ascending + total arch replacement	11103 (29%)	1313 (31%)	9790 (29%)	<0.001
Root + hemi-arch replacement	7615 (20%)	991 (23%)	6624 (20%)	<0.001
Concomitant descending stent graft	1561 (4%)	242 (6%)	1319 (4%)	<0.001
Other	572 (1.5%)	91 (2%)	481 (1.4%)	0.886
RBC transfusion (units)	2 (0, 5)	1 (0, 3)	2 (0, 5)	<0.001
Length of stay, d	14 ± 13	15 ± 14	14 ± 13	<0.001

Major morbidity				
Reoperation	3538 (9%)	388 (9%)	3147 (9%)	0.626
Stroke	4065 (11%)	471 (11%)	3594 (11%)	0.281
Prolonged ventilation	17412 (46%)	1946 (46%)	15466 (46%)	0.601
Renal failure	5232 (14%)	638 (15%)	4594 (14%)	0.006
Lower extremity malperfusion	1030 (3%)	115 (3%)	915 (3%)	0.118
Sepsis	1625 (4%)	204 (5%)	1421 (4%)	0.054
Deep sternal wound infection	118 (0.3%)	14 (0.3%)	104 (0.3%)	0.787
Disposition				
Home	19614 (52%)	2559 (61%)	17055 (50%)	< 0.001
Acute-care hospital	881 (2%)	108 (3%)	773 (3%)	0.256
Rehabilitation	10220 (27%)	858 (20%)	9362 (28%)	<0.001
In-hospital mortality	1936 (5%)	192 (5%)	1744 (5%)	0.095
30-day mortality	6015 (16%)	531 (13%)	5484 (16%)	<0.001

Prevalence of Subclinical Papillary Thyroid Cancer by Age: Meta-analysis of Autopsy Studies

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Introduction: Papillary thyroid cancer (PTC) is most often diagnosed in middle aged adults (45-64 years). It is unclear whether the observed changes in PTC incidence across different age groups reflect a true increase or the detection of subclinical disease due to increased diagnostic scrutiny. This meta-analysis of thyroid autopsy studies is the first to evaluate how subclinical PTC prevalence changes with increasing age.

Methods: We searched PubMed, Embase, and Web of Science databases and included studies that reported the prevalence of PTC found at autopsy from database inception to May 2021. Studies of populations with known radiation exposure (e.g., Hiroshima or Nagasaki bombings, Chernobyl accident) and those that did not report age at death were excluded. Two investigators extracted the number of subclinical PTCs by 10-year age groups and whether the whole or partial thyroid gland was examined. A validated quality assessment scale was used to assess the presence of nine safeguards to minimize bias. Logistic regression models with random intercepts for each study examined pooled age-specific subclinical PTC prevalence.

Results: Of 1773 studies screened, 99 full text articles were reviewed and 9 studies with age-specific data met inclusion criteria. These studies included 2261 autopsies with four studies examining whole glands (n=427). Pooled analyses found subclinical PTC prevalence was 11% (95% CI 5-18) with whole gland and 5% (2-8) with partial gland examination. Age-specific prevalence by decade (3rd to 9th) adjusted for extent of examination was: 9.8% (3-16.7), 10.3% (3.6-17), 10.9% (4.2-17.5), 11.4% (4.6-18.2), 12% (4.8-19.2), 12.6% (4.8-20.4), and 13.2% (4.5-21.9); *Figure 1*. In the regression model, the odds ratio by decade was 1.06 (0.93-1.18, p=0.37).

Conclusions: This meta-analysis showed no statistically significant association between the prevalence of subclinical PTC and age in adults, in contrast to clinical detection patterns that peak in middle age. The observed maximal incidence clinically between ages 45-64 may stem from a combination of the likelihood of developing higher-risk cancer variants later in life and healthcare utilization over patients' life spans, allowing detection of subclinical disease.

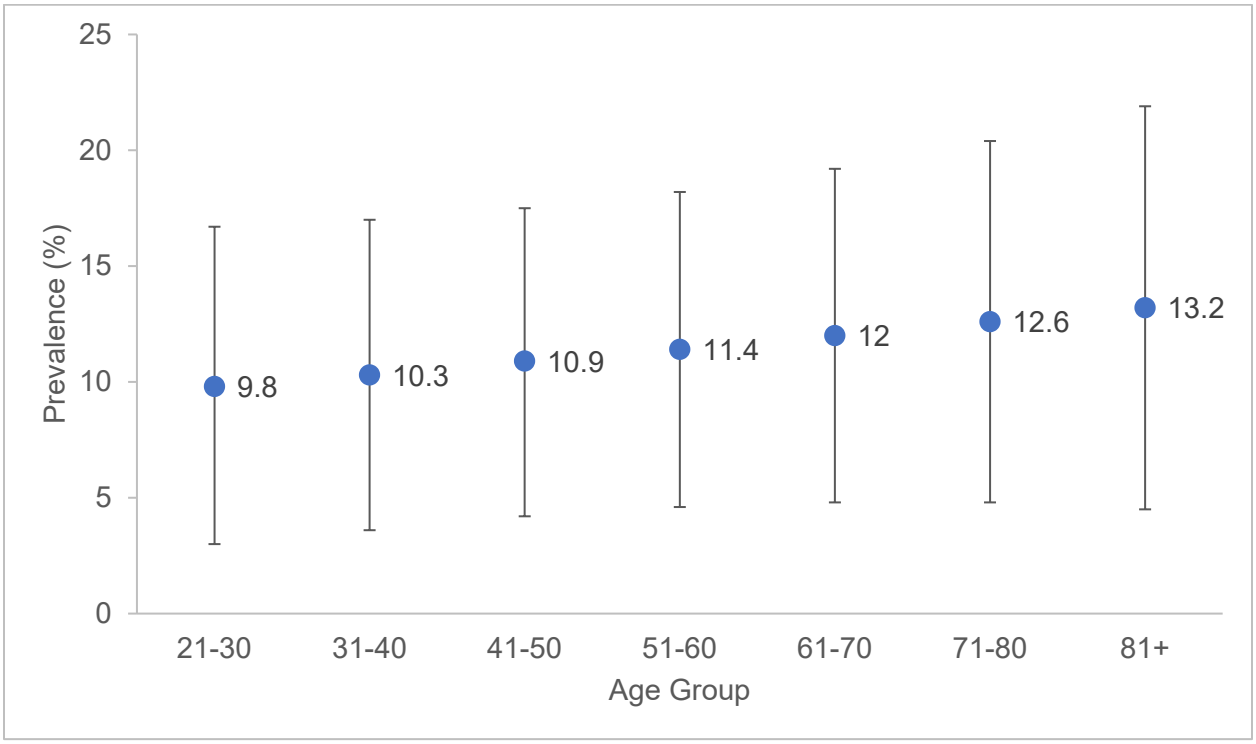

Figure 1. 10-year age-specific prevalence in logistic regression model; error bars represent 95% confidence intervals

Predicting Young Adults at High Risk for Weight Gain Using Machine Learning

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Introduction: Weight gain during early adulthood is associated with decreased quality of life and increased risk of developing obesity-related comorbidities and cancers. Identification of at-risk adults could allow for early intervention to prevent weight gain. Our objective was to predict which young adults in overweight or class 1 obesity categories were at highest risk for gaining weight using machine learning models.

Methods: We included patients aged 19-39 who had a body mass index (BMI) between 25.0-34.9 kg/m^2 and ≥2 weight measurements 2-3 years apart within the University of Wisconsin electronic health record from 2008-2019. We excluded patients with any history of cancer or bariatric surgery, or a pregnancy diagnosis within 1-year of their weight measurements. Four categories of variables were included: 1) demographics; 2) obesity-related health conditions; 3) laboratory data and vital signs; and 4) neighborhood-level variables (area deprivation index, walkability, urbanicity). Two logistic regression models (linear predictor terms and restricted cubic spline terms), a random forest model, and two regularized regression models (lasso and ridge with restricted cubic spline terms) were trained with 60% of the cohort and validated with the remaining 40%. Area under the receiver operating characteristic curves (AUC) were calculated to determine the models' accuracy at predicting high-risk individuals, defined by ≥10% total body weight (TBW) gain 2-3 years after baseline. Variable importance was determined using model specific metrics.

Results: Of the 24,183 patients included in the study, 3,428 (14.2%) gained ≥10% TBW. Lasso regression was the most accurate model (AUC 0.671). The AUCs for the other models had similar accuracies: ridge regression (AUC 0.670) logistic regression with cubic spline predictor variables (AUC 0.670), logistic regression with linear predictor variables (AUC 0.669), and random forest model (AUC 0.649). **Table 1** displays the model performance metrics. BMI and age were the most important model components for logistic and regularized regression**.** BMI was the most important continuous variable and tobacco use was the most important categorical variable for the random forest model.

Conclusions: Using machine learning methods based on existing electronic health record data to predict weight gain for at risk younger adults may not be accurate enough for intervention

development and targeting. Further exploration of other machine learning methods, such as gradient boosted decision trees and neural networks, along with a richer set of variables that includes behavioral characteristics is warranted. Early identification of individuals would allow for targeted interventions to prevent weight gain.

Table 1. Comparison of model performance
Numbers presented are for a predicted probability cut-off of 0.2

Model	Sensitivity	Specificity	Accuracy	Negative predictive value	Positive predictive value
Logistic regression with linear predictor variables	37.8%	82.3%	76.0%	88.9%	26.1%
Logistic regression with cubic spline predictor variables	38.1%	81.8%	75.6%	88.9%	25.6%
Lasso regression	37.4%	82.9%	76.4%	88.9%	26.7%
Ridge regression	36.9%	82.4%	76.0%	88.8%	25.7%
Random forest	40.7%	78.0%	72.7%	88.9%	23.4%

Association between neighborhood food environment and bariatric surgery outcomes

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Introduction: Individual factors associated with weight loss after bariatric surgery are well established, but relationships between neighborhood characteristics and optimal weight loss after bariatric surgery are unknown. We examined if neighborhood characteristics were associated with weight loss after bariatric surgery.

Methods: Patients who underwent bariatric surgery from 2008-2017 within a single health system with ≥1 year follow-up were included. Demographics, neighborhood characteristics, 90-day and 1-year outcomes, and weight loss were reported. At the neighborhood-level, three social determinants (area deprivation index [ADI], urbanicity, walkability) and six lifestyle factors (organic food use, fresh fruit/vegetable consumption, dieting, soda consumption, fast-food consumption, and exercise) were analyzed. The lifestyle factors were neighborhood-level, composite variables obtained from the Esri® database, which uses Geographic Information System (GIS) mapping tools to track and map customer and environmental data. The composite variables were constructed by the Esri® database using survey data. We used median regression with percent total body weight (%TBW) loss as the outcome to examine factors associated with weight loss.

Results: Of the 647 patients who met inclusion criteria, 70% were from metropolitan areas with 3.1 years of average follow-up and 22% mean TBW loss. In adjusted median regression analyses, longer follow-up time (-2.42% TBW loss, 95% CI [-4.63, -0.20]) and a pre-operative diagnosis of diabetes (-1.00% TBW loss, 95% CI [-1.55, -0.44]) were associated with less %TBW, whereas Roux-en-Y gastric bypass (11.22% TBW loss, 95% CI [8.96, 13.48]) was associated with more %TBW than sleeve gastrectomy (**Table 1**). Neighborhood characteristics were not associated with weight loss outcomes.

Conclusions: Compared to neighborhood-level characteristics, patient characteristic and type of bariatric procedure are more strongly associated with weight loss following bariatric surgery. Patients who live in higher-risk neighborhoods from an environmental perspective can achieve equivalent bariatric surgery weight loss outcomes as patients from “healthier neighborhoods.”

Table 1. Median regression with %TBW loss as the outcome

	Model 1	**Model 2**	**Model 3**
Variable	**Median % TBW loss (95% CI)**	**Median % TBW loss (95% CI)**	**Median % TBW loss (95% CI)**
Patient characteristics			
Age (+5 yrs)	-0.08 (-0.60, 0.45)	-0.17 (-0.71, 0.37)	-0.24 (-0.85, 0.37)
Female sex	0.32 (-1.97, 2.61)	0.62 (-2.08, 3.32)	0.60 (-2.25, 3.44)
Race/ethnicity Non-White White, non-Hispanic	 Ref -0.09 (-3.52, 3.35)	 Ref 0.61 (-3.17, 4.39)	 Ref -0.15 (-4.49, 4.19)
Insurance type Private/self-pay Medicare Medicaid	 Ref -0.54 (-3.48, 2.40) 1.24 (-0.83, 3.30)	 Ref -0.71 (-3.75, 2.34) 1.22 (-0.94, 3.38)	 Ref -0.31 (-3.19, 2.57) 0.96 (-1.47, 3.40)
Preoperative BMI	0.11 (-0.03, 0.26)	0.13 (0.00, 0.27)	0.07 (-0.10, 0.23)
Preoperative type 2 DM	**-2.77 (-4.77, -0.77)**	**-2.70 (-4.80, -0.60)**	**-2.42 (-4.63, -0.20)**
RYGB (vs. sleeve)	**10.82 (8.65, 13.00)**	**10.81 (8.35, 13.27)**	**11.22 (8.96, 13.48)**
F/U time (+1 yr)	**-1.06 (-1.61, -0.51)**	**-1.07 (-1.58, -0.56)**	**-1.00 (-1.55, -0.44)**
Neighborhood characteristics			
ADI Low (<70) High (≥70)	 --	 Ref 1.17 (-1.80, 4.13)	 Ref -0.02 (-3.62, 3.57)
Urbanicity	--	-0.20 (-0.58, 0.18)	-0.36 (-0.91, 0.18)
Walkability	--	-0.02 (-0.40, 0.M35)	-0.09 (-0.47, 0.29)
Organic food	--	--	-0.02 (-0.13, 0.09)
Fresh fruit/vegetable consumption	--	--	-0.21 (-0.66, 0.23)
Control diet	--	--	0.04 (-0.06, 0.14)
Soda consumption	--	--	-0.01 (-0.17, 0.14)
Exercise	--	--	-0.03 (-0.14, 0.08)

Impact of Covid-19 on the post-operative bariatric surgery patient experience

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Introduction: Recent studies have demonstrated that Covid-19 negatively impacts weight-related behaviors, however patient and provider perceptions of its impact are unknown. The objective of this study was to characterize patient and provider perceptions of how Covid-19 impacted dietary habits, physical activity, and adherence to recommended follow-up care after bariatric surgery.

Methods: Semi-structured interviews with bariatric surgery patients, primary care providers (PCPs), and health psychologists from multiple academic and private practice settings in Wisconsin were conducted from April-November 2020. Patients who had undergone primary bariatric surgery and had at least one-year of postoperative follow-up were eligible for inclusion. PCPs and health psychologists were required to have cared for bariatric surgery patients. Participants described how the Covid-19 pandemic affected their postoperative experience within three domains: dietary habits, physical activity, and adherence to recommended follow-up care. Interview guides were created from a hybrid of two conceptual models: Torain's Surgical Disparities Model and Andersen's Behavioral Model of Health Services Use. Five study team members generated codes, which were grouped into themes using directed content analysis.

Results: Thirty-four participants were interviewed, including 24 patients (12 Roux-en-Y gastric bypass and 12 sleeve gastrectomy), six PCPs, and four health psychologists. Patients were predominately female (83%) and white (79%). Providers were predominately female (90%) and white (100%). **Table 1** displays three themes that describe how Covid-19 disrupted weight-related behaviors along with representative patient and provider quotes. Changes to dietary routines arose from increased grazing behaviors due to more time at home and decreased fresh food access due to fear of grocery shopping. Physical activity routines were altered due to facility closures, fear of Covid-19 exposure, and an increase in sedentary lifestyle. The shift to telemedicine visits provided more scheduling flexibility but was sometimes perceived as impersonal. Financial and psychosocial stress arose from job losses and furloughs that led to loss of health insurance and food insecurity. Covid-19-related deaths among family and friends also disrupted social support networks.

Conclusions: Covid-19 has exacerbated patient vulnerability. The pandemic is not over, thus

bariatric surgery patients need ongoing support to access mental health professionals, develop new physical activity routines, and counteract increased food insecurity.

Table 1. Representative patient and provider quotes

Themes	Quotations
Disruption of established routines caused changes in patients' diet, physical activity, and follow-up care	"I'm finding now that with Covid and me being more restricted to the house, I'm not getting enough exercise and to me that's very frustrating. I want to go back and swim so bad." (Patient)
	"Before Covid happened I was able to go to the grocery store several times a week. And now I only go every ten days to two weeks. I try to buy fresh veggies if I can." (Patient)
Follow-up care transitioned to telemedicine visits	"[Telemedicine] actually has helped with cancellations and no-shows, because patients don't have to worry about the services not coming in time to pick them up, their car breaking down or things like that." (Health psychologist)
Increased financial and psychosocial stressors	"We've had a lot of folks who sadly will have a series of deaths in the family. We just had one that had two deaths related to Covid. They were her friends, not family. But, when you have those kind of spiraling things, those are things we want to catch as quickly as possible." (Health psychologist)

Provider Perspectives on Challenges during Emergency General Surgery Transfer Calls: Importance of Surgeon-to-Surgeon Communication

Diana Gutierrez-Meza, MPH; Megan Saucke, MA; Esra Alagoz, PhD; Angela Ingraham, MD

Introduction: Transferred emergency general surgery (EGS) patients experience worse outcomes than directly admitted patients. Improving communication between referring (RP) and accepting (AP) providers may improve patient outcomes. This qualitative study aims to understand the communication challenges experienced by RPs and APs during EGS transfer calls.

Methods: Guided by previous interviews with transfer center nurses (TCNs) and the Relational Coordination Framework, we have thus far interviewed seven APs (surgeons) and four RPs (emergency medicine physicians and surgeons) involved in transfers of EGS patients. A trained qualitative interviewer conducted all interviews through WebEx. Interview recordings were transcribed, de-identified, and managed in NVivo. Four researchers met regularly to develop a codebook, co-code transcripts, build consensus, and discuss emergent themes.

Results: While emergency medicine physicians (EMPs) initiate most EGS transfer calls, all providers expressed that communication challenges tend to arise when APs do not talk directly to local surgeons. APs explained how talking to someone other than the local surgeon makes it harder to understand the full picture of patients' clinical situation and reasons for transfer. When APs heard *"my surgeon is not comfortable*" from the EMP, they wondered why the local surgeon could not manage the patient there. EMPs also highlighted the difficulties of being the "middle man" because they have to advocate and explain the thought process of their local surgeon in the APs' language. EMPs recognized that surgeon-to-surgeon communication *"would just be better for patient care because [surgeons] can relay their concerns to each other, because I oftentimes don't know the intricacies of why one won't do it. And if the [AP] feels as if our personnel should be able to do it, then [both surgeons] can talk about why."*

Conclusions: Our preliminary findings revealed that both APs and RPs acknowledge the importance of surgeon-to-surgeon communication during transfers of EGS patients. Most APs expressed that they prefer local surgeons call them as a professional courtesy. If surgeon-to-surgeon conversation is not feasible, non-surgeon RPs should provide a concise report of the patients' clinical situation and reasons for transfer such as limited hospital resources. To develop a comprehensive understanding of provider communication during transfer calls, we will continue to interview APs and RPs. These data will inform the development of strategies to optimize communication during interhospital transfers of EGS patients.

Altering Supraglottic Pressure to Improve Phonation Threshold Pressure During Semi-Occluded Vocal Tract Therapy Using a CPAP in Human Subjects

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Introduction: Semi-Occluded Vocal Tract (SOVT) therapy is a commonly used voice therapy that involves a patient phonating for an extended period into a straw in either air or water. SOVT therapy improves vocal economy by increasing supraglottic pressure and acoustic impedance. By increasing supraglottic pressure by a fixed amount, SOVT therapy decreases the phonation threshold pressure (PTP), lowering the amount of effort needed to speak. There is no existing literature that examines the effects of altering supraglottic pressure on post-SOVT PTP in human subjects, and the optimal supraglottic pressure to aid phonation has not been determined.

Methods: 30 college aged students at the University of Wisconsin-Madison were volunteers for this study. Participants were randomly assigned to a supraglottic pressure value of either 2, 4, 6, or 8 cmH_2O. Experimenters recorded PTP measurements before and after the participant completed a short-duration (50 seconds) task of phonating into a CPAP device with supraglottic pressure held constant at the randomly assigned value. After a 15-minute rest period, PTP measurements were taken before and after a long-duration (500 seconds phonation) SOVT task.

Results: Preliminary results show decreases in PTP following all four short-duration tasks and following long-duration tasks at 4, 6, and 8 cmH_2O. The largest difference following the short-duration task was with a supraglottic pressure input of 6 cmH_2O. The largest difference following the long-duration task was with a supraglottic pressure input of 4 cmH_2O.

Conclusions: These results suggest that 6 cmH2O is the optimal supraglottic pressure to improve vocal economy during short-duration SOVT exercises, such as vocal warmups. However, for prolonged SOVT exercises intended as voice therapy, a pressure closer to 4 cmH_2O may be optimal. Future SOVT models should be designed to create pressures around the range from 4-6 cmH_2O. Additionally, CPAP machines could potentially improve vocal economy better than straws due to their ability to alter supraglottic pressure to fit the situation.

A Statewide Approach to Reducing Re-excision Rates for Women with Breast Conserving Surgery

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Introduction: The Surgical Collaborative of Wisconsin (SCW) is a surgeon-led practice change community that includes 85 hospitals and 224 surgeons and quality leaders. An inaugural SCW initiative was to reduce re-excision rates for women undergoing lumpectomies for breast cancer. Re-excision rates at WI hospitals following lumpectomy ranged from 5% to over 50% in 2017. Studies suggest a target re-excision rate of 10%. A statewide initiative was undertaken in 2018 to support surgeon efforts to reduce re-excisions by implementing evidence-based strategies that promote best practices (the intervention). The objective was to describe SCW surgeon engagement and assess the impact of the intervention on re-excision rates over time.

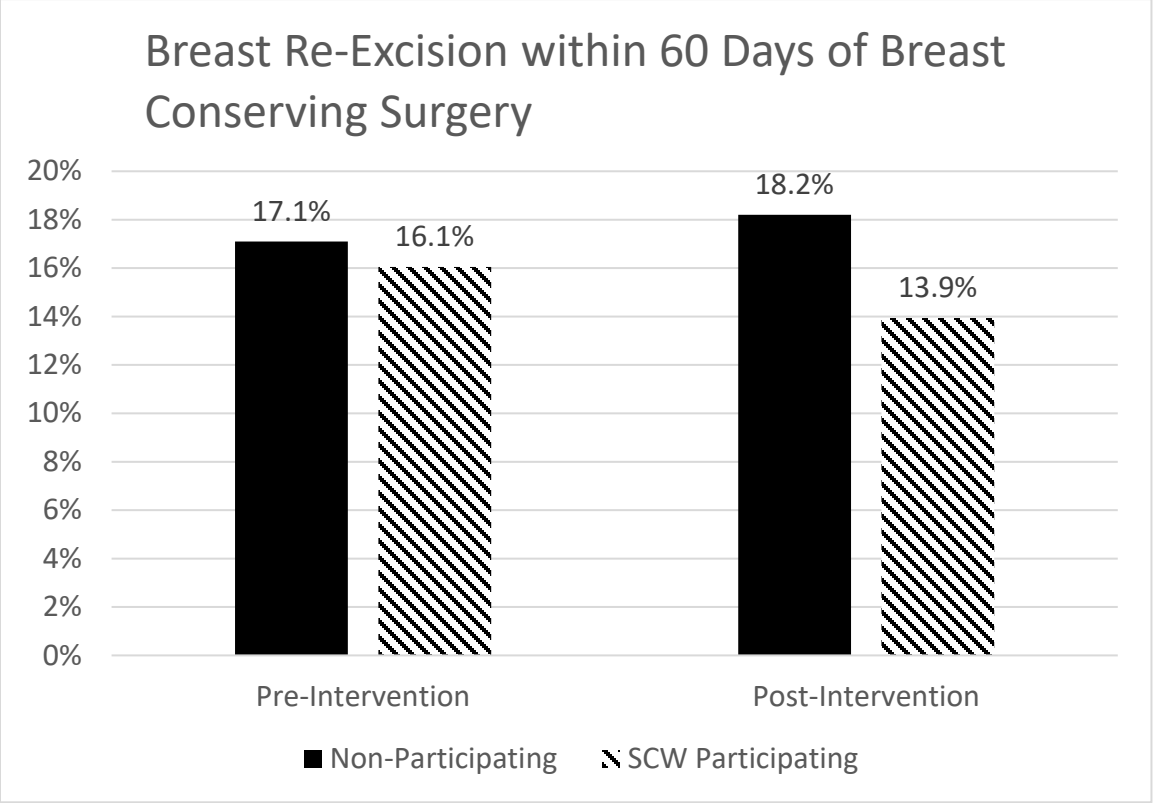
Methods: *Surgeon Engagement:* Five in-person and virtual collaborative meetings were held in 2018-2019. During meetings, surgeon champions shared guideline updates and facilitated discussions to share challenges, best practices and experiences with guideline implementation. Confidential surgeon reports containing benchmarked risk- and reliability-adjusted surgeon and hospital-level re-excision and mastectomy rates were provided. In-person discussions facilitated action plan development. Discussion summaries were created and analyzed for use at meetings.

Outcomes Evaluation: Wisconsin Hospital Association discharge data from 2017 (baseline, pre-intervention) through 2019 (post-intervention) were used to compare 60-day re-excision rates following lumpectomy for women diagnosed with non-metastatic breast cancer. Mastectomy rates were compared as a balance measure. T-tests for continuous variables and chi-square tests for proportions assessed differences in hospital re-excision rates and patient case-mix (age, payer) between SCW participating and non-participating hospitals. The primary analysis estimated the difference in the average change pre-to post-intervention in outcomes between participating and non-participating hospitals. This intervention effect was tested in the context of a multivariable logistic mixed effects model with repeated measures, adjusting for age, payer, and including hospitals as random effects.

Results: Surgeons engaged in SCW have utilized the network to discuss difficult cases and support each other in practice. In 2017, 2592 procedures were performed in SCW participating and 883 in non-participating hospitals. There was a statistically significant difference in re-

excision rates between SCW participating and non-participating hospitals in the post- but not pre-intervention time-period (Figure). Findings were consistent in the adjusted model (OR=0.68, 95% CI = 0.52-0.89). There was no statistically significant between-group difference in mastectomy rates (OR=1.2, 95% CI=0.87-1.6).

Conclusion: A collaborative approach to statewide quality improvement that aims to engage surgeons to educate them about guideline concurrent care, network and share best practices can significantly impact outcomes and patient care compared to standard practice.



Collaborative learning networks based on Wisconsin's Public Health Regions to promote statewide surgical quality improvement

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Introduction: Variation in surgical management and postoperative outcomes is well documented. The Surgical Collaborative of Wisconsin (SCW) aims to broadly improve the quality of surgical care across the state by providing benchmarked performance reports and best practices and by creating a practice change community to facilitate shared learning. To promote local collaboration and address the financial and time burdens associated with travel, we proposed developing five learning networks using the public health regions created by the Wisconsin Department of Health Services. The objective of this project was to describe these regions in terms of socioeconomics and outcomes for patients undergoing breast and colorectal surgical procedures.

Methods: Discharge data from the Wisconsin Hospital Association (WHA) (2019) was used to identify adult patients (≥18 years old) who underwent a lumpectomy procedure for breast cancer or a colorectal surgical procedure. Patients were grouped by hospital and by public health region: Northeastern, Northern, Southeastern, Southern, and Western. Outcomes examined included re-excision rates following lumpectomy procedures and postoperative length of stay and readmission following colorectal surgery. County-level data from the Department of Health Services' Wisconsin Interactive Statistics on Health (WISH) system was used to characterize socioeconomic characteristics for each region.

Results: The population included 3575 patients who underwent lumpectomy and 4154 patients who underwent a colorectal surgery. The number of hospitals in each region ranged from 34 hospitals in the Northern region to 106 hospitals in the Southeastern region. The Northern and Western regions contained the most critical access hospitals, whereas the Southeastern region had only one critical access hospital. The largest hospitals by volume were located in the Southeastern and Southern regions. Hospitals in each region had similarly wide ranges in variation of breast reexcision rates ranging from 7.6% to 31.3% across the state. This hospital-level wide variation was also seen in length of stay following colorectal surgery, ranging from 2.41 days to 8.13 days, and readmission rates ranging from 1.41% to 8.52%. The variation within each region was always wider than the variation between the public health regions. Mean household income between the regions ranged from $52,000 in the Northern Region to $69,000 in the Southeastern region and mean unemployment rate ranged from 3.1% in the Southern Region to 4.6% in the Northern Region.

Conclusions: The Wisconsin Department of Health Services public health regions are a reasonable model for creating collaborative learning networks to facilitate surgical quality improvement. We identified significant hospital-level variation in postoperative outcomes for patients undergoing breast and colorectal surgical procedures in each region, indicating a need for broad quality improvement interventions. Understanding the characteristics of hospitals in each region and the patient populations they serve may facilitate creation of smaller collaborative learning networks for tailoring of surgical quality improvement interventions.

Best Case/Worst Case: A Multisite Randomized Clinical Trial of Scenario Planning for Patients with End-Stage Kidney Disease

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Introduction: Given the burdens of treatment and poor prognosis, older adults with end-stage kidney disease would benefit from interventions that both improve decision making about dialysis and encourage delivery of palliative care in order to clarify goals, address symptoms, and reduce unwanted invasive procedures. We adapted the Best Case/Worst Case communication tool, previously developed to support acute surgical decisions, and applied it to older seriously ill patients with end-stage kidney disease considering dialysis. This describes the protocol for a multisite, cluster-randomized trial to test the effect of the Best Case/Worst Case communication tool on receipt of palliative care, quality of life, and quality of communication. We hypothesize that patients exposed to the Best Case/Worst Case communication tool will be more likely to receive palliative care and have fewer intensive treatments at the end of life resulting in better quality of life.

Methods: We plan to enroll 32 attending nephrologists, at 8 study sites, who see at least 5 outpatients a year with late-stage chronic kidney disease considering dialysis. In total, we aim to study 320 patients with an estimated glomerular filtration rate (eGFR) of less than 20mL/min/1.73m^2 who are age 60 and older and have a predicted survival of 18 months or less. Nephrologists will be randomized to receive the intervention (training in the communication tool) at study initiation or after study completion (wait-list control). Patients in the intervention group will receive care from their nephrologist trained to use the BC/WC communication tool. Patients

in the control group will receive usual care. Using chart review and surveys of patients and caregivers, we will test the efficacy of the BC/WC intervention on (1) receipt of palliative care and (2) intensity of treatment at the end of life for older patients with ESKD. Secondary outcomes include the effect of the intervention on quality of communication between nephrologists and patients (using the Quality of Communication [QOC] scale) and the change in quality of life (using the FACIT-Pal scale) over time for patients.

Ethics and dissemination: Approvals have been granted by the Institutional Review Board at the University of Wisconsin with each study site ceding review to the primary IRB. This study is funded by the National Institutes of Health (R01AG065365) and registered at clinicaltrials.gov. Results will be reported in peer-reviewed publications and presented at national meetings.

Reduction in Opioid Prescribing Following Lung Transplantation Utilizing Intercostal Nerve Cryoablation

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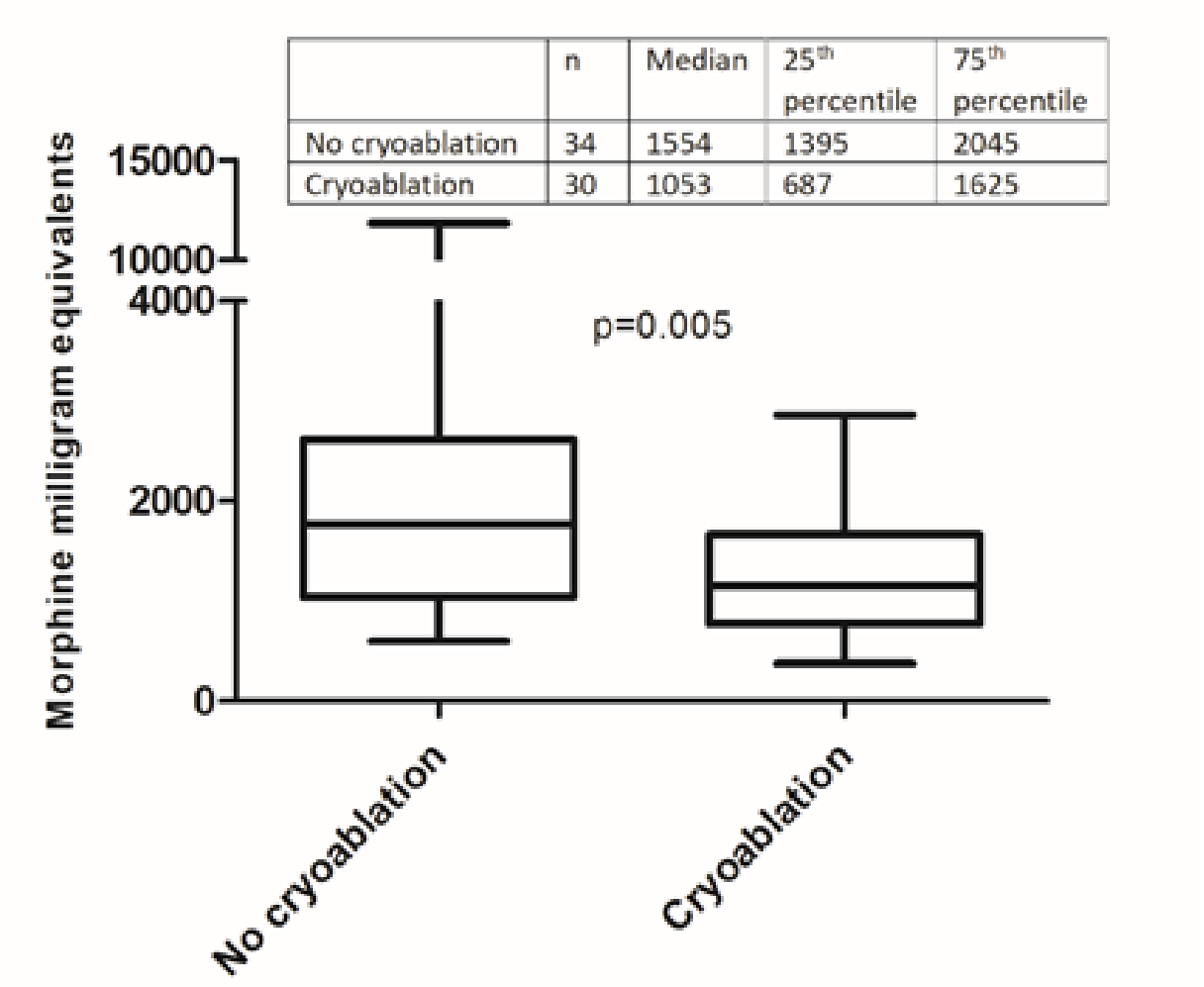
Introduction: Inadequate pain control increases perioperative complications, yet narcotic-based analgesia is associated with serious acute and chronic side effects. Epidural catheters can reduce opioid use but contraindications and technical challenges are common. We report on the use of intercostal nerve cryoablation to enhance perioperative pain control as part of an opioid-sparing protocol.

Methods: We conducted a retrospective cohort study of adult lung transplants from 10/2017-8/2021 to compare practices before (pre-cryo) and after (post-cryo) initiation of an opioid-sparing protocol utilizing intraoperative intercostal nerve cryoablation. The pre-cryo cohort included consecutive patients treated with opioids and selective use of epidural catheters. The post-cryo cohort received cryoablation at levels 3-7, scheduled acetaminophen, gabapentin, and tramadol. Additional opioids or epidural catheters were used for breakthrough pain. Patients were excluded for intubation >48 hours, reintubation, or <8 week follow-up. Morphine milligram equivalents (MME) were collected and analyzed at several time points. Outpatient use was estimated by prescriptions written within 8 weeks of transplant.

Results: A total of 34 pre-cryo and 30 post-cryo patients were analyzed. Baseline demographics were similar aside from a significantly older post-cryo cohort (61 vs 56 years, p=0.043). Total inpatient and outpatient opioid use decreased by 32% (**Figure**, p=0.005). In addition, epidural use declined from 53% to 3% (p<0.001). These decreases occurred even though the post-cryo cohort included significantly more bilateral lung transplants (93% vs 56%, p=0.001). Post-cryo patients were prescribed significantly fewer opioids at discharge (p<0.001) but received similar post-discharge outpatient prescriptions.

Conclusions: The implementation of a perioperative pain protocol that includes intercostal nerve cryoablation was associated with a significant reduction in epidural utilization and total opioid consumption in the first 8 weeks post-transplant. Further research is needed to understand how these findings impact clinical outcomes.

	n	Median	25th percentile	75th percentile
No cryoablation	34	1554	1395	2045
Cryoablation	30	1053	687	1625



Incidence of Radiation-associated Sarcoma After Breast Conserving Surgery Plus Radiation

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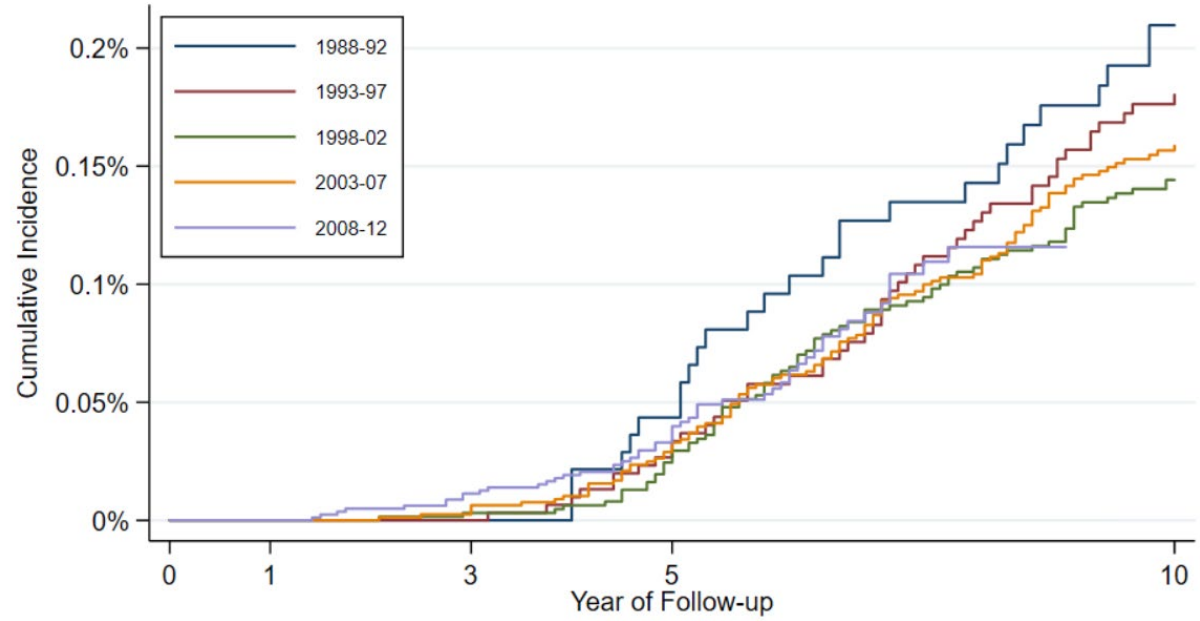
Introduction: Radiation-associated sarcoma (RAS) is a rare complication of radiation therapy for breast cancer. Since the first descriptions of RAS, radiation therapy modalities for breast cancer treatment have changed significantly. We sought to determine if the incidence of RAS after breast cancer treated with breast conservation and radiation (BCT) has changed over time.

Methods: The Surveillance, Epidemiology, and End Results (SEER) Program was used to identify breast cancer survivors (diagnosed 1988-2012) who were treated with BCT with the following exclusion criteria: patients who were male, ≤18 years, had history of prior cancer, had<1y follow-up/survival, and who didn't receive external beam radiation (final cohort n=276,301). We identified patients who subsequently developed a chest soft tissue sarcoma, excluding diagnoses within 1y of breast cancer diagnosis. Incidence of sarcoma after breast cancer by 5-year periods of breast cancer diagnosis year was estimated using Kaplan-Meier survival analysis. Patients were censored at the time of sarcoma diagnosis, death, last follow-up (available through 12/2017), or at 10-years post-breast cancer diagnosis. Given the known latency for RAS, we used Joinpoint analysis to identify the time point at which the rates of RAS incidence significantly increased. We used this point (5-years post-breast cancer diagnosis) as the start of the analytic window. A log-rank test was then used to assess differences in the survival functions of the diagnosis year groups.

Results: Overall incidence of RAS was 0.03% at 5-years (95% CI: 0.03-0.04%) and 0.16% at 10-years (95% CI: 0.14-0.18%) (Figure). There was no statistical difference in RAS incidence across the 5-year period diagnosis year groups (p=0.5).

Conclusions: Radiation-associated sarcoma consistently remains a rare but possible event for breast cancer survivors treated with breast conservation and external beam radiation. As new radiation modalities such as partial breast and hypofractionated regimens become more common, ongoing surveillance is necessary to track these rare events.

Figure. Cumulative Incidence of Radiation Associated Sarcoma by Year of Diagnosis



Number at risk

1988-92	14923	14288	13497	11571
1993-97	32180	30900	29310	25253
1998-02	65372	63099	60176	52086
2003-07	80377	77646	74309	50536
2008-12	81380	77797	57778	0

Incidence of Second Primary Melanoma in Survivors of Cutaneous Melanoma

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Introduction: Cutaneous melanoma survivors are at increased risk of second primary melanoma. Most estimates of 5- and 10-year incidence of second melanomas are from older cohorts and/or single-institutions. Valid estimates facilitate counseling on recommended surveillance after melanoma diagnosis. We sought to determine the 5- and 10-year incidence of second primary cutaneous melanomas in survivors of cutaneous melanoma.

Methods: The Surveillance, Epidemiology, and End Results (SEER) Program was used to identify cases of non-metastatic, first cutaneous melanoma diagnosed 1998-2012 (follow-up through 12/2017). Eligible survivors were ≥18 years and underwent surgery as a treatment component. Survivors who died within 3 months of initial diagnosis were excluded. 5- and 10-year incidence of second melanoma, excluding new diagnoses within 3 months of initial diagnosis, were estimated using Kaplan-Meier survival analysis. Follow-up was censored at second melanoma diagnosis, death, or 10-years. Log-rank tests assessed differences in incidence rates by survivor characteristics.

Results: Our cohort included 155,482 patients, 54,325 of whom have 10-year follow-up. Overall incidence of second primary melanoma was 4.0% at 5-years (95% CI: 3.9-4.1%) and 6.9% at 10-years (95% CI: 6.8-7.1%). Median time to diagnosis of second melanoma was 2.8 years (range 0.25-9.8 years). Older survivors, males and those with initial regional disease had significantly higher incidence of second melanoma (Table).

Conclusions: Melanoma survivors are at risk of second melanoma, making routine skin surveillance part of recommended follow-up. We observed higher incidence of second melanoma with older age and regional disease at presentation, possibly explained by increased healthcare utilization providing more diagnostic opportunities.

Table. Second primary cutaneous melanoma incidence by patient and first primary cutaneous melanoma characteristics with log-rank test for equality of survivor functions within sub-groups

	Cohort numbers	5 year incidence (95% CI)	10 year incidence (95% CI)	P value
Overall	155,482	4.0% (3.9-4.1)	6.9% (6.8-7.1)	
Age at diagnosis of first primary				<0.001
<45	30,672	2.1% (2.0-2.3)	3.3% (3.1-3.5)	
45-54	29,439	2.6% (2.5-2.8)	4.7% (4.4-5.0)	
55-64	33,212	3.8% (3.6-4.0)	6.9% (6.6-7.2)	
65-74	29,956	5.4% (5.1-5.7)	10.2% (9.8-10.7)	
≥75	32,203	6.8% (6.5-7.1)	11.5% (11.0-12.0)	
Sex				<0.001
Male	88,051	5.4% (5.2-5.5)	9.1% (8.8-9.3)	
Female	67,431	3.1% (3.0-3.3)	5.0% (4.8-5.2)	
Extent of disease of first primary				<0.001
Local	140,716	3.9% (3.8-4.0)	6.8% (6.6-6.9)	
Regional	14,766	5.8% (5.4-6.2)	8.7% (8.0-9.3)	

Validation of the Breast Cancer AJCC 8th Edition Pathologic Prognostic Stage vs. Anatomic Stage in Legacy Alliance Trials

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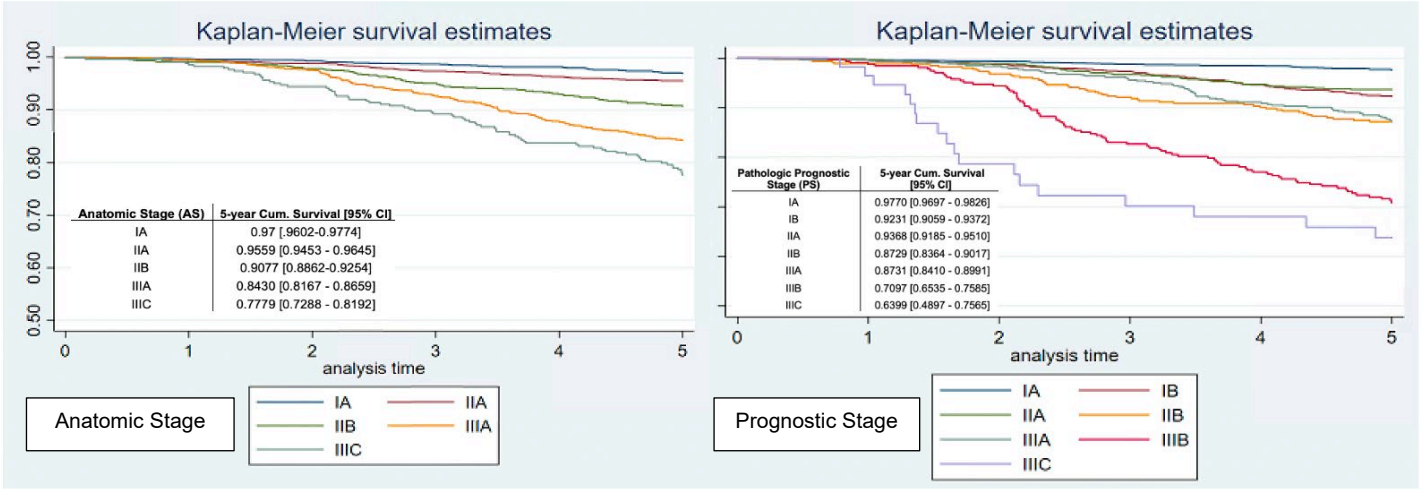
Introduction: The 8th edition AJCC breast cancer staging system created prognostic stage (PS) by augmenting anatomic stage (AS) with receptor status and grade. PS has been validated in single institution and cancer registry studies; however, missing HER2 status and variable follow-up create limitations. Our objective was to compare survival by pathologic PS versus AS using legacy Alliance clinical trial data from patients who received modern-era treatment.

Methods: Six adjuvant Alliance trials were included (40101, 49907, 9741, N9831, Z0010, Z0011) (1997-2010). Patients with missing receptor status or who did not receive modern-era therapies (e.g., trastuzumab if HER2+) were excluded. AS and PS were constructed using pathologic T and N, ER/PR/HER2neu status, and grade. Missing pathologic T stage and missing grade were imputed and the impact studied with sensitivity analyses. Unadjusted Cox proportional hazard models were estimated to predict overall survival (OS) and recurrence-free survival (RFS) within 5 years, with AS and PS as primary predictor variables. The relative predictive power of the AS and PS models was assessed by comparing Harrell concordance indices (C-index).

Results: We included 6924 women with breast cancer (stages I-III). Median age was 53 years. 45.2% of patients were ER+/PR+/HER2-, 26.2% were HER2+, and 17.1% had triple-negative breast cancer. Cumulative OS by AS and PS is presented in Figure 1. PS had significantly improved predictive performance (C-Index=0.720) compared to AS (0.699) for OS (difference = -0.021, t=-2.32, p=0.020). Significance was maintained in age-adjusted models (PS C-index: 0.728; AS: 0.707) (difference=-0.021, t=-2.31, p=0.021) and following sensitivity analyses accounting for missing grade and T stage. PS did not appear to distinguish risk as well between intermediate stages (e.g., IIB and IIIA).

Conclusions: In this cohort of women with standardized modern-era treatment and follow-up for breast cancer, PS has significantly improved overall predictive performance compared to AS.

Figure 1: Kaplan-Meier OS estimates and 5-year cumulative survival by AS and PS



Ongoing Symptoms Experienced by Low Risk Breast Cancer Survivors Following Active Treatment

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Introduction: Over 3.5 million U.S. breast cancer survivors require follow-up for recurrence, treatment adherence, and symptom management. Due to the time-limited nature of oncology visits, the current approach does not readily allow for a comprehensive assessment of survivor symptoms or concerns during visits. Though prior studies have described the symptom experience of survivors during treatment or diagnosed at a later stage, less is known about the symptom experience of survivors with early stage disease and low recurrence risk. The objective was to assess the prevalence of symptoms/concerns experienced by early stage breast cancer survivors.

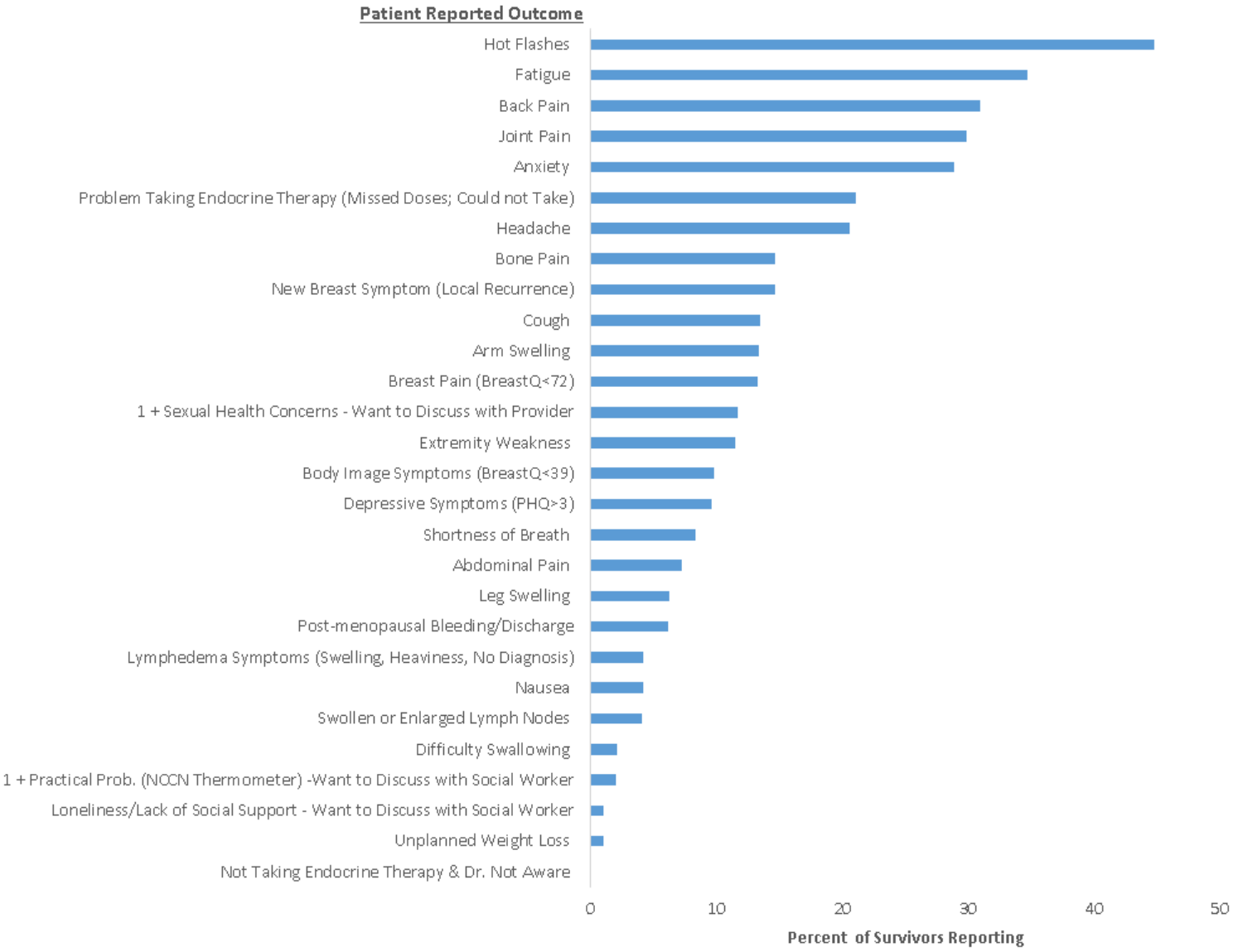
Methods: Survivors were eligible if they had stage I-II estrogen or progesterone receptor positive, HER2neu negative breast cancer, were 6 months to 5 years post-diagnosis, were cancer free, and did not receive chemotherapy. Survivors were enrolled at the time of their follow-up visit at the UW Breast Center and emailed a link to a REDCap survey (mail if preferred). The survey included patient reported outcomes (PRO) addressing domains informed by ASCO survivorship guidelines and 10 survivor and provider stakeholders (Figure). Survivors were asked about the presence/absence of concerns and their frequency/severity. Concerns were clinically significant if they: 1) were moderate to severe, 2) interfered with life quite a bit or very much, or 3) otherwise met a validated clinically relevant threshold identified for the PRO scale (e.g., depression). The proportion of survivors experiencing clinically significant concerns are reported.

Results: Of 130 patients approached, 76.1% (n=99) enrolled and 98 completed the assessment. On average, survivors were 61.3 years old (SD=11.5) and 2.5 years post-diagnosis (SD=1.2). The percentage of survivors who chose not to respond to certain topics was low (2.0%), with the topic of sexual health skipped most frequently (14.3%). The majority (86.7%) of survivors experienced clinically significant concerns, with 38.8% reporting 1-2 and 47.9% reporting $\geq$3 concerns. The most common clinically significant concerns are presented (Figure).

Conclusions: Early stage breast cancer survivors report a high burden of symptoms and concerns. Given that nearly 50% of survivors report $\geq$3 concerns, many topics may not be discussed during the course of a regular time-limited follow-up visit. Some concerns, such as sexual health, may not be feasible to address in the clinic visit given their complex and sensitive

nature. Use of PROs to assess symptoms/concerns in early stage survivors allows for a comprehensive evaluation with identification of previously unrecognized needs. This represents a clear opportunity to improve survivorship care.

Figure. Percent of Survivors Reporting Significant Patient Reported Outcomes Symptoms (n=98)



Quantifying the Cost of Surgical Instrument Errors in the OR in a Two-hospital Facility

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Introduction: Sterile processing (SP) departments are responsible for the repair, sterilization, storage, and transport of all surgical instruments. Due to limited resources and intrinsic inefficiencies, surgical instrument errors (SIEs) by SP result in waste and lost capacities; however, their cost and impact on operating room (OR) efficiency remain unmeasured. We hypothesized that SIEs were substantially underreported and a major source of waste and lost capacities in the OR.

Methods: IRB exemption was obtained. SIEs across nine surgical specialties at a full-service children's hospital with 8 ORs were recorded via direct observation from June – August, 2021. Data collection took place on elective OR days (EODs), defined as non-holiday, Monday – Friday, 07:30 – 17:00 hours. Type of SIE, instrument(s) affected, work-around method, and length of surgical delay were recorded. SIEs included failed sterilization/bioburden, missing instruments, damaged instruments, assembly and packaging errors, and fleet management. Delays were defined as the time required to execute a work-around if the error required one.

Results: 254 SIEs were recorded in 154 EODs (1.65 errors/EOD). Missing instrument was the most common SIE (n = 148), followed by broken instrument (n = 55), assembly or packaging error (n = 18), wrong instrument (n = 11), failed sterilization/bioburden (n = 8), fleet management (n = 7), extra instrument (n = 6), and transport error (n = 1). SIEs were also analyzed by specialty with an emphasis on those specialties with the largest sample size: SIEs in plastics (n = 46), orthopedics (n = 43), ophthalmology (n = 42), general (n = 31), ENT (n = 31), and urology (n = 20). Surgical delays due to SIE occurred at a rate of 0.39 delays/SIE and averaged 4:27 (min:sec). Average length of delay was also analyzed by specialty: orthopedics (6:25), plastics (3:55), ophthalmology (2:47), general (1:30), ENT (4:40), and urology (1:49).

Conclusions: Surgical instrument errors are prevalent and impact OR efficiency. Our analysis of 154 EODs represents 1.5% of annual EODs (10,373) in our two-hospital campus that shares 41 ORs and a SP department. Extrapolating the measured error rate (1.65 errors/EOD) and delay rate (0.39 delays/error) for our campus there are approximately 17,048 SIEs annually resulting in 29,586 minutes of delays. At $153/OR minute, the cost of these SIEs is $4,526,727. Significant improvements in the management of surgical instruments (accurate detection of bioburden, inspection for damage, instrument tracking) will need to be implemented to address the waste created in our current system.

Association between Medical Maximizing Preferences and Beliefs About Cancer in U.S. Adults

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Introduction: Overutilization of the medical system contributes to significant healthcare expenditures in the United States (U.S.). Overuse is particularly prevalent in oncology where many tests and treatments have significant costs with low relative value. We sought to understand public attitudes towards medical utilization and their association with beliefs about cancer.

Methods: An online survey was conducted among a nationally representative sample of 1,205 adults (>17y) in the U.S. using Prolific Academic. Participants with a personal history of cancer or who failed attention checks were excluded. Medical utilization preferences were characterized with the validated, single-item Maximizer-Minimizer elicitation question (MM1). Those who favored taking action in situations where the necessity of a medical test or procedure is unclear were considered “Maximizers” and compared to those who answers were neutral or leaned towards waiting and seeing (“Neutral/Minimizers”). Beliefs about the incidence, survivability, preventability, and fear and worry of cancer were assessed with validated questions from the Health Information National Trends Survey. Univariate analysis was conducted using chi-squared and Student’s t-test.

Results: A total of 1,131 eligible participants responded (93.9%). The respondents were 52.6% male, 74.1% White, and had an average age of 45 years (SD 16 years). When asked their medical usage tendencies, 25.4% (n=287) were maximizers, 45.5% (n=514) were neutral, and 29.2% (n=330) were minimizers. When comparing maximizers to neutral/minimizers, there were no differences in age or sex, but maximizers had a significantly higher percentage of black respondents (16.7% vs. 10.4%) and lower percentage of White (71.4% vs. 75.1%), Asian (4.5% vs. 6.4%) and Hispanic (5.9% vs. 7.2%, p=0.04) respondents. Maximizers more often overestimated the average person’s lifetime incidence of cancer (19.1% vs. 13.0%, p=0.01) and believed they personally were more likely than average to develop cancer (23.6% vs. 17.4%, p=0.03). Maximizers also were more likely to have a high level of worry about cancer (15.7% vs. 11.3% p=0.05). There were no differences between the groups based on fear, the perceived survivability, or preventability of cancer.

Conclusions: While U.S. adults with medical maximizing tendencies do not believe cancer is more deadly or preventable, they are more likely to believe they are personally at higher risk of being diagnosed with cancer and overestimate the overall incidence of cancer. Targeted and

personalized education about cancer and its risk factors may help reduce the overutilization of oncologic medical care.

Revision Surgery Following Alloplastic and Autologous Breast Reconstruction: A Systematic Six-Step Approach from a Single-Institution Experience

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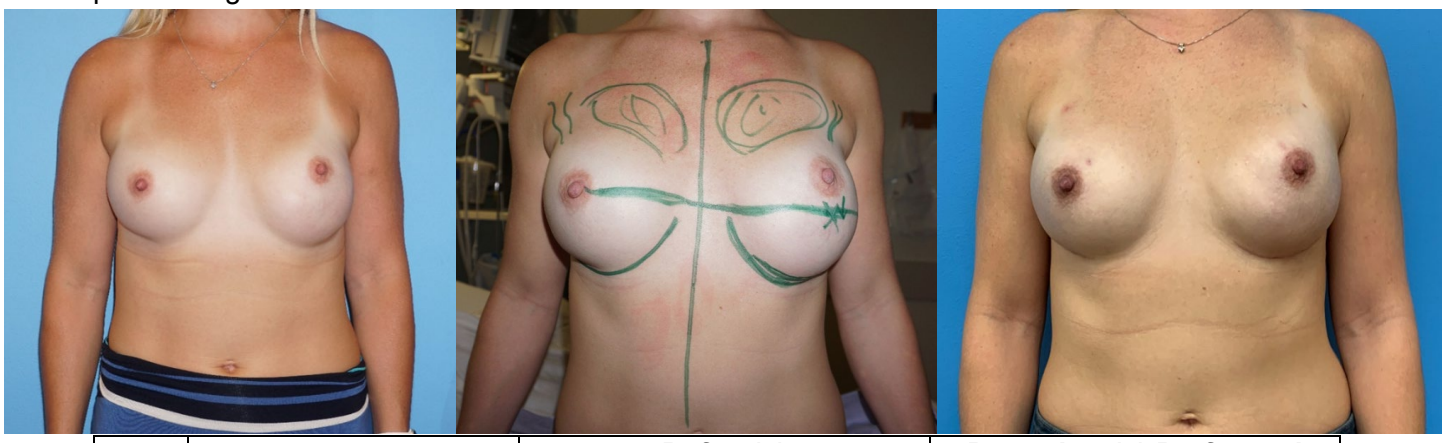
Introduction: Both alloplastic and autologous reconstruction play an integral role in improving patients' quality of life following mastectomy. However, post-mastectomy reconstruction is frequently a multistage process that necessitates additional revision surgeries to enhance the aesthetic nature of the breast. In this article, we propose a methodical approach for analyzing the reconstructed breast known as the "WISHED" System. By using this stepwise system, we break the breast down into individual components to assess what defects are present within specific areas. We aim to compare this system among patients undergoing revision surgery following alloplastic and autologous reconstruction.

Methods: We retrospectively reviewed 200 patients who underwent post-mastectomy alloplastic or autologous breast reconstruction from 2011 to 2019 by a single surgeon at our institution. Primary outcomes of interest included number of revision surgeries, number and type of revision maneuvers, as well as number and type of WISHED System parameters addressed during revision. The WISHED System addressed defects present within the breast based on (W) width, (I) inframammary fold position, (S) size, shape, symmetry, (H) height, (E) external skin changes, and (D) dynamic breast changes (**Figure 1**). Continuous variables were compared using independent samples t-tests, while categorical variables were compared using chi-square tests.

Results: A total of 127 patients met inclusion criteria. Fifty-three patients underwent alloplastic reconstruction while 74 patients underwent autologous reconstruction. Patients who underwent alloplastic reconstruction received significantly more revision maneuvers on average ($M = 7.17$) compared to autologous reconstruction ($M = 5.49$, $p = 0.03$). The most common revision maneuver performed following both reconstructive modalities was autologous fat grafting. On average, alloplastic reconstructive patients had significantly more pectoralis muscle denervation and scoring performed ($p < 0.05$) while autologous reconstructive patients had significantly more scar revision, fat necrosis removal, breast reduction, and nipple reconstruction performed ($p < 0.05$). The most common indication for revision following alloplastic reconstruction was to address defects related to breast (H) height. Conversely, the most common indication for revision following autologous reconstruction was to address (S) size, shape, and symmetry defects.

Conclusions: Patients require different revision maneuvers in order to address distinctive concerns based on reconstructive modality. The WISHED System helps determine which specific revision maneuvers will best address a patient's post-reconstructive breast defects. Furthermore, the WISHED System may serve as an effective education tool to advise patients

on the reconstructive process, as well as guide shared decision-making between patients and plastic surgeons.



		Defect(s)	Procedure(s) Performed
W	Width	Slightly too narrow	Implant exchange
I	Inframammary Fold	Low on left side	Direct excision with skin removal
S	Size, Shape, Symmetry	Slightly too small, per patient	Implant exchange
H	Height	Upper pole hollowness	Upper pole AFT
E	Exterior	Left nipple too high	Lower pole skin excision
D	Dynamic Correction	Animation deformity	Selective pectoralis denervation

Figure 1. Patient desiring revision surgery following alloplastic breast reconstruction. Photos depict the patient prior to revision surgery (left), preoperative revision markings (middle), and postoperative breast results (right).

The Relationship between Neuropsychiatric Diagnoses and Revision Surgery Following Breast Reconstruction

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Introduction: Both alloplastic and autologous breast reconstruction are often multistage processes that may involve additional revision surgeries to further enhance the breast's aesthetic outcome. However, the number of revision surgeries following breast reconstruction varies among patients and is largely driven by patient satisfaction. Neuropsychiatric diagnoses (ND) are common among breast cancer patients and have the potential to affect patient satisfaction regarding breast outcomes. As such, it has been theorized that ND may result in an increased number of revision surgeries. Yet, literature regarding the interplay between ND and subsequent revision surgeries after reconstruction remains sparse. The primary aim of this paper is to determine if ND result in increased breast revisions following alloplastic and autologous breast reconstruction. The secondary aim is to assess whether ND lead to increased healthcare utilization within plastic surgery following breast reconstruction surgery.

Methods: We retrospectively reviewed 196 patients who underwent post-mastectomy breast reconstruction by a single surgeon at our institution. 96 patients underwent alloplastic reconstruction, and 100 patients underwent autologous reconstruction. We evaluated for the presence of ND, type of ND, number and types of revisions, and number of post-reconstruction plastic surgery appointments. Continuous variables were compared using independent samples t-tests, while categorical variables were compared using chi-square tests.

Results: Overall, the presence of a preoperative neuropsychiatric diagnosis was not significantly associated with increased revisions after breast reconstruction ($p = 0.15$). Patients with ND preoperatively or postoperatively had significantly longer length of plastic surgery follow-up than patients without ND ($p = 0.04$). Furthermore, preoperative ND were significantly associated with increased plastic surgery follow-up appointments ($p = 0.03$).

Conclusions: Neuropsychiatric diagnoses may not impact the number of revision surgeries a patient undergoes following breast reconstruction. However, the presence of ND significantly influences the length of follow up, as well as number of plastic surgery appointments, following breast reconstruction. This may result in increased patient risk and long-term healthcare costs. These findings highlight the importance of optimizing the management and counseling of breast cancer patients with ND to allow for collaborative goal setting between the plastic surgeon and patient.

Electrical Stimulation on Acute Bone Fractures in a Human Model

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Introduction: The clinical market for electrical stimulation is expected to reach 1.27 billion by 2026, however despite 60 years of research on electrical stimulation (ES), literature on stimulation in human models is scarce. Electrical stimulation has proven to increase osteoblastic proliferation and accelerate the healing of non-union and acute fractures in *In Vitro and In Vivo* models respectively. Additionally, non-invasive ES has proven to be less effective than invasive methods in large animal models. The lack of research in human models has made implementation in clinical settings difficult. This systematic evaluation catalogs key findings on capacitive coupling (CC), pulsed electromagnetic field (PEMF), and direct current electrical stimulation (DCES) in human models. The objective is to identify key gaps that prevent a wide uptake of clinical use.

Methods: The authors investigated the limitations of CC, PEMF and DCES by examining radiographic, histomorphologic and biomechanical outcomes in acute fractures in human models. The key words: “electrical stimulation”, “bone healing”, “human”, “animal”, “acute”, “fracture” “direct current”, “pulsed electromagnetic field” and “capacitive coupling” were searched on PubMed. 192 studies were found, 12 of which matched our criteria for ES on acute fractures. All 12 studies were evaluated for injury location, protocol, and device specifications such as current, voltage, equipment type, magnetic field and magnetic field strength.

Results: Only one study on DCES fit our criteria. This study found a statistically significant acceleration in time to fracture healing when compared to the sham ($P > 0.001$). Of the 6 PEMF studies evaluated, 4 (66.7%) found significant differences in healing when compared to the sham control. Two of the 5 studies on CC found reliable and significant differences in healing (40%). Of all 12 studies, 7 showed significant differences (58.3%). It is important to note that each study had different device specifications, protocols, definitions of radiological union, exclusion criteria, and outcome measurements.

Conclusion: Clinical use of electrical stimulation on humans, specifically with DCES, is widely underutilized as very few studies have been conducted on the topic. Those that have been published show mixed results, and inconsistent protocol, specifications and measurements. A greater focus on DCES in clinically translatable animal models must be completed to obtain a reliable understanding of the efficacy of electrical stimulation in clinical models.

To Delete or Accept: A Guide for Determining the Legitimacy of Academic Conference Invitations

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Introduction: Following the rise of predatory journals characterized by false claims of legitimacy and a pay-to-publish model, similar “predatory conferences” have become increasingly common. Features of these conferences include websites and emails filled with false claims of international presence, inadequate peer review resulting in rapid submission turnaround, and overpriced attendance fees. These conferences are typically overly broad in scope and may boast connections to known predatory journals. The email inbox of an academic physicians can be filled with daily email announcements encouraging attendance, abstract submission, and often panel or keynote speaker invitations. It therefore becomes important for the plastic surgeon to be able to discern these invitations from legitimate conference invitations and career advancement opportunities, especially early in practice.

Methods: To address this issue, we explore one academic plastic surgeon’s experience encompassing 56 unique conference invitations received by email in a four-month period. These conferences were then organized into three groups based on affiliation with known professional societies.

Results: This resulted in 15 affiliated conferences, 28 unaffiliated conferences, and 17 conferences of undetermined affiliation. Unaffiliated conferences were more likely to solicit speaker invitations ($p<0.001$), claim to be “international” ($p=0.001$), send emails with grammatical errors ($p<0.001$), use unprofessional headshots ($p<0.001$), and have reduced virtual conference fees ($p=0.0032$) as compared to conferences affiliated with known professional societies. Affiliated conferences were more likely to take place in the United States ($p=0.014$). When comparing attendance fees for in-person, virtual and hybrid venues, there was no significant difference between affiliated and unaffiliated conferences.

Conclusions: Based on our literature review and thorough evaluation of conference invitations and associated websites, we present a system by which the academic physician can confidently evaluate the legitimacy of a conference by way of a few important questions. This method was developed through the exploration of the academic plastic surgeon’s conference invitations and associated website content. In this way we hope to steer the conference invitee in the right direction and defend against predatory organizations.

Surgical and Demographic Predictors of Free Flap Salvage After Takeback: A Systematic Review

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Introduction: Microsurgical free tissue transfer (FTT) is a widely employed surgical modality utilized for reconstruction of a broad range of defects, including head and neck, extremity, and breast. Flap survival is reported to be 90-95%. When FTT fails, salvage procedures aim at establishing reperfusion while limiting ischemia time – with salvage rates between 0-82%. However, there are no data-driven predictors of successful salvage present in the literature. This systematic review aims to summarize and identify predictors of flap salvage.

Methods: A systematic literature review was conducted per PRISMA guidelines using PubMed, Scopus, and Web of Science databases. Articles included in the final analysis were limited to those investigating FTT salvage procedures of any anatomic location and included factors impacting outcomes. Cohort and case series (>6 flaps) studies from the earliest available date until March 2021 were included. Statistical analysis was completed using chi-square tests and linear regression modeling.

Results: Our query yielded 9515 records using predetermined search terms, (“free flap AND salvage AND predictors”). After title and abstract screening, 153 articles underwent full-text review; 36 of these were included in the final analysis. Patient-specific factors significantly associated with successful salvage included the absence of hypercoagulability and no previous salvage attempts. Case-specific factors significantly associated with successful salvage included trunk/breast flaps, fasciocutaneous/osteocutaneous flaps, venous compromise, and shorter time from index procedure to salvage attempt.

Conclusion: FTT is one of the most useful tools in a reconstructive surgeon’s armamentarium. However, there are no evidence-based guidelines to aid in decision making for flap salvage attempts. To our knowledge, this is the first systematic review of factors impacting FTT salvage outcomes. Based on our findings, patients without documented hypercoagulability, no previous salvage attempts, fasciocutaneous/osteocutaneous flaps, trunk/breast flaps, and a shorter time interval post-index operation are the best candidates for a salvage attempt.

Designing an Enhanced Recover After Surgery (ERAS) Protocol for Patients Undergoing Mastectomy with or without Alloplastic Breast Reconstruction using Consolidated Framework for Implementation Research (CFIR) principles.

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Background: There has been a rise in the use of evidenced-based enhanced recovery after surgery (ERAS) protocols since they were initially introduced in 2010. Although ERAS protocols have been implemented in several other surgical fields, their utilization in patients undergoing mastectomy with or without breast reconstruction is underwhelming. The goal of this study is to explore potential facilitators and barriers to successful ERAS implementation for mastectomy patients at a large academic health center.

Methods: Structured interviews based on the Consolidated Framework for Implementation Research (CFIR) framework were conducted with stakeholder groups including breast surgeons, plastic surgeons, nursing staff and anesthesiologists. Interviews were conducted via a secure video conferencing platform and focused on topics related to ERAS implementation, including system factors and work processes that might impact successful implementation. Focus group discussions were recorded and transcribed. Directed content analysis was independently performed on each set of transcripts using an established coding structure based on CFIR. Any disagreement among coders was resolved through discussion and consensus.

Results: Stakeholders had multiple criteria for defining successful ERAS implementation. These included traditional “patient outcome” variables (e.g. decreased post-operative nausea/vomiting and narcotic use, etc.). However, success was also defined as “minimal additional workload” and the “ability to adhere to protocol, given the current complexities of the organization.” A variety of factors were characterized as either barriers or facilitators to “successful” implementation. Many of these were described similarly, with the same factor being described either as a necessary condition (facilitator) or a potential impediment to success if poorly done (barrier). Examples included the need for “clear communication” across disciplines as well as “clarity of roles and responsibilities” associated with the new ERAS protocol. Other themes were associated with “logistics and resource management” such as the nature and timing of patient education, order set input, as well as “patient preferences” or social support. Results of our analyses also revealed a small number of potential unintended consequences (both positive and negative), such as nurses having fewer opportunities for enjoyable interactions with “healthier” patients, who will now qualify for ERAS (potential negative).

Conclusion: Potential facilitators and barriers to implementation of an ERAS protocol were identified. Designing the implementation process to proactively address these issues will ensure successful rollout of this protocol with increased user adoption and adherence. Ultimately, these efforts will result in a standardized ERAS protocol and implementation toolkit

that will foster the broader dissemination and uptake of this evidence-based intervention.

Surprise Billing Legislation: Context and Significance for Plastic and Reconstructive Surgeons

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Introduction: Surprise billing occurs when privately insured patients receive care from an out-of-network provider, resulting in unexpected, or “surprise”, medical charges. The incidence of surprise billing has grown drastically in recent years, exposing patients to significant financial risks. After much controversy on how to address surprise billing, Congress passed the No Surprises Act in December 2020. While this legislation will protect patients from surprise bills, the implications this new legislation will have on plastic surgeons remains unclear. In this paper, we examine how the No Surprises Act will affect the field of plastic surgery.

Methods: PubMed and Google Scholar search were queried for relevant search terms pertaining to surprise billing, the No Surprises Act, and plastic surgery.

Results: The No Surprises Act will go into effect January 1, 2022. As a result of this Act, privately insured patients who receive out-of-network services at in-network facilities may only be billed for the in-network cost-sharing amount, effectively ending majority of out-of-network billing. Patients will be removed from the provider-insurer dispute process through an arbitration-based system. However, the arbitration process implemented under the No Surprises Act may be time-consuming and costly, potentially incentivizing plastic surgeons to contract their services at reduced rates to avoid such inconvenience. Conversely, winning arbitration disputes may result in higher payments for plastic surgeons than in-network service costs. This may consequently incentivize providers to work out-of-network, impacting physician consolidation and inflating long-term healthcare expenses.

Conclusions: The No Surprises Act will protect patients from unexpected bills when receiving emergency care. However, plastic surgeons should expect to get paid only in-network fees while providing emergency care to patients. They would have to engage in costly and time-consuming procedures to get reimbursed for more than in-network fees.

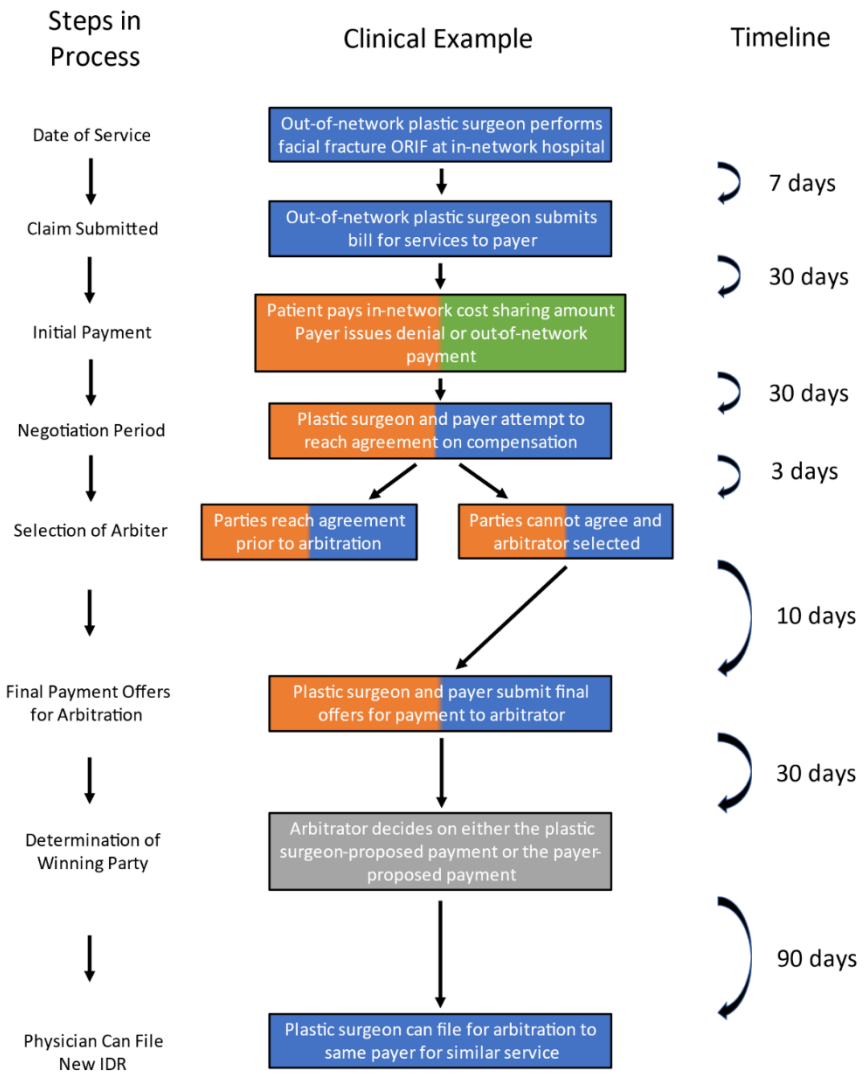

Figure 1. Depicted is a schematic that represents the process of arbitration under the No Surprises Act. On the left, the steps of arbitration are delineated. Centrally, there is a clinical example color-coded for action required by different parties. Blue represents actions required of the plastic surgeon. Orange represents actions required of the payer. Green represents actions of the patient. Gray represents actions required of the arbitrator. Finally, there is a representative timeline for these steps on the right.

The Emergency Medical Treatment and Labor Act (EMTALA): Historical Context and Implications for Plastic and Reconstructive Surgeons

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Introduction: The Emergency Medical Treatment and Labor Act (EMTALA) was enacted by Congress in 1986 to protect uninsured patients against economic discrimination. While this law has been well established for several decades, recent passage of the No Surprises Act may invoke new implications for the healthcare system under EMTALA. As such, it is worthwhile to review EMTALA's applications to the practice of plastic surgery, as well as review EMTALA in the context of the recently passed No Surprises Act.

Methods: PubMed and Google Scholar search were queried for relevant search terms pertaining to EMTALA, the No Surprises Act, and plastic surgery.

Results: Under EMTALA, providers are mandated to administer a medical screening examination (MSE) to any patient presenting for emergent care. Secondly, providers must administer medical stabilization if the MSE reveals an emergent condition. If the hospital lacks specialized capabilities to provide stabilizing care, they are required to transfer the patient to a facility that can provide care.

There are several concerns related to EMTALA within plastic surgery. These concerns include overburdening of plastic surgeons due to unequal and inconsistent access to on-call plastic surgeons in emergency departments, as well as increased rates of inappropriate interfacility transfers that may occur as a result of this Act.

Insured patients presenting to the emergency department may inadvertently receive stabilizing emergency care from an out-of-network provider resulting in an unexpected medical bill, a phenomenon known as surprise billing. These surprise bills have been inextricably linked to services rendered under EMTALA. Congress recently passed the No Surprises Act which will effectively end majority of these surprise bills beginning January 1, 2022, in both emergency settings and air ambulance transport. However, the No Surprises Act will not protect emergent plastic surgery patients from surprise bills if they require interfacility transfer via ground ambulance transport.

Conclusions: Since its enactment in 1986, EMTALA has served as a safeguard against economic discrimination in uninsured patients. Though EMTALA's provisions provide patients with substantial leverage to obtain emergency care, the Act has been associated with out-of-network, or "surprise" medical bills in the insured population. Furthermore, it may be detrimental to plastic surgeons in emergency settings. While recent enactment of the No Surprises Act will end majority of surprise bills associated with care provided under EMTALA, plastic surgeons, as

well as patients, should remain cognizant that out-of-network bills may still arise in emergency settings.

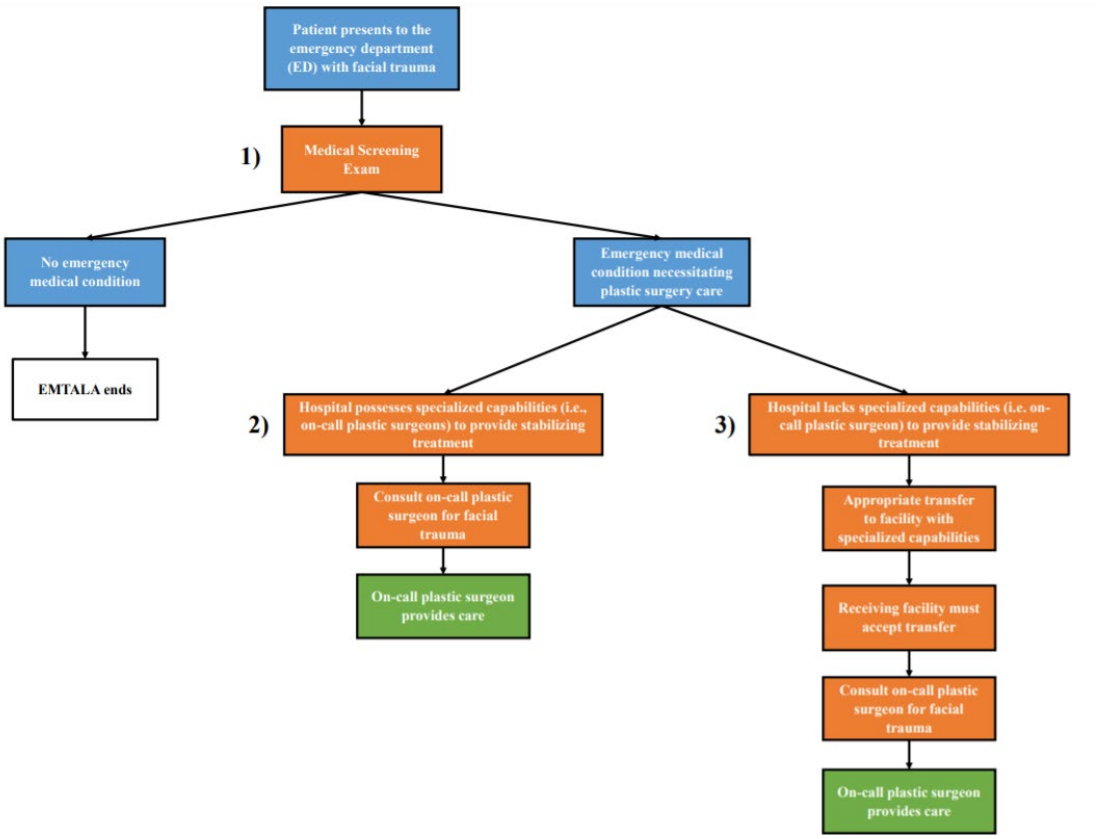

Figure 1. Depicted is a schematic representing the major requirements of EMTALA including 1) Providing a medical screening exam, 2) Providing stabilizing medical treatment if an emergent medical condition exists, and if the hospital lack capabilities to provide stabilizing treatment, 3) Appropriate transfer to a hospital possessing specialized capabilities. Blue represents the patient. Orange represents the hospital's responsibilities. Green represents the plastic surgeon's responsibilities.

The Management of Post-Surgical Pyoderma Gangrenosum Following Breast Surgery

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Introduction: Post-surgical pyoderma gangrenosum is a rare, inflammatory condition characterized by ulcerative lesion development at surgical sites that is often misdiagnosed as post-operative infection. It is most commonly associated with breast surgery and is frequently mis-managed with surgical debridement of wounds, which only worsens the condition. Achieving the correct diagnosis is imperative to delivering the correct treatment, which consists of medical management with either immunosuppressants or immunomodulators. This paper presents four clinical cases of post-surgical pyoderma gangrenosum in breast surgery patients, and reviews their clinical course and treatment regiments. This paper also proposes a work-up schematic to aid in the diagnosis of post-surgical pyoderma gangrenosum based on literature review and author experience.

Methods: Four patients who developed post-surgical pyoderma gangrenosum following breast surgery were identified by chart review at our institution.

Results: This paper describes the clinical courses of four patients who developed post-surgical pyoderma gangrenosum following breast surgery at our institution. The cases include two breast reduction patients, an abdominally based breast reconstruction patient, and a breast augmentation patient. The time to diagnosis and treatment varied greatly between the patients, with diagnosis achieved as early as 13 days post-operatively ranging to one year post-operatively. Two of the four patients were initially mismanaged with surgical debridement, and all of the patients were initially treated with at least one course of antibiotics for a misdiagnosis of surgical site infection. All of the patients were started on a course of steroids once the correct diagnosis was made.

Conclusions: Post-surgical pyoderma gangrenosum is a rare, ulcerative condition that is difficult to diagnose, and often mismanaged with surgical interventions that exacerbate the disorder. Diagnosis requires a high clinical suspicion and should be considered in patients with ulcerative lesions resistant to antibiotic therapy, in patients who have bilateral lesions with NAC sparring, and in those with systemic inflammatory conditions. Symptoms typically develop one week after surgery, and may be accompanied by leukocytosis and fever. Diagnosis is usually delayed, sometimes by several months, and such delays can result in unnecessary surgeries and other potentially harmful treatments. This paper provides a novel schematic to aid in the work-up and diagnosis of post-surgical pyoderma gangrenosum in an effort to minimize such delays. Treatment is usually steroids, and patients may require a prolonged duration of immunosuppression before complete wound healing. It is imperative that surgeons keep this diagnosis in mind when treating breast patients with post-surgical wounds.

Prevalence and Risk Predictors of Anal Dysplasia-Cancer in Solid Organ Transplant Recipients: Is Screening Worth the Risk?

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Introduction: Anal cancer is a rare highly morbid disease that is increasing in incidence in the US. Precancerous anal dysplasia can be detected and treated prior to progression to cancer. Drivers of anal dysplasia-cancer are persistent infection with Human Papilloma Virus (HPV) and prolonged immunosuppression. Immunosuppressed solid organ transplant recipients are recognized as an at-risk population for anal dysplasia-cancer. This risk has not been quantified and screening transplant recipients is not standard. We aim to describe the prevalence of anal dysplasia-cancer using a large cohort of transplant patients and identify risk predictors that could inform screening practices.

Methods: We queried the electronic health record (EHR) for patients who received solid organ transplantation between 2001-2019 using relevant ICD codes. We cross referenced our existing UW-Madison anal dysplasia-cancer database to determine disease prevalence. To evaluate for risk predictors, patients with transplant and anal dysplasia-cancer were matched to those without anal dysplasia-cancer at a 1:3 ratio using age at transplant, gender, and transplant type by greedy propensity scoring. Statistical significance was defined at $p < 0.05$.

Results: Of 11456 transplant recipients, 27 had a post-transplant diagnosis of anal dysplasia-cancer (11 Anal cancer, 7 High-grade dysplasia, 2 Low-grade dysplasia, 7 Condyloma). Mean follow-up time was 6.16 years. These 27 patients received Renal(59.3%), Liver(18.5%), multi-Organ(11.1%), Lung(7.4%), or Heart(3.7%) transplants. Those with anal dysplasia-cancer were younger at time of transplantation (43 years old v. 51 years old, $p = 0.005$) and had lower BMIs (24 v. 28, $p = 0.035$) compared to those without dysplasia-cancer. Patients with anal dysplasia-cancer were more likely to have a history of: non-HPV STIs (22.2% v. 7.1%, $p=0.008$), HIV infection (14.8% v. 0.3%, $p <0.001$), and MSM status (16.7% vs 0.3%, $p<0.001$) (Table 1). Smoking status was not different between groups (Table 1). After greedy propensity score matching, history of HIV infection ($p=0.003$), diabetes ($p=0.024$), and lower BMI ($p=0.009$) were associated with a diagnosis of anal dysplasia-cancer. History of STIs, MSM status, and smoking status was not different between matched groups (Data not shown).

Conclusion: The prevalence of anal dysplasia-cancer was only 27/11304 (0.24%). Risk predictors for anal dysplasia-cancer in this cohort include younger age at time of transplantation, lower BMI, non-HPV STIs, diabetes, and HIV infection. With such a low prevalence of disease in this cohort it is difficult to recommend screening in this patient population. However, more data

needs to be obtained to guide clinical decision making on who to screen.

Figures:

Table 1: Demographics and Comparison of Transplant Recipient Patients with and without Anal Dysplasia-Cancer

		Patients with Anal Dysplasia-Cancer	Patients without Anal Dysplasia-Cancer	*p value*
Patients, n		27	11429	
Gender (%)	Female	15 (55.6)	4455 (39.0)	0.177
	Male	12 (44.4)	6974 (61.0)	
Mean Age at Diagnosis (SD)		49.15 (15.70)	N/A	N/A
RACE (%)	American Indian or Alaska Native	0 (0.0)	186 (1.7)	0.512
	Asian	0 (0.0)	467 (4.2)	
	Black or African American	4 (14.8)	883 (7.8)	
	Native Hawaiian or Other Pacific Islander	0 (0.0)	21 (0.2)	
	White	23 (85.2)	9693 (86.2)	
Transplant Type (%)	Heart	1 (3.7)	640 (5.6)	0.556
	Intestine	0 (0.0)	28 (0.2)	
	Kidney	16 (59.3)	5253 (46.0)	
	Liver	5 (18.5)	1366 (12.0)	
	Lung	2 (7.4)	629 (5.5)	
	Multi-Organ	3 (11.1)	3346 (29.3)	
	Pancreas	0 (0.0)	151 (1.3)	
	Unspecified	0 (0.0)	16 (0.1)	
Mean Age at Transplant (SD)		43.37 (14.27)	51.30 (14.60)	0.005
Sexually Transmitted Infection (%)	No	21 (77.8)	10615 (92.9)	0.008

	Yes	6 (22.2)	814 (7.1)	
HIV (%)	No	23 (85.2)	11400 (99.7)	<0.001
	Yes	4 (14.8)	29 (0.3)	
Diabetes (%)	No	13 (48.1)	6314 (55.2)	0.584
	Yes	14 (51.9)	5115 (44.8)	
Mean Body Mass Index (SD)		23.58 (4.87)	28.39 (10.16)	0.035
Smoking Status (%)	Current Smoker	1 (5.0)	555 (8.8)	0.489
	Former Smoker	6 (30.0)	2464 (39.3)	
	Never	13 (65.0)	3256 (51.9)	
MSM (%)	No	10 (83.3)	4286 (99.7)	<0.001
	Yes	2 (16.7)	15 (0.3)	
Follow-Up Time		5.64 (5.08)	6.16 (4.95)	0.694

Outcomes After Surgery for Liver Cancer in Low- and Middle-Income Countries

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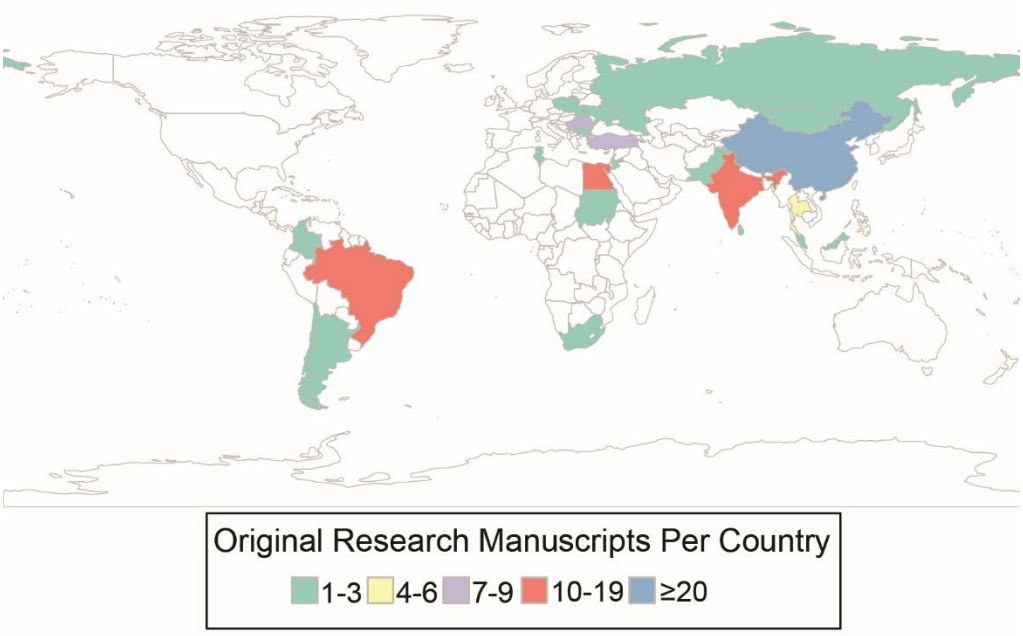
Introduction: Low- and middle-income countries (LMICs) have a high burden of patients requiring surgery for liver cancers. However, little is known about the surgical capacity or collective outcomes of patients undergoing resections in resource-constrained settings. We sought to review the literature on liver surgery in LMICs and evaluate the short- and long-term outcomes associated with hepatectomies.

Methods: A systematic review of the literature was performed. We searched for original articles with patients from LMICs undergoing liver surgery for any cancer using PubMed, Embase, Web of Science, and the Global Index Medicus. Exclusion criteria included articles with less than 20 patients, non-English articles, articles with patients undergoing only liver transplantation or percutaneous procedures (e.g. microwave ablation), and publications before 2005. Country income classification was based on the 2019 World Bank list of economies. The resulting search was deduplicated and abstracts and full-text reviews were performed by two independent team members with conflicts resolved by a third member.

Results: A total of 46,699 abstracts were identified with our initial search. Following manual and automated de-duplication, 28,458 abstracts were reviewed. After abstract and full-text review a total of 531 articles met the inclusion criteria for the study. Of the 531 articles, only 1 (0.3%) was found to be from a low-income nation (Figure 1). Conversely, 493 (93%) were from upper-middle-income nations – the majority of which were from the People's Republic of China (432/531; 82%). Furthermore, only 3 (0.6%) articles were from Sub-Saharan Africa.

Conclusions: We found a stark underrepresentation of research from low-income nations, especially in Sub-Saharan Africa. This highlights the critical need to build capacity for complex cancer surgery in LMICs. In future work, we will conduct a metanalysis of the short- and long-term outcomes from the articles generated in this review, which may reveal opportunities for interventions to improve the surgical care of patients from LMICs.

Figure 1: Distribution of outcomes research on liver cancer surgery in LMICs



Peritoneal Recurrence after Resection for Stage 1-3 Colorectal Cancer - A Population Analysis

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Introduction: Colorectal cancer (CRC) often recurs in the peritoneum however, the pattern and factors associated with peritoneal recurrence (PR) have received less attention. The purpose of this study was to describe the presentation, timing, and risk factors for PR following stage I-III CRC resection in a nationally representative sample in the United States.

Methods: We performed a cohort study of patients undergoing resection of stage I-III colorectal cancer from 2006 to 2007 using merged data from the Commission on Cancer Special Study on CRC Recurrence and the National Cancer Database (NCDB). We estimated the incidence, timing, method of detection, risk factors, and treatment for isolated PR. We compared differences in demographic, tumor, and facility characteristics for patients with PR versus no recurrence and PR versus other distant recurrence (DR) using multivariable logistic regression.

Results: A total of 8,991 patients were included in the study. PR without other distant recurrence occurred in 77 (0.9%) patients. The median time to PR was 16.2 months (interquartile range [IQR] = 9.3 months to 28.0 months). The most common methods of detection included new signs or symptoms (36.4%) and evaluation following locoregional recurrence (20.8%). Independent factors associated with increased odds of PR included higher T stage (odds ratio for T3 vs T2 = 4.8, 95% confidence interval = 1.5 to 15.7), N stage (N1 versus N0, OR = 2.00, 95% CI = 1.1 to 3.7), signet ring (OR = 8.2, 95% CI = 3.0 to 22.3) or mucinous histology (OR = 2.6, CI = 1.5 to 4.7), and rural residence (OR = 3.6, CI = 1.2 to 10.5). Factors associated with PR compared with other DR included signet ring (OR 5.3, 95% CI = 1.8 to 15.5) and mucinous histology (OR = 3.1, 95% CI = 1.7 to 5.7). Advanced T and N stage were not associated with PR versus other DR.

Conclusions: In this national dataset we describe patterns, and associated risk factors of PR amongst patients with stage I-III CRC. Majority of PR was detected within 18 months of surgery and relatively few were identified by surveillance imaging. Advanced T and N stage, signet ring histology, and mucinous histology were among pathologic factors associated with increased odds of PR.

Patients Follow Different Financial Hardship Trajectories in the Year after Injury

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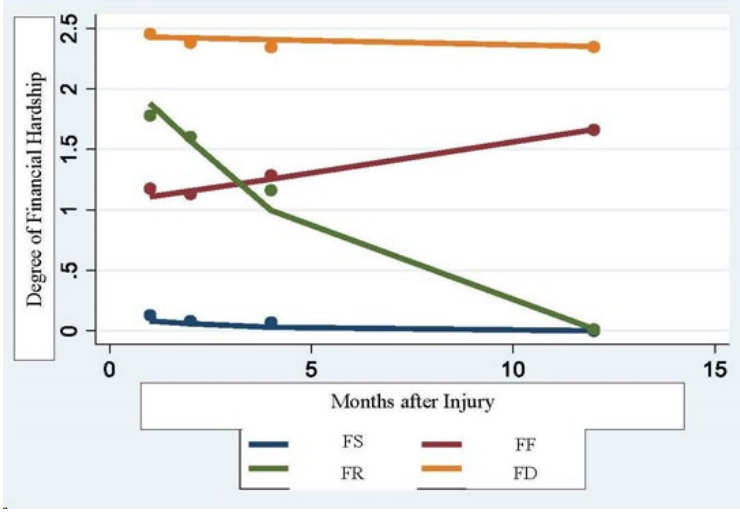
Introduction: Financial hardship after injury measurably impacts Health-Related Quality of Life outcomes. Financial hardship, encompassing material losses, financial worry, and poor coping mechanisms, is associated with lower quality of life and increased psychological distress. However, recovery is dynamic and financial hardship may change over time.

Methods: In this prospective longitudinal study of 500 moderate-to-severe non-neurologic injured patients, financial hardship and Health-related Quality of Life outcomes were measured at 1, 2, 4, and 12 months after injury using survey instruments (Short Form-36). Enrollment occurred at an urban, academic, Level 1 trauma center during January 2009-December 2011 and follow-up completed by December 2012.

Results: 474 patients had sufficient data for Group-Based Trajectory Analysis. Four distinct financial hardship trajectories were identified: Financially Secure patients (8.6%) had consistently low hardship over time; Financially Devastated patients had a high degree of hardship immediately after injury and never recovered (51.6%); Financially Frail patients had increasing hardship over time (33.6%); and Financially Resilient patients started with a high degree of hardship but recovered by year end (6.2%). At 12- months, all trajectories had poor Short Form-36 physical component scores and the Financial Frail and Financially Devastated trajectories had poor mental health scores compared to US population norms.



Conclusions and Relevance: The Financially Resilient trajectory demonstrates financial hardship after injury can be overcome. Further research into understanding why and how this occurs is needed.

ORAL ABSTRACTS: GROUP THREE

Education Research

Internal Laboratory Audit Revealing Gender and Race Polarity Towards White Men in Citation Behavior

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Introduction: The underrepresentation of women and authors of colors root beyond economic, social, and political aspects. Specifically, the broader spectrum of academia and medical disciplines have been persistent in recognizing and changing race and gender imbalances at all levels of systemic inclusion. Theoretical studies such as The Matilda effect and The Matthew effect hold strong pertinence in statistical correlations, revolving around the relationship between quality of work and author identity. The homophily taken place throughout professional networking has brought unintentional bias practices to light in several subspecialties of medical research. In this study we perform an internal audit of our own laboratory citation behavior, looking at the underrepresentation of women authors and authors of color.

Methods: For our data analyses, we used a simulation from CleanBib to analyze authorship sequences. The articles were broken down by date (2015-2020) and senior author, Dr. Samuel O. Poore. The simulation categorized the names of the first and last author of each cited paper by gender: man or woman, and by race: white author or author of color. The assignments of gender and race were solely determined by its relative statistical likelihood according to external database records (Gender-API and Census Bureau) between a 0.3-0.7 positive correlation.

Results: Of the 785 citations, the authorship sequences displayed to be 63.13% man/man, 9.23% man/woman, 15.19% woman/man and 12.81% woman/woman for the first and last author. Looking at race, 50.09% of sequences were categorized as white/white, 14.92% as white/author of color, 17.04% as author of color/white, and 17.12% as author of color/author of color. Relating citation practices to the primary publication author from our lab, the men-led papers overcited man/man papers by 73.17% compared to citing female authors. Women-led papers cited more female authors (14.91%) than men-led papers (4.86%) as well. Analyzing race, men-led publications tended to sight authors of color (18.67%) slightly more than women-led papers (14.07%).

Conclusions: Overall, there is a significant difference in citation behavior toward race and gender. White, male authors tend to be overcited across all 5 years analyzed compared to women and authors of color who tend to be under cited. This statistical data provided us a framework of actionable information to improve citation practice trends that can be applied at the surgical research level. With this being discovered, we ought to alter and discuss equitable citation practices within our lab and break the consequences of research homophily.

The Availability of Podcast-Based Education in Plastic Surgery

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Introduction: Asynchronous remote learning has become a valuable adjunct to traditional methods of medical education. Clinicians across multiple specialties have identified podcasts in particular as a beneficial educational medium. The aim of this study is to identify and describe recent trends in plastic surgery-specific podcast-based education.

Methods: Podcast streaming platforms Apple Podcasts, Google Podcasts, Spotify, Stitcher, TuneIn, and independent websites were searched for plastic surgery education podcasts in the span of 2011-2021. The number of podcasts, episode frequency, total episodes, genre, and subspecialty focus were identified for descriptive analysis.

Results: The first 3 plastic surgery podcasts were developed in 2016, releasing a total of 58 episodes that year. To date, there are now 16 plastic surgery education podcasts with a total of 794 episodes available. Of these podcasts, 56% were general educational topics, 38% were literature-focused, and 6% were a mixture of both. The majority of podcasts had no specific subspecialty focus, while 19% were focused on hand surgery.

Conclusions: Plastic surgery educational podcasts have grown exponentially over the last 5 years, suggesting a growing demand for educational resources that are more amendable to the busy plastic surgery trainee.

A Retrospective Case Study on the Valuation of a Full-Time Microsurgeon Educator in Training Highly Skilled Surgical Residents at Academic Centers

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Introduction: The precise value and benefit of a hired lab-based microsurgeon at an academic plastic surgery institution are largely unknown. Most plastic surgery divisions around the country do not have a dedicated microsurgeon who specializes in training residents. Our study aims at quantifying the value of a full-time microsurgical educator who provides coveted procedural skills in research and educational settings.

Methods: A daily one-on-one microsurgery training curriculum and annual one-day microsurgical training course with novel high-fidelity simulator models were developed for surgery residents from plastics, ENT, urology, neurosurgery, among others. Live animal rat models were replaced with our blue-blood chicken thigh, pig chest wall, and cadaver models. Meticulous recordings of the resident's dexterity during microsurgical training sessions were collected and analyzed for skill level. Additional parameters included the residents' specialty, postgraduate years (PGY), skill-level, speed, anastomosis method, average time, and total anastomoses performed per PGY level.

Results: Twenty-nine residents spent a total time of three hundred seventy-nine hours and five minutes in the lab practicing five hundred and twenty-two anastomoses. One hundred and ninety-eight rats were saved by our simulated practice sessions which decreased the purchasing and maintenance cost of rats in our rodent facility by $150,000. Relative to past plastic surgery residents whose performance peaked at PGY6, the residents trained using our methods had a performance peak during their PGY4 year. The residents performed assisted anastomoses at PGY3 and independent anastomoses at PGY4 accelerating the learning curve by 2 years compared to previous years without the full-time dedicated microsurgical educator. Our model has also supported twelve grant-funded projects, seven of which are currently active, five grants of more than one million dollars raging over 2-8 years. Our microsurgeon fostered six lab collaborations on projects including liver transplant in rats, prosthetic limb anastomosis, and microsurgical skill assessments with 3D imaging technology

Conclusions: A microsurgeon-run training program at our academic institution accelerated resident learning curves and microsurgical performance. Hiring an expert microsurgical educator to train residents and lab members alike has promise in improving microsurgical mastery. This study investigates the value of expert microsurgeons in supporting grant applications and multidisciplinary project progression. Additionally, we explore novel training modules that address ethical alternatives to animal models. The research opportunities, academic excellence, and potential for collaboration by hiring an expert microsurgeon at an academic medical institution could improve the quality of surgeons across the globe.

Gender Disparities in Citations in Plastic Surgery Tiered Journals

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Department of Plastic Surgery

Introduction: Gender disparities are pervasive in plastic surgery, especially in the area of academic medicine. The number of citations a publication receives is commonly used to gauge scholarly impact and recognition and advancement in academia (Chatterjee, 2021). Previous research demonstrates that articles authored by women in high-impact journals received fewer citations than those written by men (Chatterjee, 2021), suggesting that research done by women is less recognized by the scientific community than their male peers. Given the importance and weight that the number of citations carry in the scientific community, we seek to characterize citation trends among plastic surgery literature to observe whether citation disparities are present between men and women in low, mid and high tier surgical journals.

Methods: Articles published between 2017 and 2019 were collected from 8 representative plastic surgery journals categorized according to journal impact factor as high, mid, low tier, and open access. Names of the primary and senior authors of the 50 most cited articles per year per journal were collected and author gender was determined via online database and manual internet search. Number of citations by primary and senior author gender were compared via Kruskal-Wallis test to account for right-skewed distribution of citations.

Results: Among 1167 articles, women wrote 318 (27.3%) as primary author and 207 of the 1151 articles (18%) as senior author. Articles written by women were just as likely to be cited as those authored by men ($p>0.05$) across all journal tiers despite women authors comprising significantly less of the top cited articles.

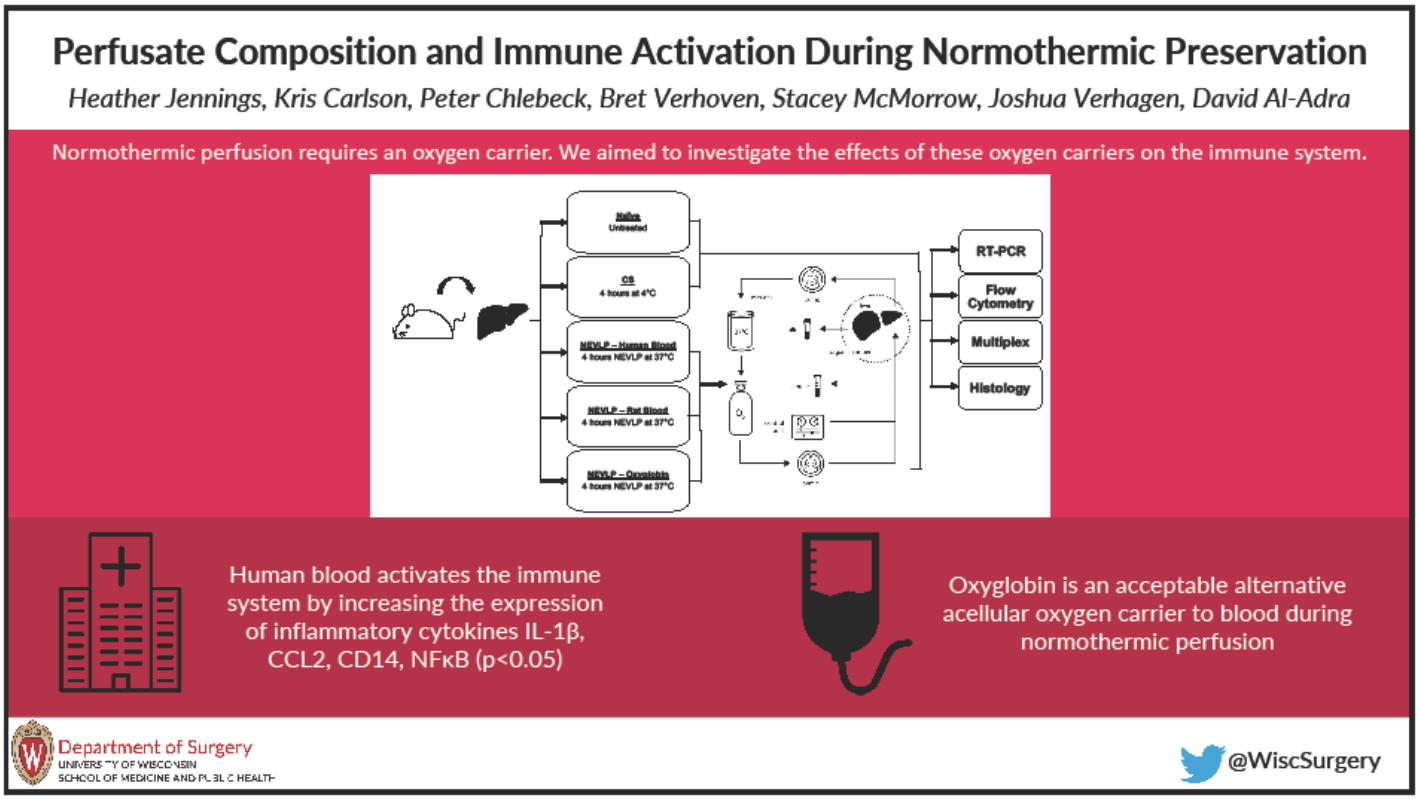
Conclusions: Given the value the scientific community places on citations as a marker for academic impact and promotion, it is important to understand the disparities that exist between the number received by men versus those by women. Our data demonstrates research published by women contributes meaningfully to academia and receives the same caliber of response given to men. Therefore, increasing gender diversity within plastic surgery academia is imperative to the field’s advancement.

VISUAL ABSTRACTS: GROUP ONE

Basic Science and Translational Research

“Perfusate Composition and Immune Activation during Normothermic Preservation”

Heather Jennings, Kris Carlson, Peter Chlebeck, Bret Verhoven, Stacey McMorrow, Joshua Verhagen, David Al-Adra



“Effects of Thickened Liquids: A Translational Pilot of Chronic Use”

Linda M. Rowe, John A. Russell, Michelle R. Ciucci, Nadine P. Connor

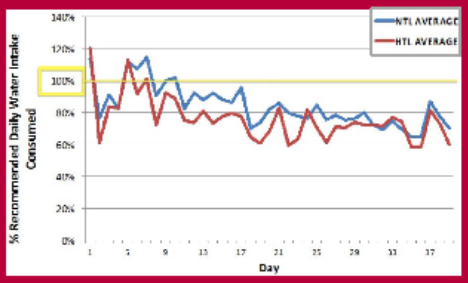
Effects of Thickened Liquids: A Translational Pilot of Chronic Use

Linda M. Rowe, John A. Russell, Michelle R. Ciucci, Nadine P. Connor

Background: It is not known how use of thickened liquids for treatment of dysphagia affects underlying biology. We used a rat model to examine the effects of nectar-thick (NTL) and honey-thick (HTL) liquids on swallowing.

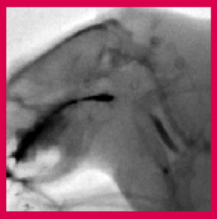
Finding: 100% survival rate / compliance at 7 weeks

Finding: Reduced consumption of recommended fluid intake after 7 weeks of thickened liquids



Week 7 Average (SD) **NTL = 70.1% (6.5%)** **HTL= 59.9% (9%)**

Finding: Percentage of swallows with post-swallow pharyngeal residue increased with NTL (+37.5%) and HTL (+10%)



Conclusion: Rat model demonstrates analogous clinical trends of reduced fluid intake and post-swallow residue, suggesting a valid model for study of biological mechanisms underlying chronic use of thickened liquids.

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NIDCD, R01 DC018071; NIH, NIDCD T32DC009401; NIH, NIDCD R01 DC008149

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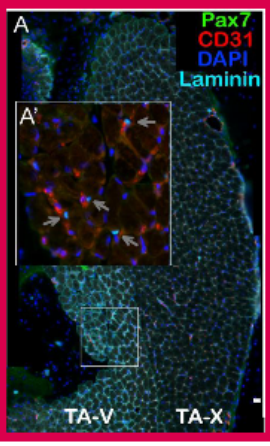
“The Impact of Aging on Muscle Stem Cell and Capillary Density in Rat Thyroarytenoid Muscle”

Jonathan E. Setzke, Tiffany J. Glass, Nadine P. Connor

The Impact of Aging on Muscle Stem Cell and Capillary Density in Rat Thyroarytenoid Muscle

Jonathan E. Setzke, Tiffany J. Glass, Nadine P. Connor

Background: Presbyphonia may be related to a decline in blood perfusion (CD31) and/or muscle stem cell supply (Pax7+) in the larynx (Thyroarytenoid [TA] muscle) with aging.

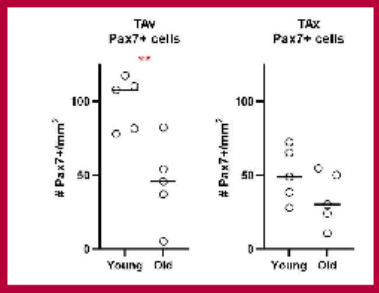


TA muscle stained for Pax7+ (stem cells) and CD31 (capillaries)

Arrows point to stem cells.
TA-V: TA Vocalis
TA-X: TA External

Finding 1:

Higher Pax7+ stem cell density found in TA-V of young adult rats than old rats

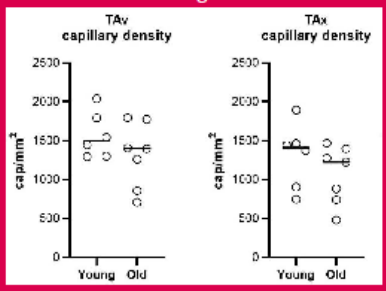


Pax7+ in TA-V, p = 0.007*

Each symbols denotes 1 animal and bars indicate median values

Finding 2:

No significant difference in capillary density as a result of age



Conclusion: Aging is associated with a decline in laryngeal muscle stem cell density, but not capillary density. Muscle regenerative capacity within the larynx may be affected by aging.

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Funding: **NIDCD** R01DC018071

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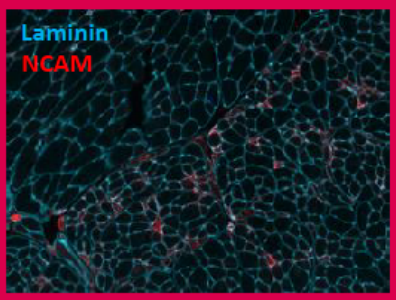
“Chemoradiation Treatment Alters Tongue Base Muscle Fiber Size in a Rat Model”

Adele F. Poser, Tiffany J Glass, John A. Russell

Chemoradiation treatment alters tongue base muscle fiber size in a rat model

Adele F. Poser, Tiffany J. Glass, John A. Russell

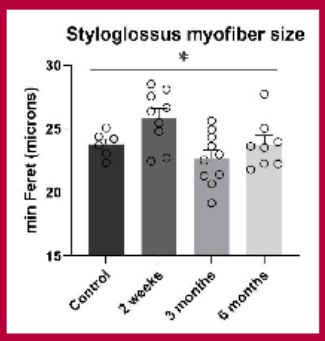
Question: Does chemoradiation treatment impact tongue base myofiber size and cause myofiber degeneration?



A microscopy study of styloglossus muscle myofiber size (laminin) and degeneration (NCAM) at three timepoints after treatment.

Result 1

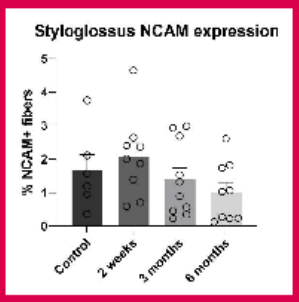
Myofiber size increases at 2 weeks post-treatment



p= .01

Result 2

No significant differences in NCAM



Conclusion: Chemoradiation causes increased myofiber size in tongue base muscle at an early post-treatment timepoint, which subsequently recovers.

Funding: NIH NCI Grant# 5R37CA225608-04

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“Cardiogenesis Pathways Inform Vocal Fold Development”

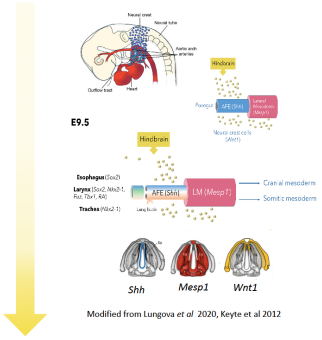
Kristy Wendt, Jared Brown, Vlasta Lungova, Vidisha Mohad, Christina Kendziorski, Susan Thibeault

Co-expression network analysis of the changing transcriptome in embryonic mouse esophagus, trachea, and larynx

Kristy Wendt[1,2], Jared Brown[3], Vlasta Lungova[1], Vidisha Mohad[1], Christina Kendziorski[3], Susan Thibeault[1,2]

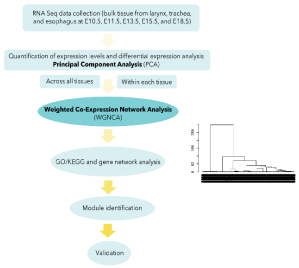
[1]Department of Surgery, Division of Otolaryngology -Head and Neck Surgery, University of Wisconsin, Madison, WI, USA; [2]Department of Biomedical Engineering, University of Wisconsin-Madison, WI, USA; [3]Department of Biostatistics and Medical Information, University of Wisconsin-Madison, WI, USA

An interrelated transcriptome builds the esophagus, trachea, and larynx from a shared origin and informs vocal fold development.

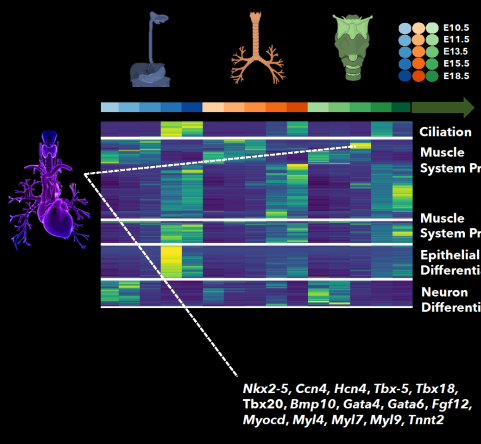


Modified from Lungova *et al* 2020, Keyte et al 2012

Methods: Bulk tissue RNAseq with co-expression network analysis



Cardiogenesis **pathways** inform vocal fold development.



Nkx2-5, Ccn4, Hcn4, Tbx-5, Tbx18, Tbx20, Bmp10, Gata4, Gata6, Fgf12, Myocd, Myl4, Myl7, Myl9, Tnnt2

Take a picture to interact with **transcriptome sparklines** from **our data**

bio RENDER

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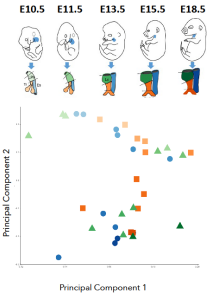
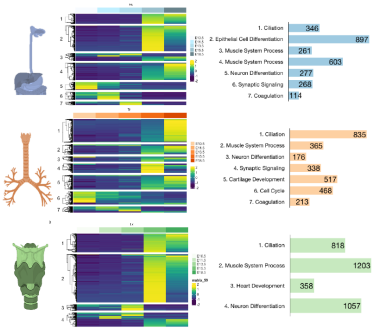
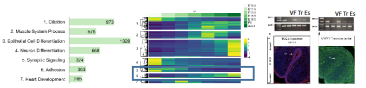
Timecourse transcriptomes cluster by tissue and developmental time



Enrichment of within tissue analysis identifies organ-specific functional modules with unique patterns of gene expression in time.



Cardiac morphogenesis regulator *Nkx2-5* localizes to vocal fold

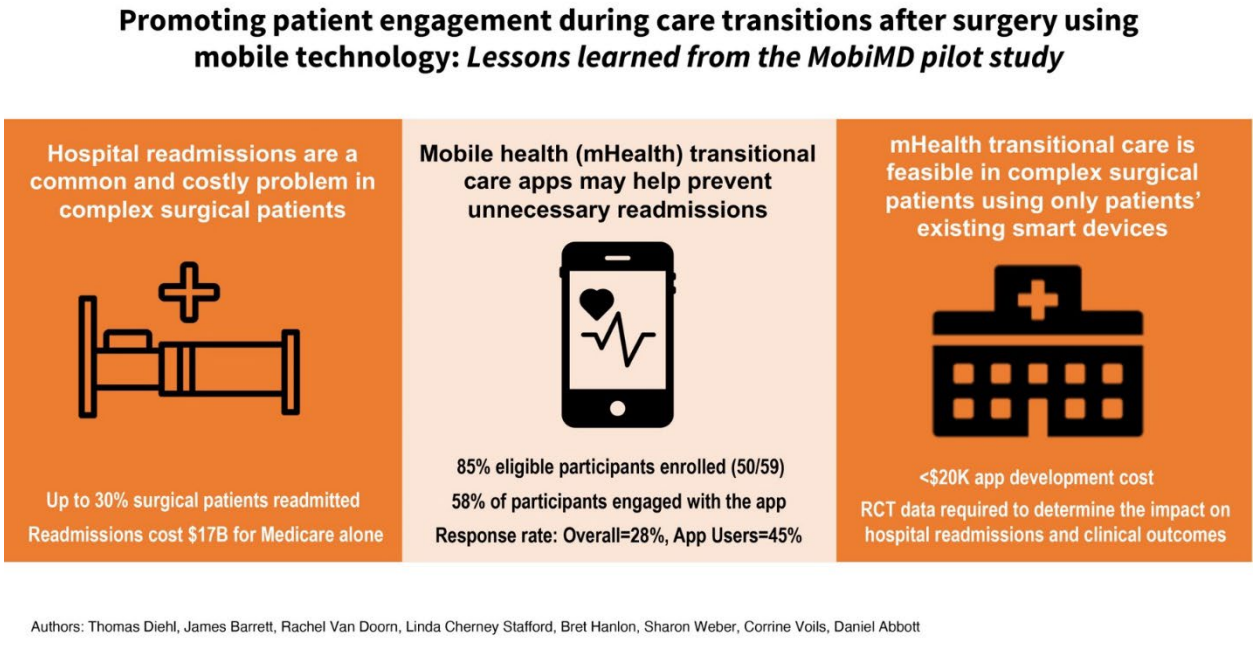


VISUAL ABSTRACTS: GROUP TWO

Clinical Science and Health Services Research

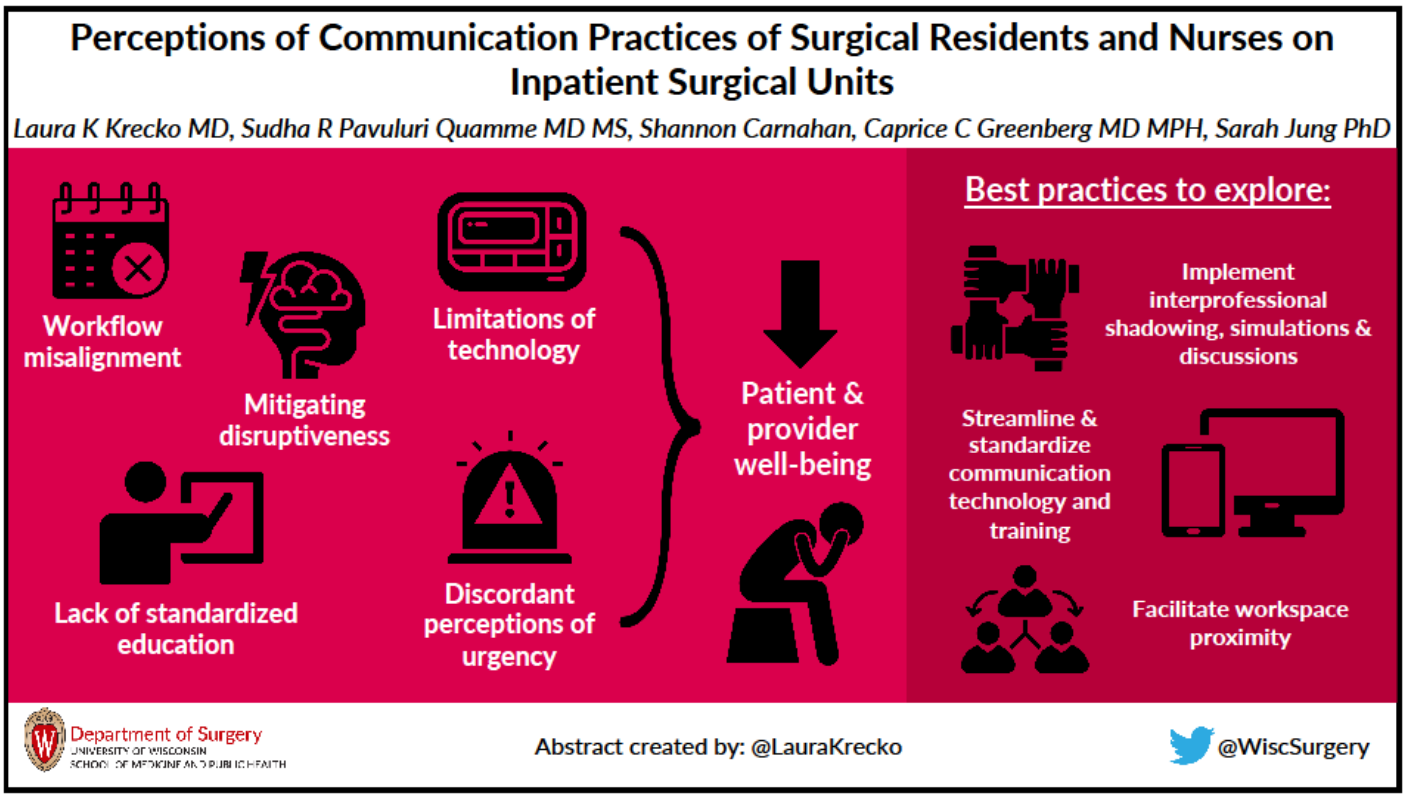
“Promoting Patient Engagement During Care Transitions after Surgery Using Mobile Technology: Lessons Learned from the Mobimd Pilot Study”

Thomas Diehl, James Barrett, Rachel Van Doorn, Linda Cherney Stafford, Bret Hanlon, Sharon Weber, Corrine Voils, Daniel Abbott



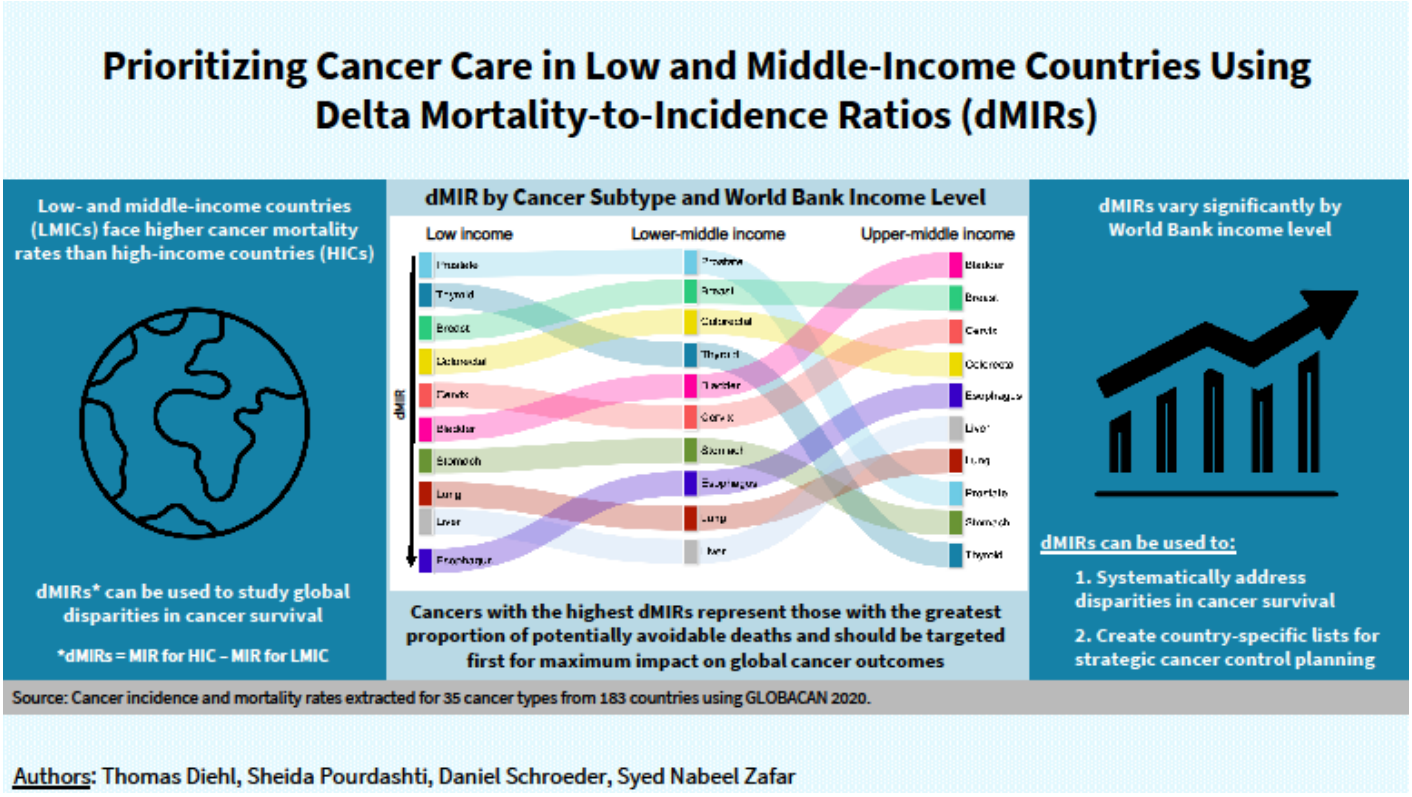
“Perceptions of Communication Practices of Surgical Residents and Nurses on Inpatient Surgical Units”

Laura K Krecko, Sudha R Pavuluri Quamme, Shannon Carnahan, Caprice C Greenberg, Sarah Jung



“Prioritizing Cancer Care in Low and Middle-Income Countries Using Delta Mortality-to-Incidence Ratios (dMIRs)”

Thomas Diehl, Sheida Pourdashti, Daniel Schroeder, Syed Nabeel Zafar

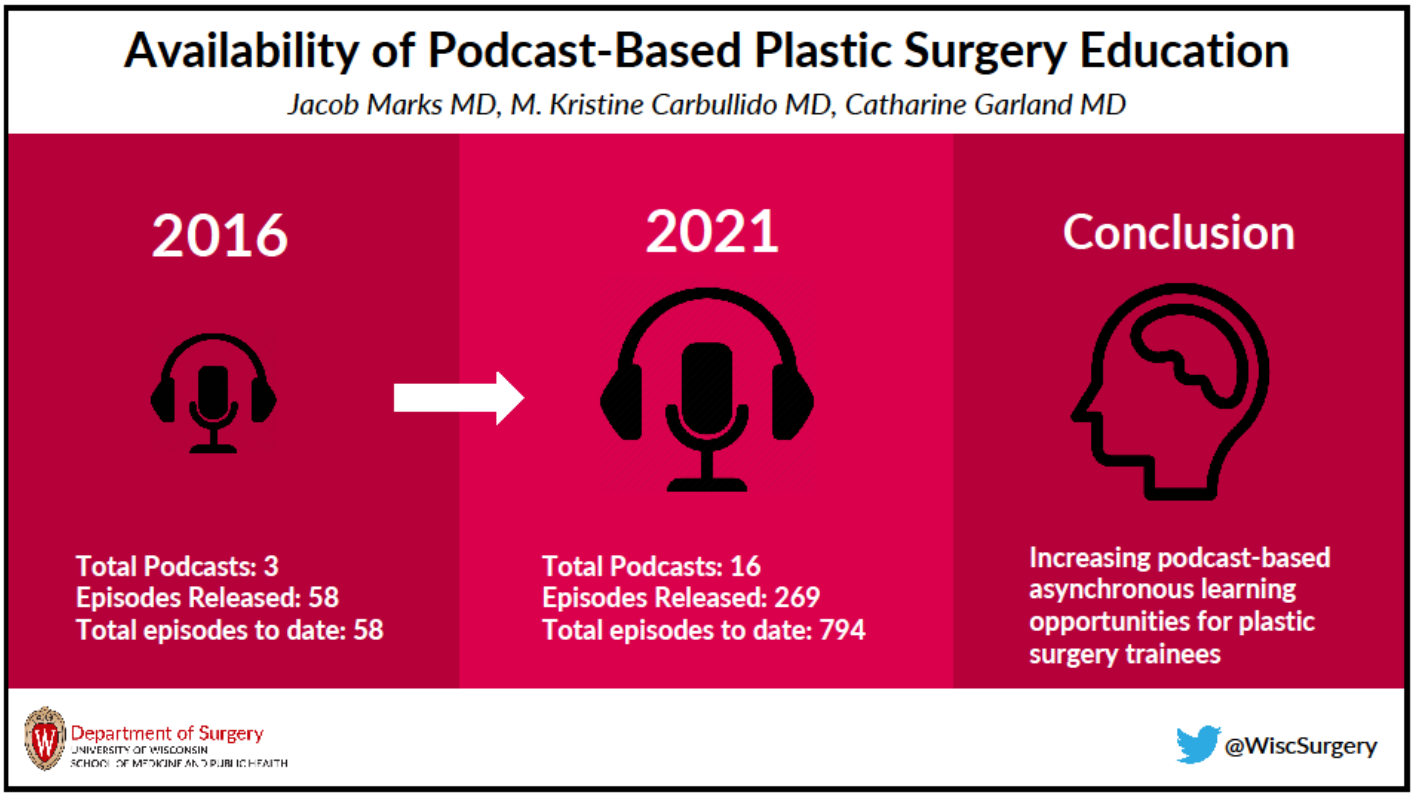


VISUAL ABSTRACTS: GROUP THREE

Education Research

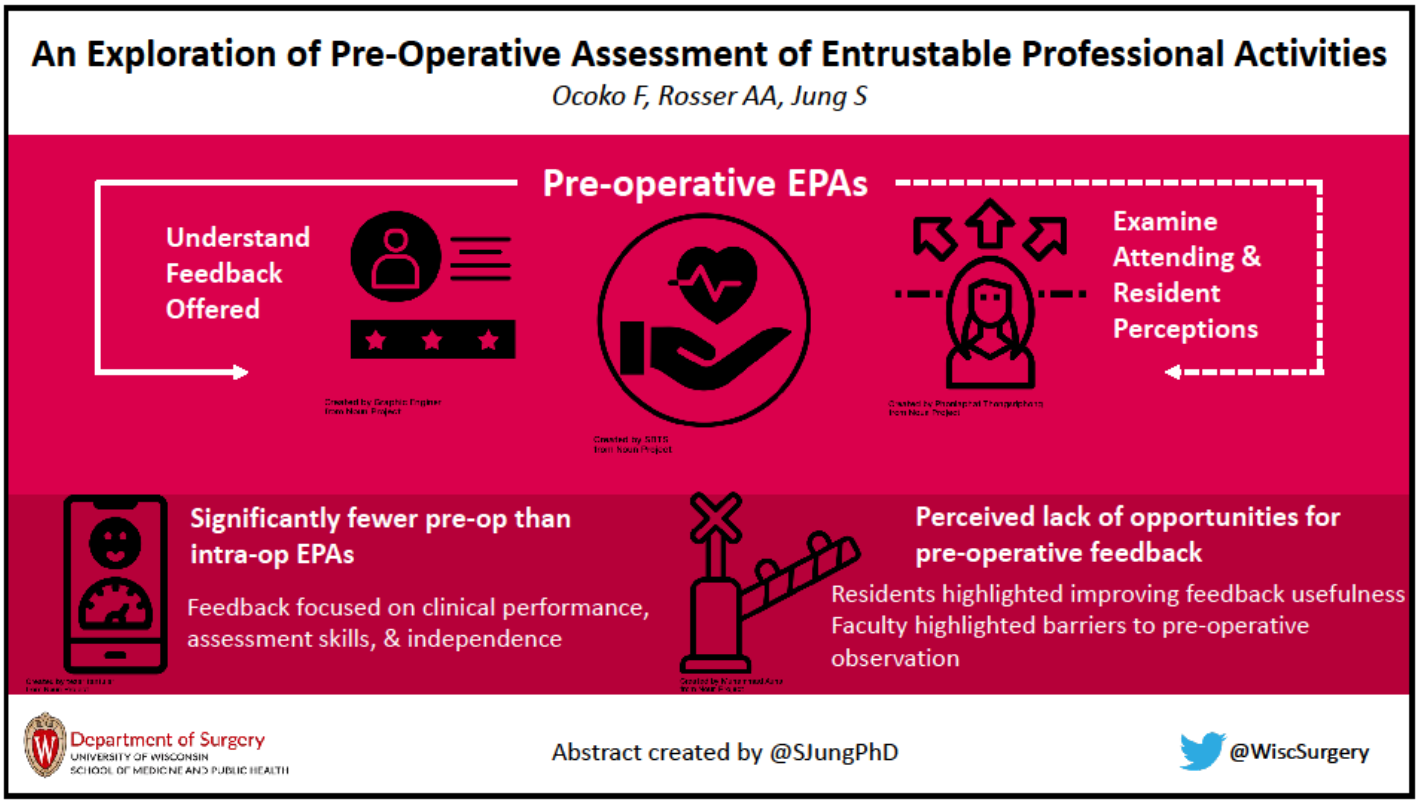
“The Availability of Podcast-Based Education in Plastic Surgery”

Jacob Marks, M. Kristine Carbullido, Catharine Garland



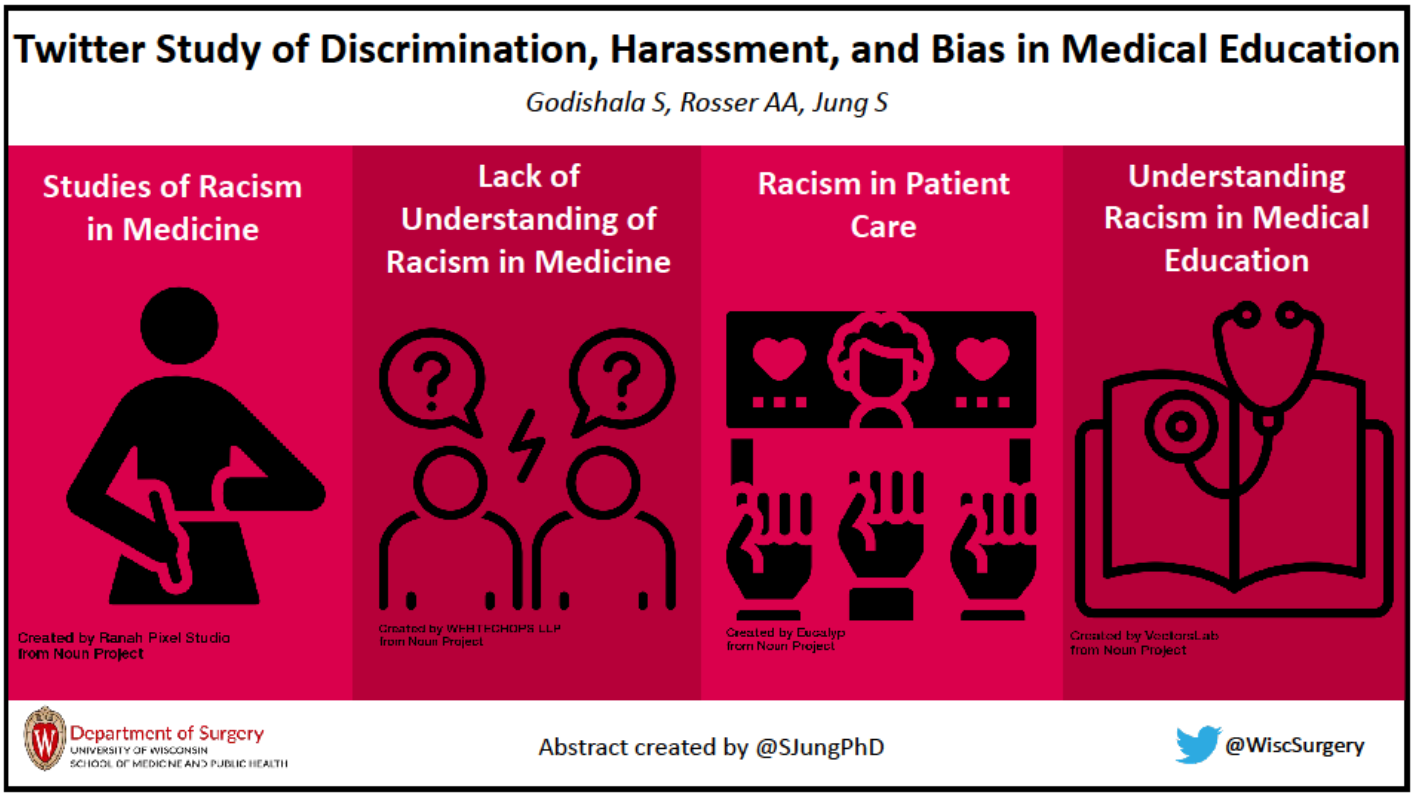
“An Exploration of Pre-Operative Assessment of Entrustable Professional Activities”

Faith Ocoko, Alexandra A. Rosser, Sarah Jung



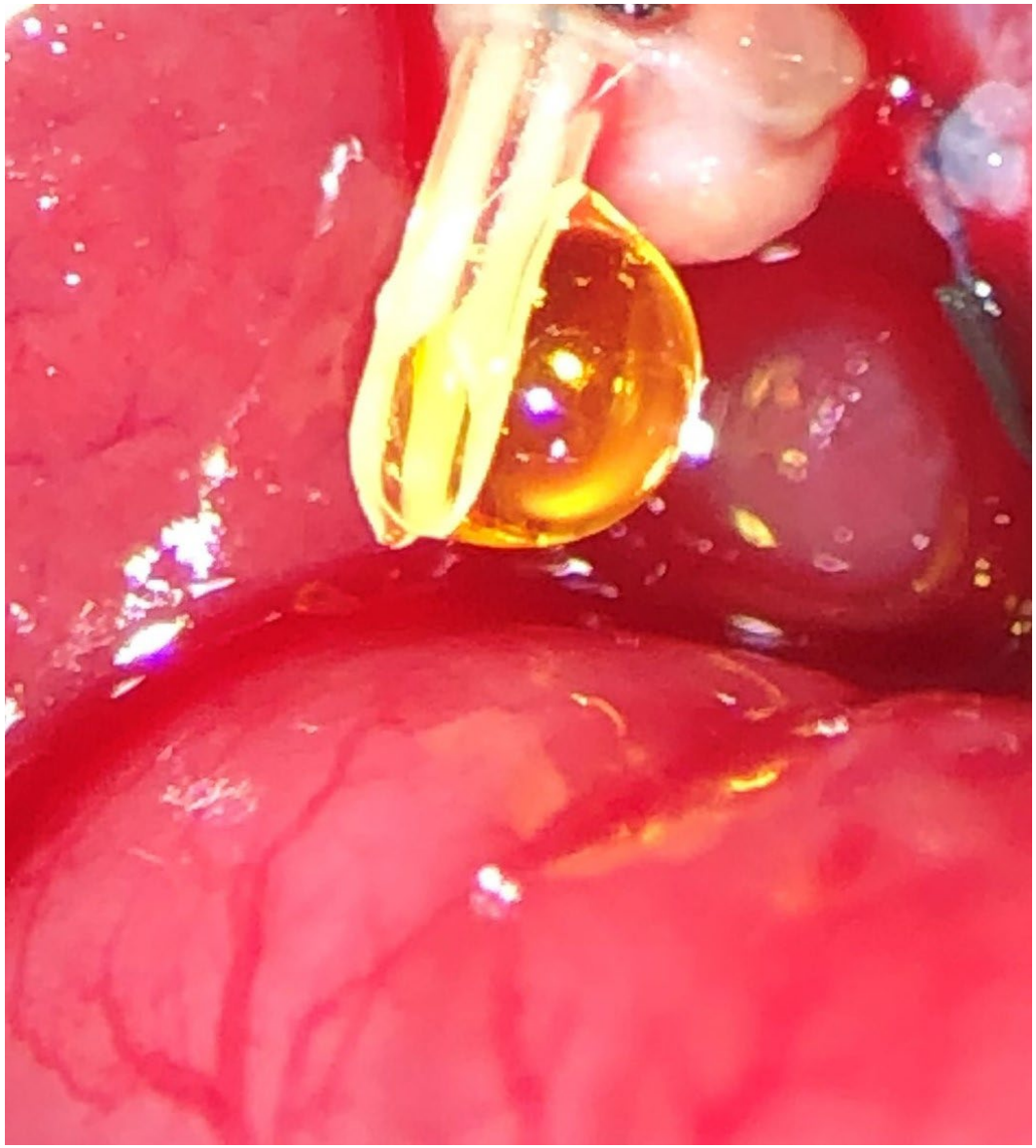
“Twitter Study of Discrimination, Harassment, and Bias in Medical Education”

Shreya Godishala, Alexandra A. Rosser, Sarah Jung



Surgery Science Images

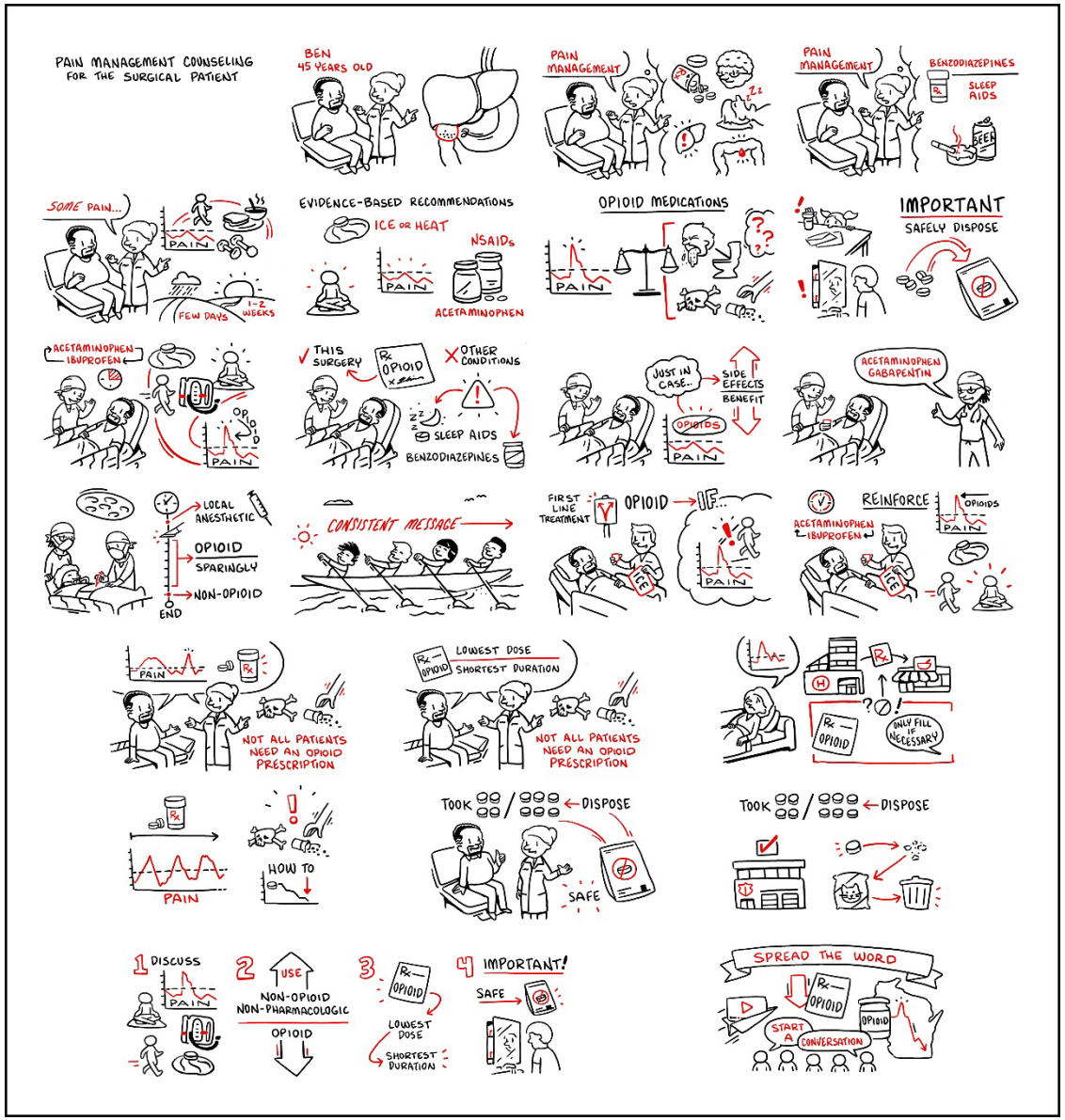
“Smiling Bile from a Happy Liver”



"We saw this smiling drop of bile during the first successful rat liver transplant at UW-Madison in more than 2 decades. This surgery provides an excellent rodent liver transplant model for studying and improving human transplant outcomes."

Photo Credit: Weifeng Zeng-Poore lab, Bret Verhoven-Al-Adra Lab

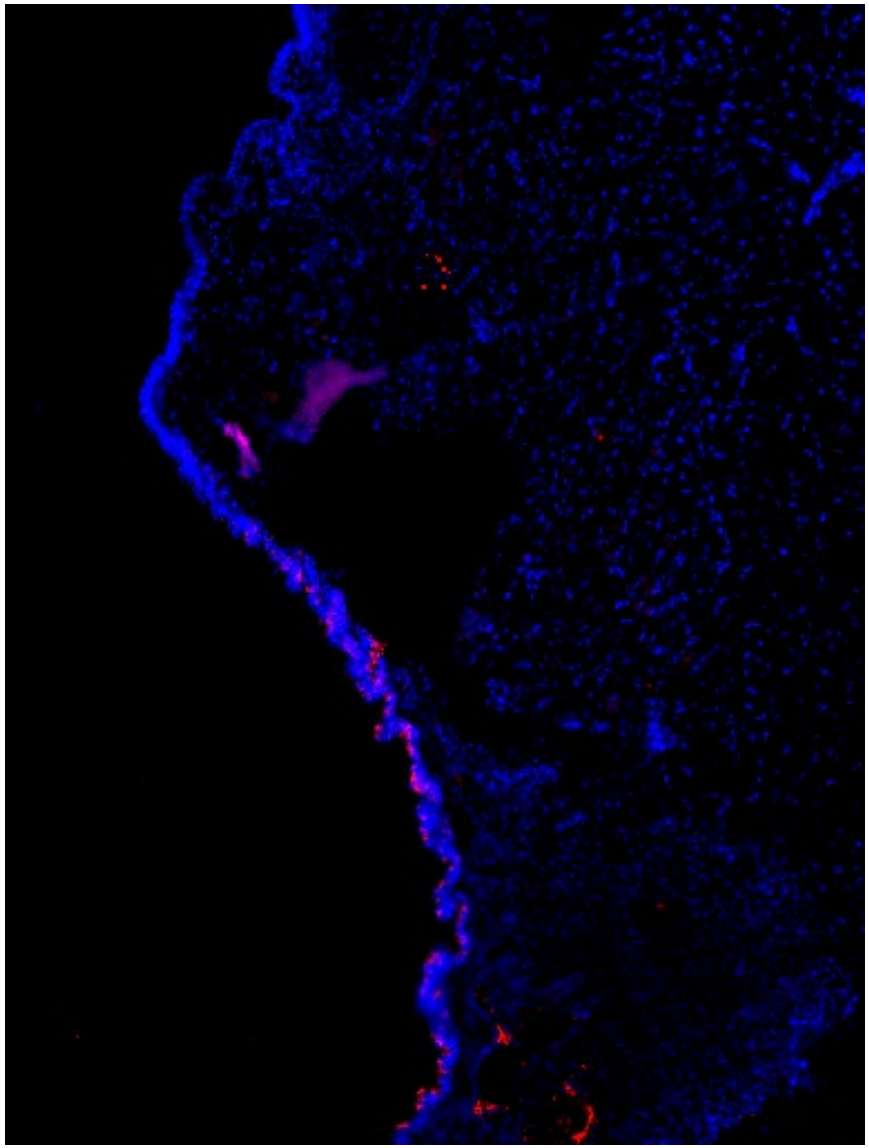
“Pain Management Counseling for the Surgical Patient”



“This cartoon depicts a comprehensive approach to safe and effective management of surgical pain for a patient undergoing a laparoscopic cholecystectomy. It highlights a spectrum of pain management strategies to show surgical prescribers how to integrate these steps into their practice.”

Photo Credit: Surgical Collaborative of Wisconsin & TruScribe: Sudha Pavuluri Quamme, MD, MS, Joanne Peters, PhD, Tudor Borza, MD

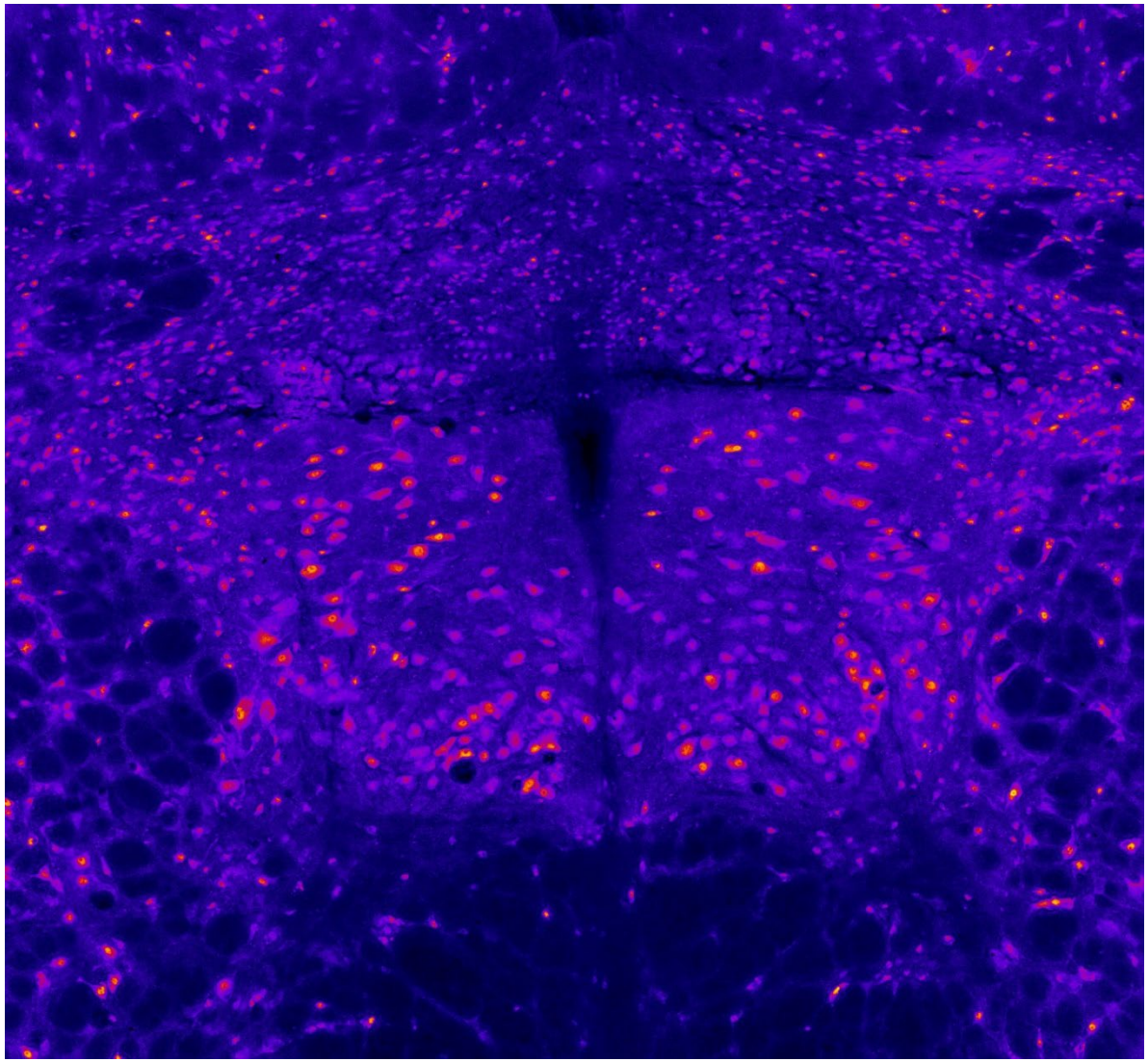
“Estrogen Receptors in the Vocal Fold”



“A cross-section of a right vocal fold (10 microns) of a Long-Evans rat. Blue labels the cell nuclei and red labels a specific estrogen receptor, GPER. GPER is present in the inferior portion of the epithelium of the vocal fold. This receptor is responsible for rapid estrogenic effects and could help explain why womenâ€™s voices are more susceptible to hormonal changes than male counterparts. Quantifying the type and ratio of hormone receptors in the vocal folds of both sexes is the first critical step to determining hormonal effects by defining receptors that potentially affect vocal fold biology.”

Photo Credit: Charles Lenell and Michelle Ciucci, Ciucci Laboratory

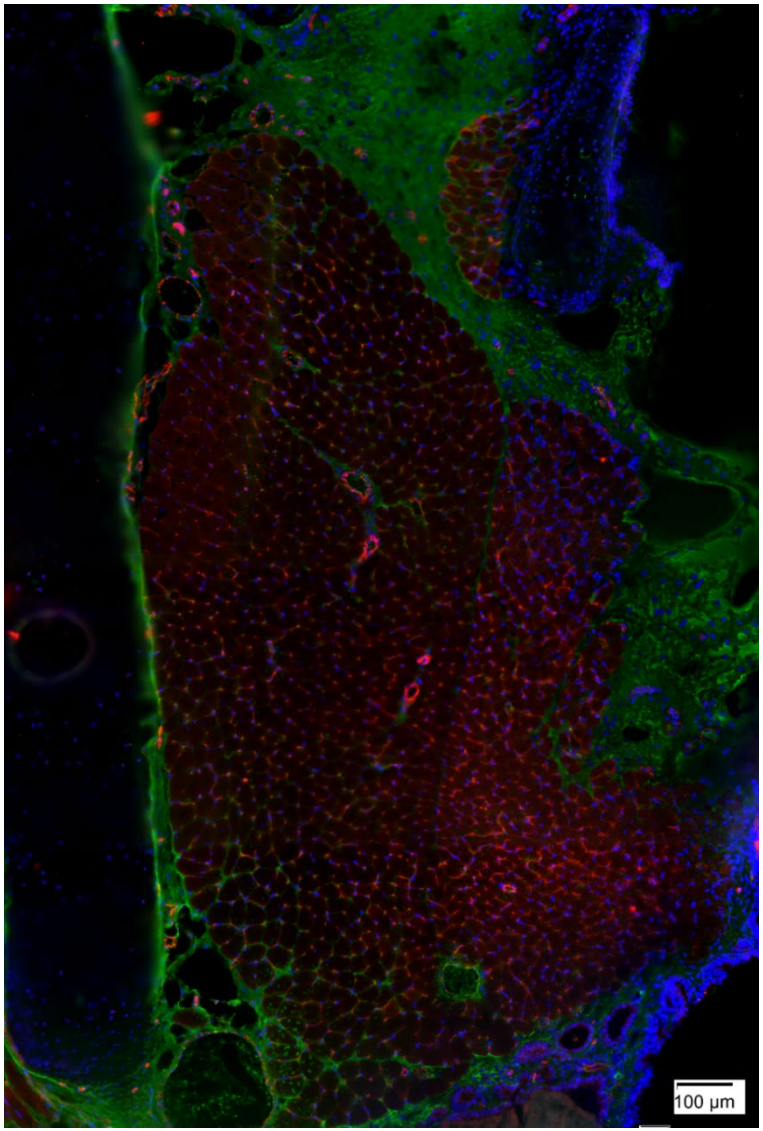
“Hypoglossal motor neurons”



“This image depicts the hypoglossal motor neurons which activate the tongue muscles. This section of rat brainstem was imaged on a microscope using an immunofluorescent stain for neurons. The motor neurons appear as the larger pink-orange spots, clustered in the bilateral hypoglossal nuclei in the center of the image. Other smaller neurons appear in the surrounding tissue. This image was collected for a study designed to determine whether a loss of motor neurons contributes to weakness of the tongue after cerebral stroke.”

Photo Credit: Miranda Cullins in the lab of Nadine Connor

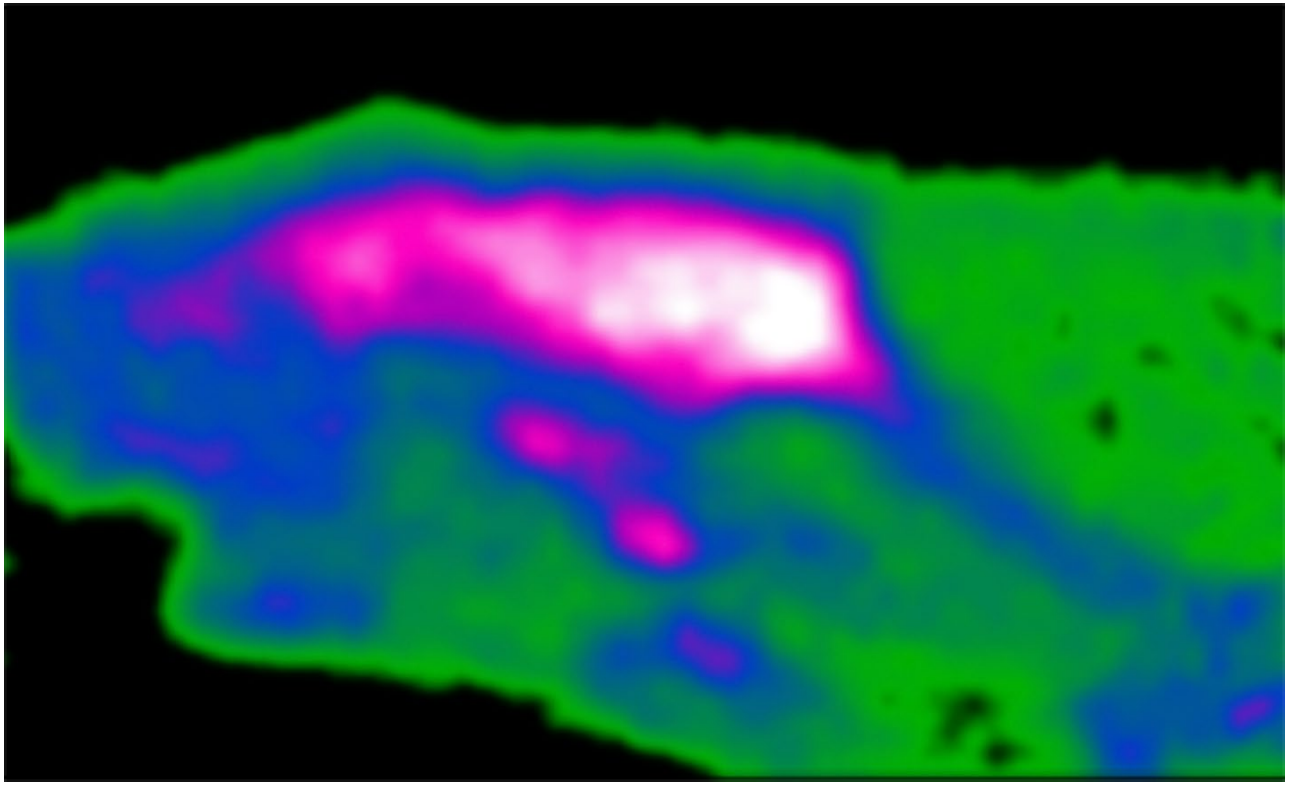
“Rat Thyroarytenoid Muscle Stained for Capillaries”



“This image depicts a section of rat thyroarytenoid (TA) muscle stained for capillaries with anti-CD31 (red) and nuclei with DAPI (blue). The thyroid cartilage is on the left and the airway is on the right. This tissue section was imaged using a light microscope at 20x magnification. The staining shows the density of capillaries found in the TA muscle. It can be very challenging to study capillary density in intact TA muscles, but capillary density is a measure for which tissue sections are very well-suited. Capillary density may be an important consideration for studies of muscle fatigue.”

Photo Credit: Jonathan Setzke and Tiffany Glass in the lab of Nadine Connor

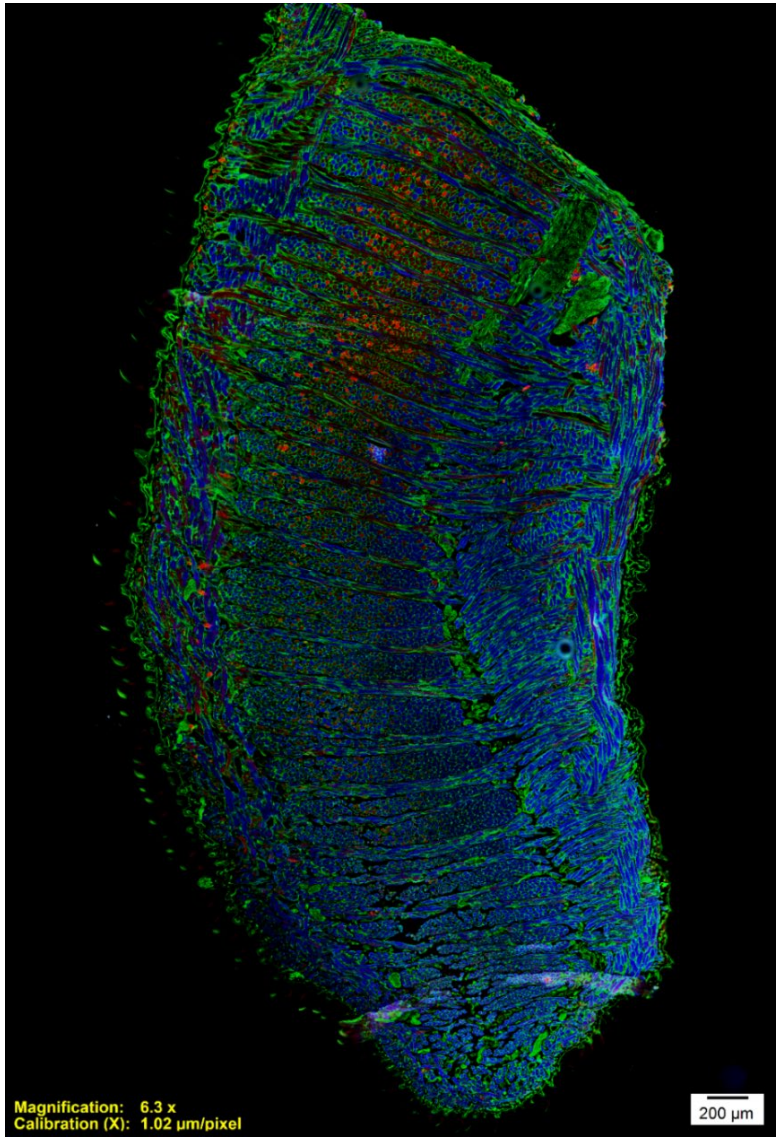
“Brain Activity in an Adult Rat”



“This is a cross-section of a rat brain taken with a positron emission tomography scanner. A tracer molecule similar to sugar is tagged with a short-lived radioactive atom and injected through a vein. It then circulates throughout the body and is trapped where sugar is consumed. The colors show brain activity. Those regions with the most activity are colored white, followed by magenta, blue, and green in descending order. These images are taken in order to determine how brain activity is different in healthy states vs. neurologic disease so we can develop better treatments. We also use this technique to determine if our treatments are slowing disease progression.”

Photo Credit: Maxim Slesarev, neuroimaging technologist, Waisman Center; John Szot, research specialist, Department of Surgery - Otolaryngology; Alex Nisbet, research specialist, Department of Surgery - Otolaryngology; Michelle Ciucci, professor, Communication Sciences and Disorders, Surgery-Otolaryngology Head & Neck Sugery; Alexander Converse, senior scientist, Waisman Center

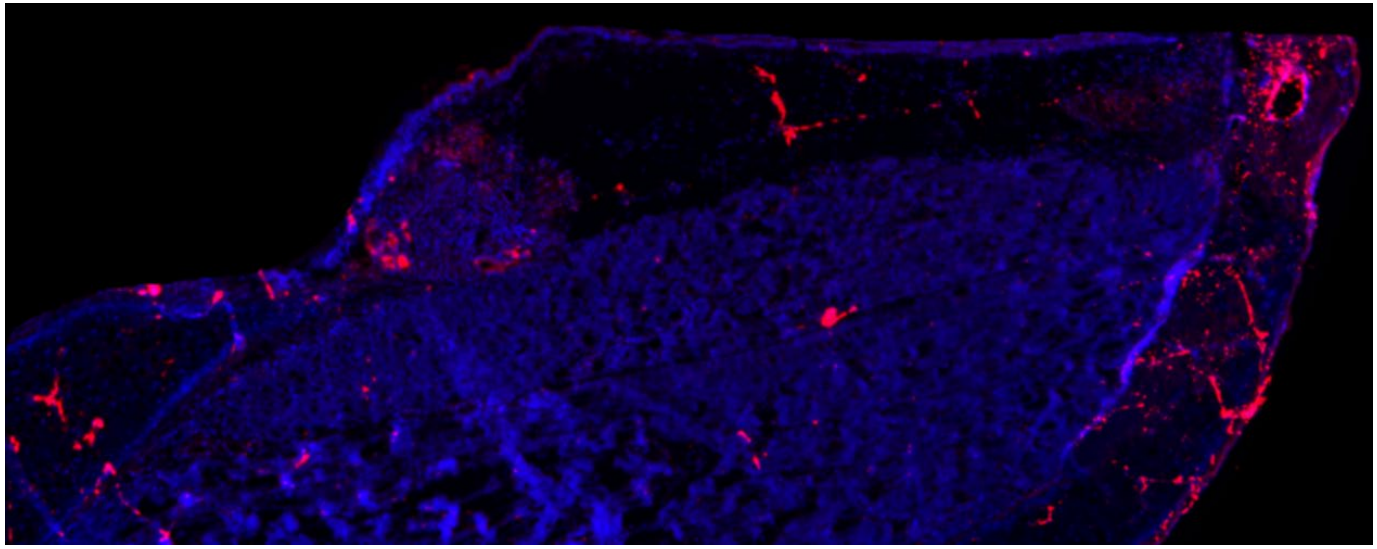
“Intrinsic Tongue of a Mouse Model of Down Syndrome”



“This is a microscopy image of the intrinsic tongue of a mouse model of Down syndrome. This image was taken with an epifluorescence microscope. The dorsal tongue is to the left and the ventral tongue is to the right. Antibody staining shows muscle fiber outlines in green, fast muscle fibers in blue, and relatively slower muscle fibers in red. This image shows us how the intrinsic tongue is comprised of complex interdigitation of multiple muscles; each with a different fiber orientation, and that different regions of the tongue are comprised of different types of muscle fibers. Down syndrome is associated with developmental differences involving tongue function, and tissue studies of mouse models can help us to understand these differences.”

Photo Credit: Tiffany Glass

“Inflammatory Biomarker in the Vocal Folds of a Parkinson Rat Model”



“A longitudinal section (4x) of a right vocal fold (10 micron) of a male rat with an early-onset Parkinsons disease gene mutation (Pink1-/-). The image is stained for Caspase-7 (a protease involved in apoptosis and inflammation) in red and cell nuclei in blue. Increased expression of Caspase-7 in the vocal fold is associated with increased inflammation and cell apoptosis which may contribute negative changes in the vocal fold biology and functions associated with Parkinson's disease. By understanding how the vocal folds are negatively impacted by Parkinsons disease, future research can investigate how to prevent and reverse these changes.”

Photo Credit: Charles Lenell and Cynthia Kelm-Nelson, Kelm-Nelson Lab

“Individuality in the Oropharyngeal Swallow”

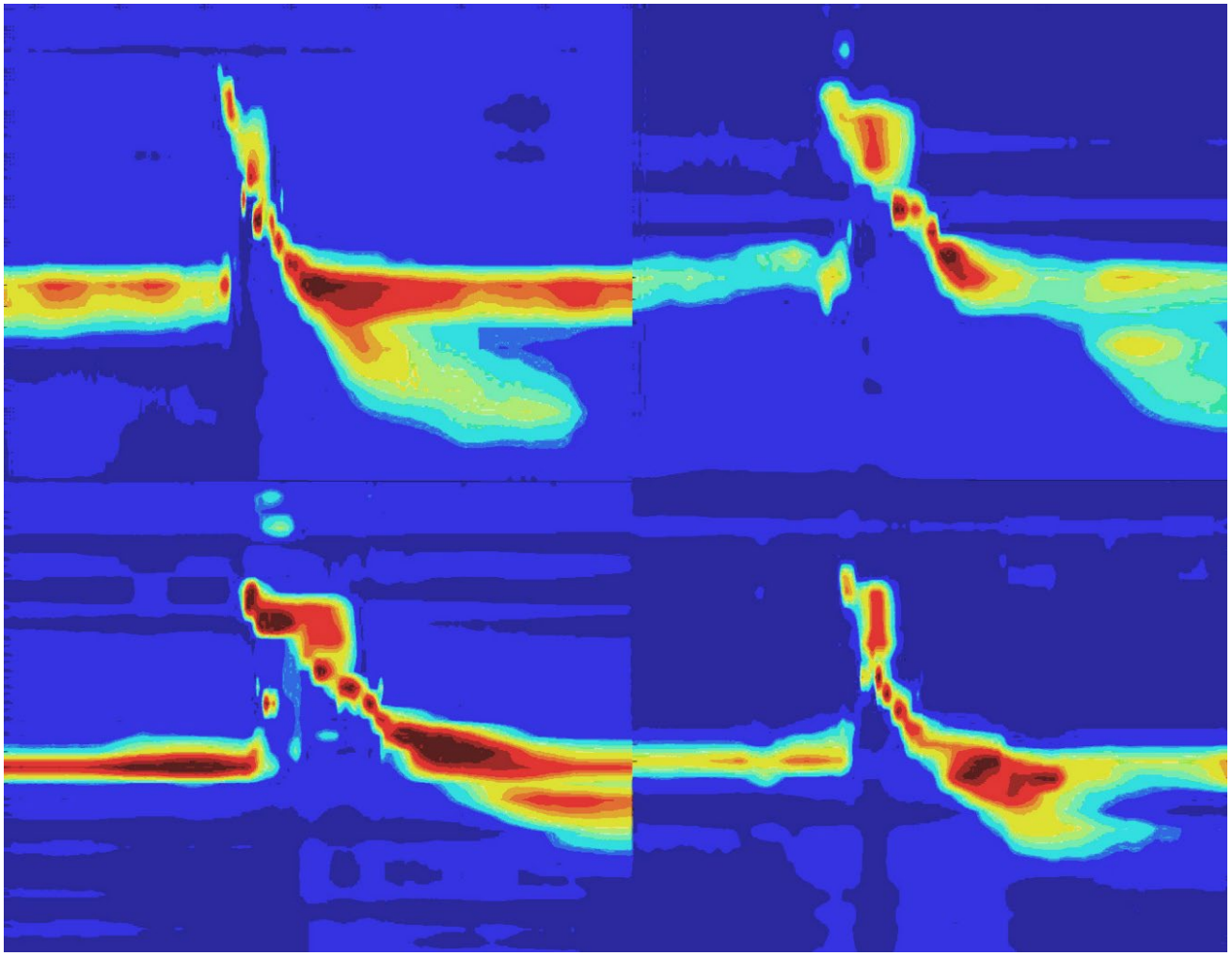
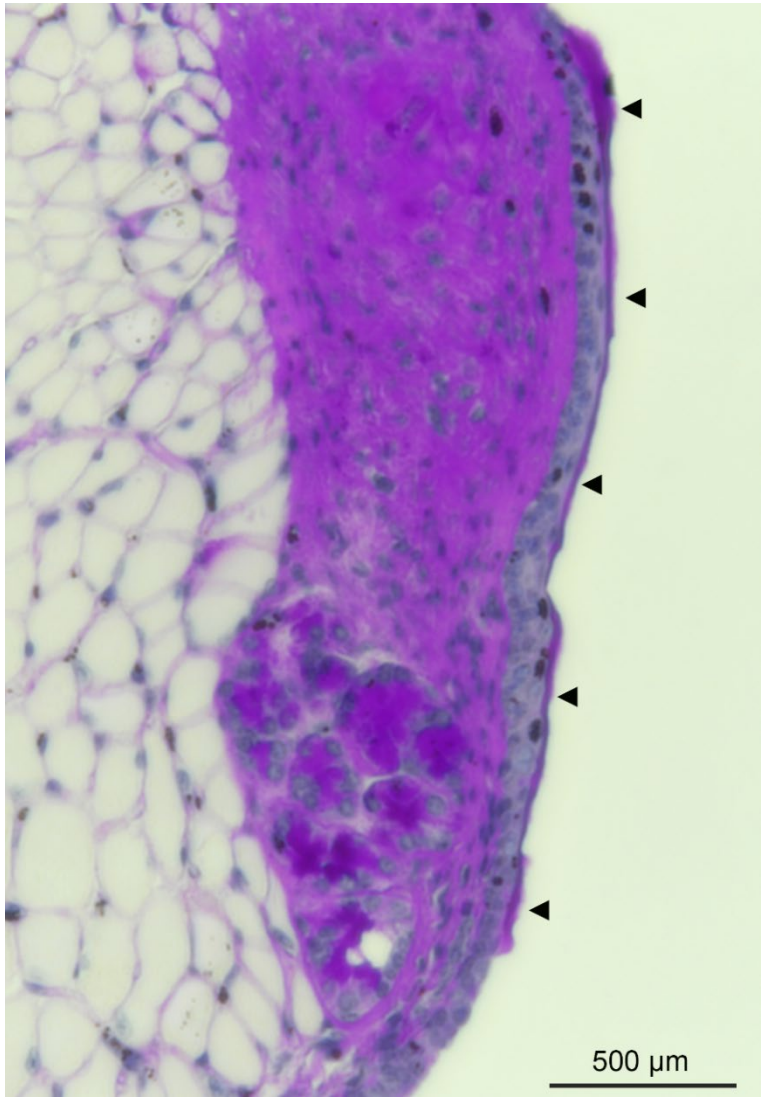


Photo Credit: Sophia M Colevas, BSE; Corinne A Jones, PhD; Timothy A McCulloch, MD

“High-resolution manometry is a technique in which closely spaced sensors are used to measure the pressure generated over time during the first phase of swallowing (between the mouth and the entry to the airway). This image depicts the swallow pressure profiles of four healthy individuals who were asked to take their normal, comfortable sip of liquid (high pressure shown in red and low pressure shown in blue). At first glance, the swallows appear uniform, but upon closer inspection, the pressure patterns differ between individuals. This reflects the complexity of the initial phase of swallowing where many sensory inputs and multiple muscles must be integrated to complete the swallowing task. A high-resolution measurement tool is necessary to accurately capture this complexity and reach a more complete understanding of human swallowing physiology.”

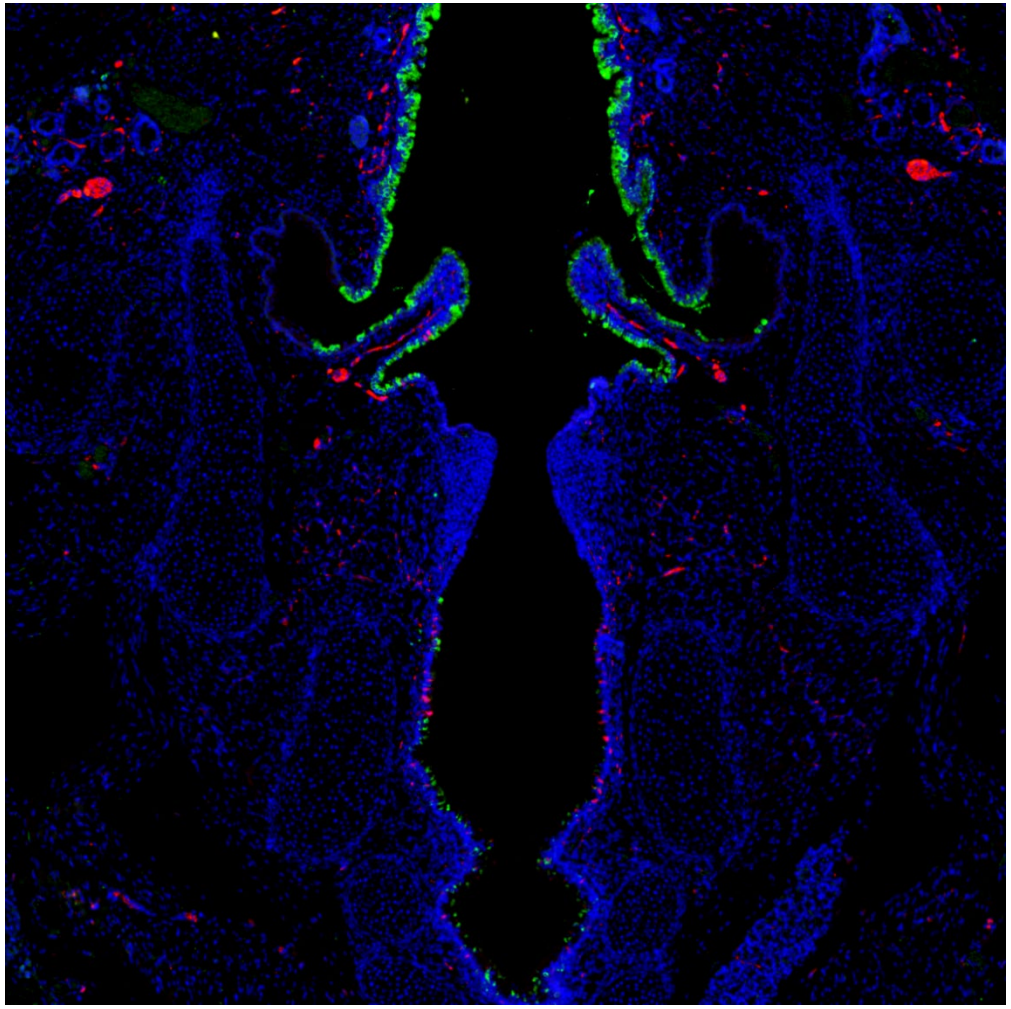
“Mucus - The Vocal Fold Warrior”



“This is the first time to depict the presence of a thin mucus layer in a mouse model, which covers the vocal fold and serves to support optimal biomechanical properties of the vocal fold and promote voice quality. To get the image, mouse vocal fold tissue was fixed, sectioned, and stained with appropriate histological methods, and subsequently imaged with Nikon Eclipse Ti2 inverted microscope. Mucus layer forms an viscoelastic physical barrier that protects the underlying tissue from being exposed to external irritants, such as pathogens, particles, and toxic chemicals in inhaled air and gastroesophageal reflux. It is also a natural habitat for laryngeal microbiota and therefore essential for the host-microbe interaction studies in the larynx. Arrows indicate the mucus layer in the image.”

Photo Credit: Ran An, Thibeault lab

“Nerve Endings Arborize near Mechanoreceptor PIEZO2-Expressing Epithelia in P0 Mouse Larynx”



“This is a cross section of the larynx from a mouse pup day 0 after birth exhibiting the mechanoreceptor PIEZO2 (green), and innervating nerve fibers/neurons labeled via PGP9.5 (red).? This image was taken with an inverted Nikon microscope located in the Thibeault lab.PIEZO proteins are cell-membrane receptors, activated by stretching of the cell by which they convert these mechanical cues to biochemical cell responses. These proteins are only expressed in mammalian cells. This image exhibits selective expression of PIEZO2 mechanoreceptor above and below the vocal folds in laryngeal regions where there exists increased innervation from nerve fibers. This suggests that PIEZO2 expressing cells in the larynx may directly or indirectly communicate with innervating sensory afferents for airway protective responses.”

Photo Credit: Section cut by Sierra Raglin, Immunostain performed by Alexander Foote (Thibeault lab)