YALE SURGERY RESEARCH DAY 2026

Department of Surgery

KEYNOTE SPEAKER

Julie Ann Sosa, MD MA FACS

Leon Goldman, MD Distinguished Professor of Surgery and Chair, Department of Surgery Professor, Department of Medicine

Affiliated faculty, Philip R. Lee Institute for Health Policy Studies

University of California San Francisco-UCSF

Julie Ann Sosa, MD MA FACS is the Leon Goldman MD Distinguished Professor of Surgery and Chair of the Department of Surgery at the University of California San Francisco (UCSF), where she is also a Professor in the Department of Medicine and affiliated faculty for the Philip R. Lee Institute for Health Policy Studies. Dr Sosa came to UCSF in 2018 from Duke. Her clinical interest is in endocrine surgery, with a focus in thyroid cancer. She is an NIH- and FDA-funded investigator and author of more than 400 peer-reviewed publications and 80 book chapters and reviews, all largely focused on outcomes research, health care delivery, hyperparathyroidism, and thyroid cancer, with a focus on clinical trials. She has authored or edited seven books. Dr Sosa serves on the Board of Directors of the International Thyroid Oncology Group; for the ATA, she co-chaired the committee responsible for writing the 2025 practice guidelines for the management of adult patients with differentiated thyroid cancer. She is an editor of Greenfield's Surgery: Scientific Principles and Practice and serves as Secretary-Treasurer of the Halsted Society. She is a past-President of the American Thyroid Association (ATA) and past-Editor in Chief of the World Journal of Surgery. She has mentored more than 90 students, residents, and fellows, for which she was recognized with induction as a full member to the American College of Surgeons Academy of Master Educators in 2020, and by the ATA with the Lewis E. Braverman Distinguished Lectureship Award in 2017 and its Distinguished Service Award in 2022. She received the Chancellor's Diversity Award in 2022 for the Advancement of Women at UCSF and the AAMC recognized UCSF Surgery and its Muriel Steele Society with the Group on Women in Medicine and Science Leadership Award for an Emerging Organization in 2025. Dr. Sosa was born in Montreal and raised in upstate New York. She received her AB at Princeton, MA at Oxford, and MD at Johns Hopkins, where she completed the Halsted residency and a fellowship.

YALE SURGERY RESEARCH DAY 2026

ABSTRACTS

Basic Science		**Pages**
Assi, R	Machine Learning-Guided Classification of Spatial Histological Domains in the Thoracic Aorta	1
	Progressive increase in axial stiffness of prosthetic aortic grafts results in elongation of the residual ascending aortic segment	2
	Decreased Cell Density in the Aortic Media Predicts Increased Resistance to Ex Vivo Aortic Dissection	3
Bonde, P	Development of a transcatheter, expandable toroidal blood pump for pulmonary support	4
	Physiologic control of rotary blood pumps by ventricular chamber size estimation using resonantly coupled sensors	5
Cai, Y	Phosphodiesterase 10A regulates medial arterial calcification through p38/MAPK-MMP3 signaling	6;**E**
	Matrix metalloproteinase-3 promotes arteriovenous fistula neointimal hyperplasia by regulating FAK-AKT signaling	7
Christison-Lagay, E	pH-targeted delivery of microtubule inhibitor in pediatric solid tumors	8
	Targeted pH sensitive peptide-exatecan conjugate demonstrates efficacy in a relapsed topoisomerase I inhibitor resistant model of pediatric rhabdomyosarcoma	9;**E**
Gruber, P	Novel functional and single nuclear transcriptomic analysis of an acellular extracellular matrix for growth-adaptive tricuspid valve replacements in sheep	10;**H**
Hsia, H	Emerging Roles of Stem Cell–Derived Exosomes in Regenerative Wound Healing	11
Khan, S	Integrated Spatial Transcriptomics, Tissue Microarray and Longitudinal Microbiome Profiling to Unravel Sex-Specific Asparagine Metabolism in Late-Stage Colorectal Cancer	12
Kim, J	From Bench to Computational Modeling: Integrating Mitochondrial Stress Data from a Rat Hepatic Ischemia-Reperfusion Injury Model into a Preclinical and Human Quantitative Systems Toxicology Platform	13;**E**
Pai, S	Assessing compartmental programs of tumor-reactive CD8 T cell clones in head and neck cancers	14;**E**
	Longitudinal Monitoring of Cell Free HPV 6/11 DNA in HPV-mediated Recurrent Respiratory Papillomatosis Patients Treated with Pembrolizumab	15
Pickering, C	Treatment with Interferon-beta (IFNB) reduces viability and activates immunologic pathways in HNSCC cell lines	16
Pomahac, B	Machine Learning–Based Quantification of Cellular Density for Objective Rejection Monitoring in Facial Vascularized Composite Allotransplantation	17;**E**

H= Highlighted Abstract Presentation; E= E-Poster

	Targeted Afferent Bypass Of Pathologic Deep Cervical Lymph Nodes: Mechanistic Basis To Guide Lymphatic Bypass And Restore Glymphatic Clearance In Alzheimer's Disease	18
Santos-Sacchi, J	The voltage operating point of real and imaginary complex nonlinear capacitance (cNLC) components diverge at high frequencies.	19
	Conformational Changes Underlying Electromechanical Transduction in Prestin Resemble a Partial Transport Transition in Pendrin	20
	Cryo-EM Structures of Prestin Reveal Compact and Asymmetric States with Ion Binding Similar to Pendrin	21
Stitelman, D	Spatial Transcriptomic Analysis Reveals Epithelial Delay as Mechanism of Pulmonary Hypoplasia in Congenital Diaphragmatic Hernia	22;**E**
	Cross-Species Analysis of Polymeric Nanoparticle Biodistribution *in Utero*	23
Turaga, K	Mass-Based Response Testing in Patients with Peritoneal Surface Malignancies: A Single-Center Pilot Study	24
	Integrated CRISPR and Metabolomic Profiling in Gastrointestinal Peritoneal Metastases	25
	Spatial Transcriptomic Profiling Reveals Compartment-Specific Epithelial-Mesenchymal Divergence in Appendiceal Neoplasms	26;**E**
Woodard, G	Radiographic Tumor Regression as a Predictor for Pathologic Response after Neoadjuvant Therapy for Non-Small Cell Lung Cancer	27
	Differential CEACAM5 Expression in Ground-Glass Opacities Versus Other Lung Cancers	28

Clinical, Outcomes, Health Services

Zhao, H-B	Noise Induced Hidden Hearing Loss is a High-Risk Factor to Influence Alzheimer's Disease Development	29;**E**
	Restoration of Hearing in Cx30 (GJB6) Knockout Mice by Compensation of Cx26 (GJB2) Expression in the Cochlea	30
Aboian, E	Extended Reality Augmented Anatomy Education: Qualitative Analysis of a Collaborative Pilot Study	31
Berger, E	Receipt of Breast Conservation Versus Mastectomy by Breast Cancer Subtype	32
Elefteriades, J	Familial Patterns in Thoracic Aortic Aneurysms and Dissections, Revisited	33
	Novel Aortic Root Measurement Technique Increases Efficacy of Identifying Patients At-Risk for Type A Dissection	34
	Change in Aortic Dimensions at Time of Aortic Dissection: A Multi-Continental Study	35

	Evaluation of radiographic predictors of adverse outcomes in medically managed acute type B aortic dissection patients	36
Haykal, S	Autoimmunity and Cancer-Related Lymphedema Development after Axillary Surgery: A Decade of Outcomes from A Tertiary Cancer Center	37
	Defining Modern Candidate Selection for Lymphaticovenous Bypass: Insights from Two Decades of Published Experience	38
	Predicting Lymphedema Following Cervical Lymph Node Dissection for Head and Neck Cancer: A Decade of Outcomes and Risk Modeling	39
	Clinical Outcomes of Robotic-Assisted Microsurgical Reconstruction	40
	Predicting Lymphedema After Groin Lymph Node Dissection: A Risk Stratification Model from a Decade of Outcomes at a Tertiary Cancer Center	41
Khan, S	Association of Facility Type and Surgical Outcomes in Early-Onset Gastrointestinal Patients	42
Kunstman, J	Frailty in Non-metastatic Pancreatic Ductal Adenocarcinoma and Its Association with Surgical Resection	43
	Frailty and Home Time Loss After Surgical Resection for Patients with Non-Metastatic Pancreatic Cancer	44
Leeds, I	Not All Wounds Are Visible: Association of Sociobehavioral Comorbidities With Outcomes after Major Elective Cancer Operations in a National Veteran Cohort	45;**E**
	Freedom From Want: A Community-Engaged Qualitative Study of Patient -Generated Solutions To Address Sociobehavioral Comorbidities Around Major Surgery	46
	Who Lives, Who Dies, Who Tells Your Story? Comparing Sociobehavioral Comorbidity Detection by Natural Language Processing Versus Structured Bedside Screening in Major Elective Surgery	47
	Actionable Sociobehavioral Comorbidities and Patient Outcomes After Major Elective Surgery	48
Mohan, S	NurseGPT: Evaluating Patient Engagement with a Voice-Enabled AI Assistant in Facial Plastic Surgery	49
	Trends in Pregnancy-Associated Bell's Palsy: A National Claims Database Study	50
Mori, M	Convolutional Long Short-Term Memory to Enhance AI-Based Anatomical Recognition in Robotic Cardiac Surgery	51;**E**
	Trends in Retractions of Peer-Reviewed Surgical Articles	52
	Characterizing Non-Utilization of Suitable Donor Hearts Following 2018 Allocation Changes: A UNOS Analysis	53

Ochoa Chaar, C I	Outcomes of infrainguinal bypass with spliced veins in patients with chronic limb threatening ischemia	54
	PCSK9 Inhibitors are Associated with Improved Amputation-Free Survival After Lower Extremity Revascularization	55
Olino, K	Drivers and patterns of disease progression as a novel schema for risk stratification in metastatic non-small cell lung cancer	56;**H**
Pantel, H	Development of an AI-Powered Platform for Object Detection and Spatial Quantification of Anatomical Structures during Robotic-Assisted Surgery	57;**E**
Pickering, C	Prognostic Impact of Tumor Suppressor and DNA Damage Repair Gene Mutations in Oral Cavity Squamous Cell Carcinoma: A Clinico-Genomic Analysis from a Real-World Database	58;**E**
	Clinicogenomic Determinants of Survival and Immunotherapy Response in Advanced Head and Neck Cancer	59
Pomahac, B	Racial Disparities in Surgical Outcomes after Hernia Repair in 708,654 Patients – A Multi-Institutional Data Analysis	60
	From Inflammation to Fibrosis: The Molecular Basis of Breast Implant Capsular Contracture – A Systematic Review	61
	Frailty Independently Predicts Postoperative Complications After Elective Surgery for Diabetic Foot Ulcers	62
	Cancer-related Lymphedema and Alzheimer's Disease Development after ALND	63
Proussaloglou, E	Patterns of Risk-Reducing Surgery in Genetic Mutation Carriers: A Claims Based Analysis	64
Ramirez, A	The Modern Endocrine Surgery Job Market (2005–2025): Analysis of Hiring Pathways, Practice Composition, and Predictors of Success	65
	Overtreatment of Minimally Invasive Oncocytic Carcinoma Relative to 2025 American Thyroid Association Guidelines	66
	Clinicopathologic and Therapeutic Insights Into Early Recurrence of Widely Invasive Oncocytic Thyroid Carcinoma	67
	Neighborhood Deprivation and Outcomes Following Parathyroidectomy for Uremic Hyperparathyroidism	68
Resio, B	The Prognostic Value of Metastatic Sites in Single-site Synchronous Oligometastatic Non-Small Cell Lung Cancer in the Era of Immunotherapy	69
	Long-term Prognosis of Thymic Neuroendocrine Tumors in the National Cancer Database	70
Strosberg, D	Malnutrition as a Predictive Indicator of Discharge Home after Carotid Revascularization	71

H= Highlighted Abstract Presentation; E= E-Poster

Turaga, K	Associations of Autoimmune Diseases with Appendiceal Cancer in a Population-Based Study	72
	Germline Mutation Profiles in Patients with Peritoneal Surface Malignancies of Appendiceal Origin	73
	Comprehensive Molecular Profiling Predicts Survival Among North American Patients with Mesothelioma	74
Valero, M	Racial and Ethnic Differences in Breast-Conserving Surgery After Neoadjuvant Chemotherapy for HER2-Positive and Triple-Negative Breast Cancer	75
Vallabhajosyula, P	Association between Genetic Variants of Unknown Significance for Thoracic Aortic Disease and Outcomes Following Aortic Surgery.	76
	Left Ventricular remodeling following zone 0 thoracic endovascular aortic repair versus ascending hemiarch replacement for ascending thoracic aortic aneurysm	77
Woodard, G	Predicting response to neoadjuvant tyrosine kinase inhibitors (TKI): a trial meta-analysis	78
Zhou, R	Postoperative Outcomes of Ventral Hernia Repair in Patients With Heart Failure: A Multicenter Analysis	79
	Prehabilitation and Postoperative Outcomes After Ventral Hernia Repair: A Multicenter Registry Study	80

Quality Improvement

Aboian, E	Utility of abdominal aortic aneurysm detection software for quality improvement at a tertiary referral center.	81
Bonde, P	Stopping Reflux Induced Aspiration Injury by Neuromodulation	82
Lee, M	Successful Manuscript Publication of Southern Thoracic Surgical Association Annual Meeting Abstracts	83
	Gender Analysis of The Southern Thoracic Surgical Association Annual Meeting Presentations Achieving Manuscript Publication	84
Maerz, L	Standardizing Cervical Collar Management with a Care Signature Pathway	85
Ochoa Chaar, C I	Validation and Establishment of the Contrast Volume Prediction Model: **F**or **O**ptimizing **R**enal **E**fficiency in **EVAR** (the FORE-EVAR calculator)	86;**H**
Turaga, K	Bridging the Gap: Integrating Undergraduate Talent in Surgical Clinical Trials	87

YALE SURGERY RESEARCH DAY 2026

BASIC SCIENCE ABSTRACTS

Machine Learning-Guided Classification of Spatial Histological Domains in the Thoracic Aorta

Fenske S., Chou A., Lieu D., Araujo G., Tellides G., Chung H., Assi R.

Introduction:
Catastrophic failure of the thoracic aorta during aortic dissection or rupture can lead to bleeding, stroke, visceral malperfusion, or death. Under current clinical guidelines, aortic diameter, growth rate, and heritable aortopathies are used to identify patients that may benefit from prophylactic surgical replacement of the ascending aorta. Histopathology of resected aortic aneurysms frequently identifies regions of myxoid degeneration but lacks precision in describing a disease process that exists along a continuum. As a result, there is limited understanding of progressive aortic remodeling during medial damage and repair processes that predispose or protect the aorta from structural failure.

Methods:
Ascending aortic specimens were collected from 182 subjects (129 surgical patients, 53 donors) and representative sections were formalin-fixed and paraffin-embedded. Movat's pentachrome stain was performed on 614 slides from the aortic root and proximal, mid, and distal ascending aorta. Digitally scanned slides were segmented and tiled into non-overlapping 256x256 pixel (65x65 μm) patches. Patch features were extracted using foundational vision models trained on diverse histology images, followed by spatial graph-based message passing to incorporate neighboring context. K-means clustering defined distinct spatial domains across the dataset. Domain abundance was calculated as the patch ratio per slide correlated with clinical features using linear models adjusted for covariates.

Results:
Propagating neighborhood information from message passing leads to improved, more biologically plausible, spatial aggregation of domains. Spatial domains show distinct qualitative and quantitative characteristics, illustrated by differing composition of stain components (ex. increased/decreased collagen/elastin stain intensity) and observation of varying elastin fragmentation. The abundance of specific spatial domains shows significant correlation with both age and dilation, potentially pointing to the presence of patterns associated with damage or repair.

Conclusion:
Preliminary results support the use of foundational models to extract spatial domains from thoracic aortic histology. Quantitative changes in domain abundance supports subtle architectural changes underlying age and dilation-related changes. Further work seeks to incorporate complementary Sirius Red and H&E stains to build multi-stain spatial domain models and leverage paired biomechanical testing and next-generation sequencing to relate spatial domain patterns from histology to more underlying, targetable mechanisms

Progressive increase in axial stiffness of prosthetic aortic grafts results in elongation of the residual ascending aortic segment

Chou, Alan, Zaky, Mina, Lieu, Dustin, Tellides, George, Assi, Roland

Introduction:
Elongation of the residual ascending aorta after aortic replacement has been anecdotally reported. Here, we evaluate the biomechanical consequences of prosthetic graft replacement on the remaining distal ascending aorta.

Methods:
Non-dilated aortic tissue, aneurysmal aortic tissue, pre-implant prosthetic graft, and explanted post-implant graft were collected from organ donors and non-consecutive subjects undergoing primary or redo aortic replacement from August 2023 to July 2024. Biomechanical testing was performed using a custom, computer-controlled planar biaxial device with equibiaxial and strip uniaxial protocols to global stretches of 1.6. Serial CTAs were used to measure changes in pre-operative and post-operative aortic dimensions of 20 patients who underwent ascending and hemiarch replacement in 2021 and 2022. Pre-operative length was measured from aortic annulus to innominate artery; post-operative length measured from distal suture line to innominate artery.

Results:
A total of 24 specimens were tested, of which 6 were nondilated aorta, 11 were aneurysmal aorta, 5 were pre-implant graft material, and 2 were post-implant graft material (in place for 6 and 11 years). Gross and histological examination of post-implant graft material demonstrated fibrous tissue with dense collagen fibers lining prosthetic material oriented both circumferentially and axially.Circumferential and axial stress increased significantly in aneurysmal aortas. Pre-implant graft material was far stiffer than aneurysmal tissue in circumferential direction but not in the axial direction. However, in post-implant graft samples, circumferential and axial stiffness increased, with greater effect in the axial direction. Comparison of pre-operative and post-operative aortic dimensions demonstrated that the rate of elongation of the residual aortic tissue was significantly increased post-operatively (15.4%±14.4 vs. 1.7%±2.3, p=0.0006), while the rate of diameter change was not significantly different (1.0%±4.2 vs. -0.2±2.5, p=0.29).

Conclusion:
While the biomechanical properties of prosthetic grafts have been previously measured, a dramatic increase in axial stiffness after implantation is a novel finding. Increased axial stiffness appears to result in an accelerated rate of lengthening of the residual distal aorta. This may trigger progressive degeneration of the residual aorta and again highlights the need for biomechanically compatible prosthetic grafts.

Decreased Cell Density in the Aortic Media Predicts Increased Resistance to Ex Vivo Aortic Dissection

Wang, M, Kristina, Chou, Alan, Lieu, Dustin, Zaky, Mina, Tellides, George, Assi, Roland

Introduction:
Aortic dissection is a catastrophic cardiovascular emergency with high mortality. Identifying structural and cellular factors beyond aortic size may help explain susceptibility and guide prevention. Our objective here is to determine histological and clinical factors associated with resistance to aortic dissection.

Methods:
An ex vivo method to investigate vulnerability to aortic dissection was performed on 83 aorta specimens from patients who underwent aortic replacement or organ donation. Fluid was injected into specimens via a small needle, and the hydraulic pressure required for dissection of the media was measured. Histological analysis was performed to quantify media size (thickness and area), extracellular matrix (elastin and collagen fraction) and cellularity (nuclei density). Correlation and comparative analyses were performed to determine if any histological and clinical factors correlated with resistance to dissection.

Results:
Ex vivo testing revealed varying susceptibility to dissection of the aortic media. Medial area and cellularity were significantly associated with resistance to dissection ($p=0.010$ and $p=0.005$), while medial elastin and collagen fraction were not ($p=0.239$ and $p=0.073$). Multivariable regression analysis showed that cellularity remained significantly associated with resistance to dissection after adjusting for sex, race, age and aortic diameter ($p=0.014$). Patients with hyperlipidemia and diabetes mellitus showed significantly lower median cellularity relative to normolipidemic ($p=0.024$) and non-diabetic ($p=0.007$) subjects. Patients with hypertension had significantly lower cellularity and increased collagen fraction within the inner third of the aortic media ($p=0.008$ and $p=0.014$).

Conclusion:
Decreased cellularity and cross-sectional area of the aortic media are associated with increased resistance to dissection in an ex vivo human aortic dissection model. Hyperlipidemia, diabetes and hypertension may induce remodeling of the aortic media, particularly in its inner third, to confer relative resilience of the aorta to dissection.

Development of a transcatheter, expandabletoroidal blood pump for pulmonary support

Paul Ayodele, Sodiq Ajose, Guruprasad A. Giridharan, Rigu Gupta, Pramod Bonde

Introduction:
Right ventricular failure occurs in a significant portion of the heart failure population. Pumps for pulmonary sided support have different requirements than systemic pumps - it needs to generate high flow rates and a lower pressure head. And hence traditional LVADs don't work well to support right sided circulation.

Methods:
To fulfill the unmet clinical need, we are developing a novel approach that utilizes an expandable pump and cage design that can be implanted using transcathter techniques through a 14 Fr sheath. The device can be implanted through jugular vein or femoral vein access. The pump is designed to be non-obstructive and has toroidal impellers that are collapsible during delivery. The impellers spring open when rotating to provide high flow and pressure heads. The performance of the impeller was characterized in a static mock loop from 3000-6500 RPM.

Results:
Preliminary data with the toroidal impeller demonstrated ability to generate >10 L/min against 15 mmHg pressure head , making it ideal for pulmonary support. The toroidal impeller did not cause significant pressure drop (<2 mmHg at 5 L/min) when the pump stopped.

Conclusion:
These results demonstrate the feasibility of a toroidal impeller to generate lower pressure heads and high flow rates. These characteristics make this design ideal for pulmonary support as well as intra-aortic support for cardiorenal syndrome using femoral access. The pump is non-obstructive and has the potential to be powered wirelessly.

Physiologic control of rotary blood pumps by ventricular chamber size estimation using resonantly coupled sensors

Guruprasad A. Giridharan, Rigu Gupta, Pramod Bonde

Introduction:
Rotary blood pumps (RBP) currently operate at a fixed pump speed and are unable to meet physiologic demand and susceptible to ventricular suction. To overcome this limitation, we developed a left ventricular end-diastolic volume (EDV) based physiologic control algorithm using resonantly coupled high-efficiency sensors.

Methods:
The resonantly coupled sensors consist of apical and outflow sensors that can accurately assess the ventricular chamber size with minimal long-term drift (~1 %) at 9 months. The ability of the control algorithm was evaluated using an in-silico circulatory system model coupled to an axial or centrifugal flow RBP with 15 % uniformly distributed measurement noise.

Results:
The EDV setpoint was set to 85 ml, and the efficacy of the EDV control algorithm was evaluated and compared to maintaining a constant pump speed during (1) rest and exercise; (2) rapid, eight-fold augmentation of pulmonary vascular resistance; and (3) rapid transitions between rest and exercise. Safety and robustness of the algorithm was also evaluated by assuming a 6 % volume drift. The EDV control algorithm provided sufficient physiological perfusion and avoided ventricular suction in all cases.

Conclusion:
Performance of the EDV algorithm was superior compared to maintaining constant pump speed for both types of RBP, demonstrating pump independence of the proposed algorithm

Phosphodiesterase 10A regulates medial arterial calcification through p38/MAPK-MMP3 signaling

Jin Y, Xie Y, Berezowitz AG, Davis S, Flores AM, WangX, Guzman RJ, Cai Y

Introduction:
Vascular calcification is a significant factor contributing to the high incidence and elevated mortality rate of cardiovascular diseases.Patients with chronic kidney disease (CKD), diabetes, and peripheral artery disease (PAD) are particularly prone to vascular calcification.Phosphodiesterase (PDE) 10A is a key regulator of the cyclic nucleotides cAMP and cGMP, andpivotalin a variety of cardiovascular events. However, the role of PDE10A involved in the medial artery calcification remains unclear.

Methods:
High phosphate media were used to induce calcification in vascular smooth muscle cells (VSMCs). Besides, qRT-PCR, immunohistology staining and immunofluorescent staining were applied to evaluate the PDE10A expression level. Von kossa staining and calcium assay were performed to assess the calcification level. Moreover, two types of in vivo rodent calcification models, vitamin D3 injection and 5/6 nephrectomy, were established to evaluate medial calcification.

Results:
PDE10A was the most highly induced isoform in the rodent model of arterial calcification. The expression level of PDE10A was increased in calcifying VSMCs in vitro, calcified arteries from rodents with CKD, and calcified human tibial arteries. PDE10A knockdown or inhibition significantly attenuated VSMC osteogenic transformation and calcification in vivo and in vitro. Furthermore, PDE10A deficiency significantly decreased arterial calcification in ex vivo aortic ring, in vivo vitamin D3 medial calcification models and in vivo 5/6 nephrectomy-induced calcification models. In addition, PDE10A regulated matrix metallopeptidases-3 (MMP-3) expression in calcifying VSMCs and could regulate vascular calcification by controllingp38 MAPK signaling and MMP-3 activity through cGMP/PKG signaling.

Conclusion:
PDE10A is critical in the development of medial artery calcification through biased activated p38 MAPK-MMP3 signaling. Our findings suggest that targeting PDE10A should offer therapeutic benefits for patients with PAD and CKD to reduce calcification, and ultimately decrease major limb amputation risks.

Matrix metalloproteinase-3 promotes arteriovenous fistula neointimal hyperplasia by regulating FAK-AKT signaling

Xie Y., Zhang W., Thaxton C., Jin Y., Yatsula B., Bai H., Davis S., Exsted T., Dardik A., Guzman R., Cai Y.

Introduction:
Surgically created upper extremity arteriovenous fistulae (AVF) are the preferred vascular access for patients requiring dialysis. It is estimated, however, that approximately 50% of AVF fail within one year due to aggressive neointimal hyperplasia, which significantly increases morbidity and mortality. Matrix metalloproteinase-3 (MMP-3), also known as stromelysin-1, is a member of the metalloproteinase family that plays a critical role in the pathogenesis of many human disorders by degrading extracellular matrix and regulating molecular signaling pathways. The role of MMP-3 in AVF neointimal failure has not been explored.

Methods:
Using cultured venous SMCs, human AVF specimens, global and SMC-specific MMP-3 knockout mice, and a CKD-AVF model with local pharmacological inhibition, we comprehensively examined the role of MMP-3 in AVF remodeling.

Results:
We observed that MMP-3 was induced in a time-dependent fashion by fetal bovine serum and the growth factor PDGF-BB in cultured venous SMCs. MMP-3 was also highly expressed in the neointimal SMCs of the outflow veins and the juxta-anastomotic area in an AVF mouse model, as well as in human AVF specimens. Knockdown of MMP-3 significantly suppressed venous SMC proliferation, whereas overexpression of MMP-3 facilitated cell growth in vitro. Importantly, deficiency of global and SMC-specific MMP-3 significantly reduced neointimal hyperplasia in the outflow veins and juxta-anastomotic area and improved AVF patency. Furthermore, local application of an MMP-3 inhibitor markedly suppressed AVF neointimal hyperplasia and increased AVF patency in mice with chronic kidney disease (CKD).

Conclusion:
These data suggest that MMP-3 is a key mediator of AVF neointimal failure. Targeting local MMP-3 activity may be a novel therapeutic strategy to prevent AVF neointimal failure and improve outcomes in patients requiring hemodialysis.

pH-targeted delivery of microtubule inhibitor in pediatric solid tumors

Rehman SU, Kim A, Basu S, Sundaram RK, Gayle S, Paralkar V, Christison-Lagay ER, Vasquez JC

Introduction:
With little progress over the last three decades in improving the survival curves of patients with pediatric solid tumors, there is a pressing need for novel therapies. Due to the Warburg effect, a metabolic shift that is common to all cancers, tumors have an acidic microenvironment that can be selectively targeted using pH-Low Insertion Peptides (pHLIPs). pHLIPs can be attached to a payload of interest, such as a chemotherapeutic agent. In the acidic tumor microenvironment, pHLIPs form an alpha helix that allows for directional insertion into the cell membrane and subsequent drug delivery. CBX-15 is a pHLIP conjugated to Monomethyl auristatin E (MMAE), a potent inhibitor of microtubule polymerization that is too toxic to administer as a free drug without a targeted delivery mechanism. As a result of pH-targeted delivery, CBX-15 selectively delivers MMAE to tumors in an antigen agnostic manner. Here, we evaluated the preclinical activity of MMAE and CBX15 in neuroblastoma (NB), Ewing's sarcoma (ES), and rhabdomyosarcoma (RMS).

Methods:
We tested MMAE sensitivity in ES (A673, SKNMC, TC71, TC32), NB (SKNAS, SKNDZ, CHP 212, SKNBE (2), IMR-32) and RMS (RH28, RH30, RH41, RD) by performing in vitro cell viability assays using serial dilutions of free MMAE to determine half-maximal inhibitory concentration (IC50) values. The cell lines selected are representative of N-Myc high vs low (NB), PAX3/7-FOXO1 fusion positive vs negative (RMS), and STAG2/TP53 mutated subtypes (ES). Orthotopic murine models were created by injecting RD (RMS) into the hind legs of mice. Treatment with CBX-15 (20 mg/kg) or vehicle was given via intraperitoneal injection on a 2-days-on/5-days-off schedule for three cycles. Tumor volumes were measured twice weekly. Study endpoints included tumor size (> 2000 mm^3) or ≥20% weight loss. Kaplan-Meier curves were analyzed using the Mantel-Cox test and a simple unpaired t-test was used to analyze mouse body weight mean fold change from baseline.

Results:
The IC50 of MMAE was in the low nanomolar concentration across all cell lines and tumor types indicating broad sensitivity. In an in vivo RMS model (RD), CBX-15 abrogated tumor growth and prolonged survival compared to control (median survival 42 vs 78 days $p < 0.005$). Of note, one mouse treated with CBX15 continued to show a complete response to treatment at study termination on day 111. CBX-15 was well tolerated with no significant change in weight after 3 cycles ($p = 0.9755$).

Conclusion:
CBX-15 leverages the acidity of the tumor microenvironment for targeted delivery of MMAE in an antigen agnostic manner that is both effective and well tolerated, significantly expanding the population of patients that could benefit. Our findings warrant further preclinical development and carry potential for clinical translation in pediatric solid tumors.

Targeted pH sensitive peptide-exatecan conjugate demonstrates efficacy in a relapsed topoisomerase I inhibitor resistant model of pediatric rhabdomyosarcoma

Rehman SU, Kim A, Hu E, Rivera Carrasquillo P, Bhatt D, Basu S, Sundaram RK, Gayle S, Paralkar V, Christison-Lagay ER, Vasquez JC

Introduction:
Outcomes for children with relapsed and refractory rhabdomyosarcoma (RMS) remain poor, highlighting the need for novel therapies. Irinotecan, a topoisomerase I inhibitor (TOP1i), is a component of salvage therapy for pediatric RMS but resistance rapidly develops through mechanisms including upregulation of the P-glycoprotein (P-gp) drug efflux transporter. Exatecan, a potent TOP1i, is not a substrate of the P-gp transporter but cannot be given as a free drug. pH-Low Insertion Peptides (pHLIPs) can incorporate into the cell membrane at low pH and when conjugated to a drug of choice, can selectively deliver their cargo under acidic conditions. CBX-12, a pHLIP-exatecan conjugate, allows for targeted delivery of exatecan to tumor cells. In a completed Phase I study in adults with advanced solid tumors, CBX-12 was well tolerated with manageable myelosuppression and demonstrated single-agent activity. Here, we report the preclinical efficacy of CBX-12 in RMS, including in a TOP1i resistant model.

Methods:
In vitro cell viability assays were performed using serial dilutions of free exatecan, SN-38 (the active metabolite of irinotecan), and topotecan to determine IC50 values in RMS cell lines: RH28, RH30, RH41, RD. Orthotopic murine models were generated via injection of tumor cells into the gastrocnemius muscle. We used both cell-derived xenografts (CDX) and patient-derived xenograft (PDX) models, the latter obtained from the St. Jude Childhood Solid Tumor Network. Mice were treated with intraperitoneal injections of CBX-12 (20 mg/kg) or vehicle on a 4-days-on/3-days-off schedule for three cycles. A modified CBX-12 dosing regimen limited to 2 cycles was also compared to the established protracted schedule of 1.25 mg/kg irinotecan on a 5-days-on/2-days-off for 2 cycles. Study endpoints included tumor size (> 2000 mm^3) or ≥20% weight loss. Overall survival was analyzed using the Kaplan-Meier method, and treatment groups were compared using the log-rank test.

Results:
Exatecan was 5 to 30 times more potent than SN38 and 20 to 300 times more potent than topotecan in our in vitro models. Across multiple CDX and PDX RMS models, CBX12 resulted in complete tumor regression and improved progression free survival. Free exatecan alone was not tolerated due to profound diarrhea and weight loss. In SJRHB012_Y, a PDX model derived from a patient whose disease progressed on salvage therapy including multiple rounds of irinotecan, we observed a significantly prolonged median survival with CBX-12 but not irinotecan (47 vs. 8 days, $p < 0.005$). No significant treatment-associated weight loss was observed.

Conclusion:
CBX-12 is effective in multiple RMS models, including a relapsed TOP1 resistant PDX. These data support the development of a Phase I/II clinical trial for patients with RMS.

Novel functional and single nuclear transcriptomic analysis of an acellular extracellular matrix for growth-adaptive tricuspid valve replacements in sheep

Anita Ghodsi, Zachary Pickell*, Sam Raredon, Eva Luna, Ryland Mortlock, Micah Wolfsohn, and Peter J. Gruber (*equal contributions)*

Introduction:
Congenital heart disease (CHD) is the leading cause of mortality among children. While many defects are repaired with a single surgery or transcatheter intervention, valvular CHD is more complex and often requires multiple reoperations due to the lack of vale tissue growth. Acellular extracellular matrix (ECM) scaffolds, including porcine-derived small intestinal submucosa ECM (SIS-ECM), have emerged as promising biologic materials for regenerative valve replacement. Although SIS-ECM patches have demonstrated success in vascular and reconstructive applications, outcomes following tricuspid valve replacement (TVR) have been inconsistent Mechanistic understanding of SIS-ECM valvular remodeling remains limited, and no prior studies have performed genomic sequencing to characterize the molecular processes underlying successful scaffold integration.

Methods:
TVR was performed in sheep via lateral thoracotomy under cardiopulmonary bypass using a porcine-derived SIS-ECM scaffold (Cormatrix Tricuspid Valve). Transthoracic echocardiography (TTE) was conducted at baseline, immediately post-operatively, and at termination timepoints (3, 4, 5, and 10 months), with additional 3-month interval imaging for long-term cohorts. Harvested tissues were paraffin-embedded, sectioned, and stained with hematoxylin and eosin, Movat's Pentachrome, Von Kossa, and CD31. Single-nuclei isolation and RNA sequencing were performed to evaluate cellular populations and transcriptional dynamics over time.

Results:
Serial TTE demonstrated preserved cardiac function and normal valve morphology at both early and late timepoints. Color Doppler imaging showed unobstructed flow, no tricuspid regurgitation, and excellent leaflet coaptation. The SIS-ECM scaffold remained well seated, thin, and pliable throughout follow-up. Gross and histologic imaging and analysis demonstrated an overall reduction of inflammatory cells, maturation of the endothelial layer and organization of collagen layers. Single-nuclei RNA sequencing revealed cellular remodeling of valve endothelial cells which demonstrated a progressive shift along an EMT gradient, with increasing mesenchymal signaling and cell density over time. Valve interstitial cells exhibited coordinated phenotypic transition toward mesenchymal states.

Conclusion:
This study provides the first comprehensive functional, histologic, and genomic characterization of SIS-ECM tricuspid valve remodeling in a large animal model. SIS-ECM TVR maintained durable valve function while undergoing dynamic, coordinated cellular transitions marked by epithelial-to-mesenchymal progression. These findings establish foundational mechanistic insight into the biological process of SIS-ECM valvular cellularization and support continued investigation of growth-adaptive biologic valve replacements.

Emerging Roles of Stem Cell–Derived Exosomes in Regenerative +E2:K5Wound Healing

Hiren Parekh, Henry Hsia

Introduction:
Chronic wounds pose major clinical and economic burdens, and current therapies remain largely palliative. Exosomes, nanoscale vesicles released by stem cells and other cell types, have emerged as promising, cell-free mediators of tissue repair. This scoping review synthesizes current evidence on exosome biology, cargo composition, mechanisms of action, delivery strategies, and translational challenges in regenerative wound healing.

Methods:
A scoping review framework was used to map the breadth of literature on exosome-mediated wound repair. Peer-reviewed studies describing exosome sources, molecular cargo, signaling pathways, delivery platforms, manufacturing challenges, or translational applications in cutaneous wound healing were identified and synthesized. Emphasis was placed on mechanistic insights, biomaterial-based delivery strategies, and emerging technologies in exosome engineering.

Results:
Exosomes regulate multiple stages of wound repair, including inflammation, angiogenesis, fibroblast activation, re-epithelialization, and extracellular-matrix remodeling, via cargo such as miRNAs, lncRNAs, circRNAs, proteins, and lipids. These molecules modulate pathways including TGF-β/Smad, ERK/MAPK, and PI3K/AKT. Stem-cell-derived exosomes, particularly those from mesenchymal and induced pluripotent stem cells, exhibit robust paracrine effects without the risks of cellular transplantation. Delivery strategies such as hydrogels, scaffolds, microspheres, and bioprinting improve exosome retention and bioavailability. Key challenges include variation in isolation methods, batch-to-batch heterogeneity, and scalability. Advances in microfluidics, bioreactor culture, and stimuli-responsive hydrogel-based smart bandages offer potential solutions.

Conclusion:
Exosomes represent a next-generation platform for personalized, cell-free wound therapies, with strong mechanistic and preclinical evidence supporting their regenerative potential. However, standardized manufacturing, optimized delivery systems, and rigorous clinical validation are needed before widespread clinical translation is feasible.

Integrated Spatial Transcriptomics, Tissue Microarray and Longitudinal Microbiome Profiling to Unravel Sex-Specific Asparagine Metabolism in Late-Stage Colorectal Cancer

Akpinaroglu C, Khan SA.

Introduction:
Colorectal cancer (CRC) prognosis can differ significantly by sex, potentially driven by the interplay between estrogen signaling (GPER1) and asparagine synthetase (ASNS) expression under nutrient stress. While the gut microbiome is known to modulate systemic metabolism, its specific role in affecting tumor asparagine availability and therapeutic resistance in CRC had not been evaluated in a large cohort clinical study. We propose a multi-omic study to characterize these mechanisms over a very large cohort.

Methods:
We established two parallel cohorts at Yale New Haven Health System and Bridgeport Hospital using EPIC database.Prospective Cohort: Treatment-naive CRC patients consenting to longitudinal sample donation. We collect paired stool samples (preoperatively and postoperatively) alongside tumor tissue collected intraoperatively to assess shifts in the microbiome and stool content. Microbial DNA undergoes Whole Genome Sequencing (WGS) for high-resolution bacterial identification while mass spectrometric (MS) analysis identifies biomolecules in the stool content. Enrolled patients are compensated for each donation.
Retrospective Cohort: A contemporary database of stage III/IV CRC patients was curated to ensure high-fidelity clinical annotation details such as: mutations including KRAS/BRAF/MSI status, recurrence intervals, BMI, metastasis and chemo/radiotherapeutic history. FFPE primary tumors, matched liver metastases and matched normal tissues are utilized to construct Tissue Microarrays (TMAs). These undergo Visium HD spatial transcriptomics to map not only ASNS/GPER1 expression within the tumor microenvironment, but also the whole genome transcriptome, with global RNA sequencing for broader discovery power. Additionally, IHC is used on TMA slides in parallel with spatial for proteins of interest.

Results:
To date, we have successfully accrued 300 patients into the retrospective biobank with extensive clinical annotation including mutations, and metastatic measurements. Clinical and pathologic confounders such as hormonal variables due to use of oral contraceptives, bilateral salpingo-oophorectomy or menopausal status are considered along with grade and histology of tumors. The prospective arm has obtained 81 stool samples successfully collected and banked for sequencing. 118 normal and 72 tumor tissues were collected after surgery and fresh frozen.

Conclusion:
This study represents one of the largest paired spatial-microbiome cohorts in CRC. By correlating specific microbial taxa with tumor asparagine levels and spatial heterogeneity, we aim to identify novel, sex-specific therapeutic targets and stratify patients for precision interventions in CRC and also uncover preventive care for early-stage patients that facilitate better prognosis.

From Bench to Computational Modeling: Integrating Mitochondrial Stress Data from a Rat Hepatic Ischemia-Reperfusion Injury Model into a Preclinical and Human Quantitative Systems Toxicology Platform

Kim J, Beaudoin JJ, Hong SK, Zielonka J.

Introduction:
Hepatic ischemia-reperfusion injury (IRI) is a key driver of liver dysfunction after surgery and transplantation, involving intricate mitochondrial, oxidative, and inflammatory mechanisms. Quantitative systems toxicology (QST) modeling provides a powerful framework to integrate mechanistic experimental data, simulate injury dynamics, and evaluate biomarkers and therapeutic strategies in IRI.

Methods:
Hepatic mitochondria were isolated from sham- and IRI-treated rats (n=5/group, 1 h ischemia + 1 h reperfusion), after which mitochondrial respiration was assessed via extracellular flux analysis. Sequential addition of substrates (pyruvate/malate, succinate/rotenone, or NADH) and modulators (oligomycin, FCCP, rotenone, antimycin A) allowed evaluation of electron transport chain (ETC) function. Cytochrome c addition assessed outer membrane integrity, while alamethicin was used to permeabilize the inner membrane for NADH delivery to mitochondrial complex I. DPI and azide were used to inhibit complexes I and IV, respectively. A QST model of preclinical and human liver biochemistry (DILIsym®) was used to explore mechanistic hypotheses in hepatic IRI based on the obtained experimental data.

Results:
In the IRI group, pyruvate/malate-induced oxygen consumption rate (OCR) was reduced to 40%, indicating impairment in the TCA cycle or complex I. Succinate/rotenone treatment yielded similar OCR between groups, suggesting intact complex II and downstream ETC function. NADH-driven respiration was preserved in IRI, indicating functional complex I and implicating TCA cycle dysfunction upon IRI. These and additional biomarker data were used to estimate a parameterization of hepatic IRI in DILIsym®, which reproduced peak aminotransferase levels observed in IRI rats and generated human aminotransferase time-courses consistent with historical post-ischemia patterns following 60 minutes of liver ischemia. The calibrated human simulation further predicted peak aspartate aminotransferase values on the order of 3,000 U/L at this ischemia duration, aligning with commonly used clinical thresholds associated with severe early graft dysfunction and consideration of emergent re-transplantation.

Conclusion:
Subcellular bioenergetic data from animal models of hepatic IRI offer mechanistic insights that can be leveraged in QST modeling to inform human translation. This integrative approach serves as a bridge between preclinical findings and clinical trial design, supporting hypothesis generation while helping to reduce reliance on further animal experimentation.

Assessing compartmental programs of tumor-reactive CD8 T cell clones in head and neck cancers

Hsin-Fang (Ruby) Tu, Michaela Nichols, Eric Schneider, Benjamin Judson, Saral Mehra, Suresh Mohan, Ansley Roche, Zafar Sayed, Avanti Verma, Christopher Garris, Nikhil Joshi, Thorsten Mempel, Mikael Pittet, Chin Siang Ong, Sara Isabel Pai

Introduction:
Antitumor immune responses are coordinated across tumor and draining lymph nodes, where T-cell priming, activation, and regulation occur in anatomically distinct but interconnected spatial niches. A recent study identified CCR7$^+$ DCs as key organizers of anti-tumor immunity involved in antigen presentation and regulation. We sought to define the relationship between CCR7$^+$ DC niches and tumor-specific CD8 T-cell clones, and whether tumor-involved nodes disrupt these interactions.

Methods:
We analyzed 788,945 cells from 26 head and neck cancer patients (HPV+ and HPV-) using single-cell RNA-seq with paired T cell receptor sequencing (TCR-seq) from 61 matched tissue samples (tumor, draining lymph nodes (LN), and tumor-involved draining nodes (tLN)). Cells were annotated by canonical markers, and CD8 T cells were reclustered into four states. High-confidence paired TCRα/β chains were reconstructed. Clonotypes were ranked by abundance and categorized into TCR expansion groups: Single (1), Small (2-5), Expanded (6-20), and Hyperexpanded (>20) cells. Shared TCRs were classified across compartments, and functional states were compared. Associations between CCR7$^+$ dendritic cells abundance and CD8 T-cell clonal expansion were then assessed within the tissue compartments across patients.

Results:
Integrated single-cell RNA-seq with paired TCR-seq revealed comparable immune cell populations across tumors and lymph nodes, with marked compartment-specific clonal architecture. Tumor exhibited the strongest TCR clonal skewing, with expanded and hyperexpanded CD8 clonotypes enriched in exhausted states. LNs were largely polyclonal, while tLNs showed intermediate clonal expansion. Across patients, tumor-shared clonotypes were more frequently detected in tLN rather than in LNs, suggesting a dissemination bias toward tumor-involved lymph node tissue. Functional comparison of tumor-shared clonotypes indicated compartment-associated differences: clonotypes shared between tumor and tLN were enriched for exhaustion phenotype (4/5) relative to those shared between tumor and LN, indicating preferential enrichment of dysfunctional tumor-reactive populations within tLN. CCR7$^+$ migratory dendritic cell abundance was positively associated with expanded and hyperexpanded CD8 clonotypes within tumors (Pearson $r = 0.51$, $P = 0.008$), with a stronger association observed in HPV16$^+$ tumors (Pearson $r = 0.77$, $P = 0.01$).

Conclusion:
Tumor-reactive CD8 T cell clones are identified across matched tumors and lymph nodes compartments in head and neck cancers. Tumor-involved lymph nodes harbored a more exhaustive functional state of tumor-specific CD8+ TCR clones. Our findings suggest an important crosstalk network exists amongst anti-tumor T cells which spans regional anatomic compartments within the head and neck.

Longitudinal Monitoring of Cell Free HPV 6/11 DNA in HPV-mediated Recurrent Respiratory Papillomatosis Patients Treated with Pembrolizumab

O'Halloran, Hannah; Mattox, Austin; Nicholas, Michaela; Tu, Ruby; Kashuba, Lindsay; Kohli, Nikita; Young, Nwanmegha; Lerner, Nwanmegha; Pai, Sara

Introduction:
Recurrent respiratory papillomatosis (RRP) is a disease characterized by chronic infection by low-risk human papilloma virus (HPV) subtypes 6 and 11, resulting in the growth of obstructive papillomas within the respiratory tract. We completed an investigator-initiated clinical trial administering a PD-1 inhibitor, pembrolizumab, to patients diagnosed with RRP. We report on the development of a novel cell free HPV DNA assay to monitor disease burden.

Methods:
21 patients diagnosed with RRP were treated with pembrolizumab for up to 2 years. Serial blood samples were collected from patients diagnosed with RRP treated with pembrolizumab at baseline and every 12 weeks. Plasma and sera were isolated and stored at -80ºC. Cell free DNA (cfDNA) was extracted from 4 mL of plasma and 1 mL of serum using MagMAX™ Cell-Free DNA Isolation Kit (Applied Biosystems). Primers and probes were custom designed to detect HPV 6 and 11 cfDNA. CfDNA of HPV subtypes 6 and 11 was detected and quantified using digital droplet PCR (ddPCR). Appropriate negative and positive controls were included in each assay.

Results:
cfDNA was identified in 21 of the 24 analyzed plasma samples and 15 of 16 analyzed serum samples. Quantification of cfDNA in these serial samples suggests a decrease in cfDNA levels following pembrolizumab treatment.

Conclusion:
We report for the first time a novel liquid biopsy assay for the detection of HPV 6/11 DNA in the blood of patients chronically infected with HPV. Our findings support the feasibility of detecting and quantifying cfHPV DNA in RRP patients treated with systemic therapy and suggest potential utility as a biomarker of treatment response.

Treatment with Interferon-beta (IFNB) reduces viability and activates immunologic pathways in HNSCC cell lines

Parisa Abedi; Alejandro Kochen; Curtis Pickering.

Introduction:
Type I interferons exhibit dual anti-tumor activity by directly targeting cancer cells and modulating the tumor microenvironment, inducing apoptosis, reducing proliferation, and promoting inflammatory cytokine secretion. STAT1, activated by IFN-beta, triggers proapoptotic proteins and caspase-mediated cell death, while also regulating immunogenic cell death through enhanced antigen presentation and secretion of T-cell and dendritic cell recruiting cytokines like CXCL10. Type I interferon also drives STAT1-dependent cell cycle arrest via CDK inhibitor upregulation. However, integration of these apoptotic, immunogenic, and cell cycle pathways in epithelial cancer cells remains poorly understood.

Methods:
Human (HN31, HN5, SCC6) and murine (MOC1, MOC2) HNSCC cell lines were treated with recombinant IFN-beta (0-1000 U/ml) for 24-72 hours. Cell viability was assessed by CTG assays, IFN pathway activation by western blotting (pSTAT1, MX1), cytokine secretion by ELISA, and long-term proliferation by clonogenic assays.

Results:
IFN-beta consistently reduced viability across models. At 72 hours, human cell lines showed 30-40% viability reduction; murine lines showed 30% (MOC1) and 10% (MOC2) decreases. Western blotting confirmed robust STAT1 activation with increased pSTAT1 and MX1 across doses and timepoints. Cytokine induction reflected inflammatory pathway activation. Clonogenic assays revealed sustained growth suppression beyond acute viability changes.

Conclusion:
IFN-beta generates consistent anti-tumor effects in HNSCC through multiple mechanisms. Viability reduction aligns with known cytotoxic/cytostatic properties of type I interferons. STAT1 pathway activation (pSTAT1, MX1 induction) supports transcriptional regulation of apoptosis and cell-cycle arrest. Concurrent inflammatory cytokine induction indicates STAT1-driven immunogenic responses linked to antigen presentation and immune recruitment. Clonogenic assay results demonstrate durable proliferative suppression extending beyond acute effects. These findings suggest IFN-beta affects three compartments—apoptotic, immunogenic, and cell cycle arrest—though their hierarchical relationship remains unclear. Further studies should elucidate how STAT1-dependent transcription, cytokine signaling, and cell-cycle regulation integrate to generate anti-tumor responses and identify therapeutic targeting opportunities.

Machine Learning–Based Quantification of Cellular Density for Objective Rejection Monitoring in Facial Vascularized Composite Allotransplantation

Klimitz, FJ; Brown, S; Freeman, J; Indilewitsch, MC; Geller, N; Milewski, M; Ko, C; Haykal, S; Kauke-Navarro, M; Pomahac, B

Introduction:
Rejection monitoring in facial vascularized composite allotransplantation (fVCA) relies on Banff-graded histopathologic assessment of skin and mucosal biopsies. Although clinically indispensable, this process is subjective and limited by interobserver variability and the scarcity of VCA-experienced pathologists. To advance standardized, multidisciplinary rejection surveillance, we evaluated whether automated quantification of cellular density on routine hematoxylin and eosin (H&E) slides can objectively discriminate rejection from non-rejection in fVCA biopsies.

Methods:
Forty-six biopsies (21 skin, 25 mucosa) from nine fVCA recipients (ten transplants) were analyzed. Samples were classified by expert dermatopathologists using the Banff criteria; grade ≥2 was considered rejection-positive. Whole-slide images were processed using a custom Python-based nuclei segmentation pipeline incorporating color deconvolution, adaptive thresholding, morphological refinement, and optional watershed separation of clustered nuclei. Cellular density (cells/mm²) was calculated by normalizing automated nuclei counts to tissue area. Group comparisons were performed using one-sided Welch's t-tests. To validate robustness, analyses were repeated using HoVer-Net, an established deep learning–based nuclei segmentation framework, with identical downstream processing.

Results:
Sixteen biopsies were rejection-positive and 30 rejection-negative. Using the custom pipeline, cellular density was significantly higher in rejection-positive biopsies compared with controls across all tissues ($p=0.014$). Stratified analyses demonstrated consistent findings in both skin ($p=0.016$) and mucosal samples ($p=0.026$). HoVer-Net–based segmentation reproduced these associations, showing significantly increased cellular density in rejection-positive biopsies ($p<0.001$), with concordant results in both tissue types. Direct paired comparisons between segmentation methods revealed no statistically significant differences in cellular density estimates, supporting methodological agreement.

Conclusion:
Automated quantification of cellular density provides an objective, reproducible marker of acute rejection in fVCA biopsies. A lightweight, resource-efficient image analysis pipeline yields results concordant with state-of-the-art deep learning methods and may facilitate broader clinical adoption. This work exemplifies a team science approach integrating transplant surgery, dermatopathology, immunology, and computational image analysis to advance standardized, precision diagnostics in facial transplantation.

Targeted Afferent Bypass Of Pathologic Deep Cervical Lymph Nodes: Mechanistic Basis To Guide Lymphatic Bypass And Restore Glymphatic Clearance In Alzheimer'S Disease

Brown S; Papadopoulos Z; Klimitz F; Haykal S; Kipnis J; Pomahac B

Introduction:
Emerging evidence suggests that impaired cervical lymphatic drainage contributes to Alzheimer's-disease (AD) pathogenesis. However, the underlying mechanisms remain undefined, creating a critical gap in understanding the lymphatic contribution to AD and in designing targeted microsurgical interventions.

Methods:
Young (2-4 mo) and aged (18-24 mo) mice received intracisternal ovalbumin tracer to assess deep cervical lymph node (dcLN) uptake. Stromal integrity was evaluated by immunofluorescence for laminin (conduit integrity), α-smooth muscle actin (αSMA; stromal activation), and lectin (extracellular matrix [ECM] deposition). To isolate nodal hydraulic resistance, afferent (proximal) and efferent (distal) cervical lymphatic vessels were sequentially imaged under three conditions: baseline, post-efferent transection (downstream to dcLN), and post-afferent transection (upstream, bypassing the dcLN).

Results:
Aged dcLNs demonstrated a twofold reduction in tracer uptake and CSF efflux ($p < 0.01$), decreased laminin coverage, and >60% increases in αSMA and lectin staining ($p < 0.05$), consistent with fibrotic stromal remodeling. Distal transection doubled lymphatic flow, whereas proximal transection bypassing the dcLN increased flow fivefold ($p < 0.001$), independent of vessel diameter (Fig 1).

Conclusion:
This study is the first to elucidate how aging remodels dcLN architecture and function, producing a high-resistance bottleneck that limits CSF clearance. These findings establish the first mechanistic basis for afferent-targeted supermicrosurgical cervical lymphatic bypass (cLVB) to bypass dysfunctional dcLNs, restore lymphatic drainage, and enhance brain waste clearance in AD.

The voltage operating point of real and imaginary complex nonlinear capacitance (cNLC) components diverge at high frequencies.

Joseph Santos-Sacchi, Winston Tan, Jun-Ping Bai and Dhasakumar Navaratnam

Introduction:
OHC electromotility underlies cochlear amplification, a 40-60 dB boost in hearing capabilities. Prestin, the molecular basis of electromotility, works by voltage-driven displacement of its sensor charge, measurable as a nonlinear capacitance (NLC). Thus, real (Re) and imaginary (Im) components of complex NLC (cNLC) report on prestin's impact on cochlear amplification. We measured high frequency responses of prestin's cNLC under voltage clamp in guinea pig (GP) OHC membrane patches.

Methods:
cNLC was measured (1-50 kHz) as described previously, using admittance-based techniques under voltage clamp in membrane macro patches. We fit with either a simple 2-state model or a better fitting 2-state-Csa model to extract Boltzmann parameters. Each component of cNLC was analyzed in this way.

Results:
Surprisingly, in membrane patches at high excitation frequencies, 2-state fits show that Vh of Re and Im cNLC separate as frequency increases. The imaginary "resistive" component is stable, but the real "capacitive" component shifts in the negative direction. This occurs in GP and mouse OHCs. Vh is stable across frequency for Im(cNLC), but not for Re(cNLC). DCsa follows a similar pattern of separation in magnitude across frequency for the Re component, but the Im component lacks a Csa contribution. As we reported previously, Re or Abs(cNLC) decreases with frequency and as expected Qmax does, as well. Across frequency, Im(cNLC) increases with frequency, but at very high frequencies both Re and Im component magnitudes fade precipitously. Slight differences exist between z complex components. Because mathematical models of NLC indicate that Vh for the two components are the same, we refitted with a fixed Vh for both components. Fixing Vh in Boltzmann fits to make each complex component Vh equal reveals an increase in Re DCsa which could be the reason for a Vh decrease during free fitting.

Conclusion:
Voltage-driven charged residue movements trigger electromotility, and the phase of those movements relative to driving voltage varies across frequency, as revealed by measures of Re and Im components of cNLC. The Re component represents sensor charge moving 90 degrees out of phase with voltage, while the Im component is in phase with voltage. Chloride has little effect on DCsa which we previously thought to be related to prestin surface area changes in the membrane. The absence of DCsa in the imaginary "resistive" component, and its presence in the real "capacitive" component could indicate alterations of the membrane dielectric properties, not prestin's conformation, per se. Finally, modelling by Rabbitt (2020,2022) indicates that the imaginary component of cNLC is related to power output of prestin. We find that the optimal operating voltage point of Im(cNLC) is stable across frequencies, indicating efficient cochlear amplification across frequency.

Conformational Changes Underlying Electromechanical Transduction in Prestin Resemble a Partial Transport Transition in Pendrin

Mariadasse R., Zhang C., Yang J., Bai J-P., Santos-Sacchi J., Navaratnam D., Beckstein O.

Introduction:
Prestin (SLC26A5) is a member of the SLC26 anion transporter family that evolved into the voltage-driven motor of cochlear outer hair cells, where voltage-dependent conformational changes drive electromotility and cochlear amplification. We previously resolved a 3.6 Å cryo-EM structure consistent with a contracted state (CS) and more recently a 3.24 Å structure revealing an external anion-binding site. Prestin transitions between compact (CS) and extended (ES) conformations in a voltage-dependent manner, with depolarization favoring CS and hyperpolarization favoring ES. Because the expanded state remains structurally undefined, we used multi-microsecond molecular dynamics (MD) simulations to model the CS-to-ES transition.

Methods:
Simulations were initiated from the compact prestin structure (PDB: 7SUN) in the presence of chloride using GROMACS and ANTON. Trajectories were compared with inward-facing (IF; PDB: 7WK1) and outward-facing (OF; PDB: 7WLE) structures of pendrin (SLC26A4), a related SLC26 transporter. In parallel, electrophysiological recordings were performed on pendrin to assess nonlinear capacitance (NLC) and voltage-dependent conformational changes.

Results:
MD simulations generated an expanded prestin model resembling the IF conformation of pendrin; however, prestin undergoes only a partial OF-to-IF-like transition. Simulations also identified a compact conformation resembling OF pendrin and predicted an extracellular chloride-binding site analogous to that of pendrin. Importantly, this external anion-binding site was confirmed in our 3.24 Å cryo-EM structure. Electrophysiology further demonstrated that pendrin exhibits NLC similar to prestin, indicating voltage-dependent structural rearrangements.

Conclusion:
Together, these findings indicate that prestin and pendrin share core structural features, including partial alternating-access–like transitions, extracellular anion binding, area expansion, and voltage dependence. However, prestin appears adapted for electromechanical function rather than full substrate transport. Its unique role in cochlear amplification likely arises from specialization within the densely packed lateral membrane of outer hair cells.

Cryo-EM Structures of Prestin Reveal Compact and Asymmetric States with Ion Binding Similar to Pendrin

Mariadasse R., Madan A., Yang J., Powers M., Agarwal A., Acton L., Zhang C., Bai J-P., Sigworth F.J., Beckstein O., Santos-Sacchi J., Navaratnam D.

Introduction:
Outer hair cells (OHCs) drive cochlear amplification through voltage-dependent electromotility mediated by prestin, a motor protein in the lateral membrane. Although prestin belongs to the SLC26 transporter family, it exhibits conformational transitions distinct from canonical transporters. Previous cryo-EM studies identified expanded and contracted states, but the mechanisms of ion binding and conformational asymmetry remain unclear.

Methods:
Purified prestin in the presence of 200 mM NaCl/ 40 mM NaSCN was applied to Quantifoil R1.2/1.3 300 Au grids and vitrified in liquid ethane. Cryo-EM data were collected on a Titan Krios G4 (300 kV) with a K3 detector. More than 15,000 dose-fractionated movies were recorded at defocus values of –2.0 to –2.5 µm. Data were processed in CryoSPARC, and atomic models were refined using COOT and PHENIX.

Results:
We determined multiple prestin structures at 3.1–3.9 Å resolution in the presence of Cl^- or SCN^-, corresponding to canonical, compact, and asymmetric states. Clear ion densities were observed at both internal and external binding sites. SCN^- forms rod-like densities and interacts with serine, lysine, and phenylalanine residues. A pronounced asymmetry was observed between protomers: one protomer adopts a compact conformation with TM6–TM7 and extracellular loop 3 (ECL3) opened, exposing an external ion-binding site analogous to the extracellular site in pendrin (SLC26A4), whereas the second protomer remains in a canonical closed-loop state without external ion binding. In the compact protomer, inward displacement of TM1 is coupled to coordinated movement of TM10, indicating structured helical rearrangement.

Conclusion:
These results demonstrate that prestin dimers can adopt asymmetric conformations with extracellular ion binding, loop gating, and coordinated TM1/TM10 motion. The compact and asymmetric states provide new mechanistic insight into prestin’s voltage-sensitive conformational transitions and the structural basis of electromotility.

Spatial Transcriptomic Analysis Reveals Epithelial Delay as Mechanism of Pulmonary Hypoplasia in Congenital Diaphragmatic Hernia

Connor V. Haynes, William Dorst, Nuoya Wang, Rachel Rivero, Micha Sam B. Raredon, and David H. Stitelman

Introduction:
Congenital diaphragmatic hernia (CDH) causes pulmonary hypoplasia and pulmonary hypertension, with survival largely determined by antenatal lung development. While fetoscopic endoluminal tracheal occlusion (FETO) promotes lung growth in severe cases, the intrinsic molecular programs underlying impaired lung maturation remain poorly defined. We used spatial transcriptomics to characterize the temporal and spatial gene expression landscape of hypoplastic lung development in CDH.

Methods:
A nitrofen-induced rat model of CDH was analyzed at embryonic days E17, E19, and E21, corresponding to pseudoglandular, canalicular, and saccular stages of lung development. Formalin-fixed lung tissue was assembled into tissue microarrays and analyzed using 10x Genomics Xenium spatial transcriptomics with a custom 480-gene panel informed by prior single-cell RNA sequencing. Spatial gene expression was integrated with histology. Cell segmentation, annotation, differential expression, cell abundance analysis, and pseudobulk modeling were performed to define developmental trajectories and CDH-associated transcriptional changes.

Results:
CDH lungs demonstrated hypoplastic airway morphology. Compared to controls, CDH lungs exhibited prolonged engagement of early developmental transcriptional programs and a slower decline in global transcriptional activity. Although broad cell class proportions converged by E21, lineage-specific abnormalities persisted, including reduced alveolar type I cell abundance. Monotonic developmental gene analysis showed that transcriptional dysregulation overwhelmingly reflected developmental delay rather than acceleration. This delay was most pronounced in epithelial populations, particularly Sox9-positive distal progenitors. At E19, CDH epithelial cells exhibited increased morphogen signaling and proliferation-associated gene expression, while mesenchymal cells showed increased proliferative signaling and reduced extracellular matrix gene expression.

Conclusion:
Pulmonary hypoplasia in CDH reflects delayed execution of normal developmental gene programs rather than irreversible arrest. CDH lungs retain developmental plasticity but fail to transition toward epithelial differentiation and structural consolidation before birth. Spatially resolved transcriptional analysis identifies critical cell populations, signaling pathways, and developmental windows that may inform next-generation prenatal molecular therapies beyond mechanical lung expansion as in FETO.

Cross-Species Analysis of Polymeric Nanoparticle Biodistribution in Utero

Emily Deschenes, Elsie Devey, Mikayla Labissiere, Adriana Kell, David Eaton, Anna Lynn, Juliana Suprenant, Rachel Rivero, Mert Ozan Bahtiyar, Mark Saltzman, David Stitelman

Introduction:
Congenital anomalies and pregnancy-related disorders that arise during prenatal development are leading drivers of fetal and neonatal morbidity with limited therapeutic options before birth. In particular, intra-amniotic infection is a significant and under-treated cause of pre-term birth and fetal inflammation, highlighting the need for safe and effective fetal therapies [1]. In utero delivery of polymeric nanoparticles (NPs) offers a promising strategy for overcoming maternal-fetal barriers, enabling early therapeutic intervention before irreversible damage occurs. This approach leverages the immature fetal immune system and abundant stem cell populations to treat conditions such as congenital diaphragmatic hernia, cystic fibrosis, and spina bifida [2-6]. NP biodistribution is influenced by NP properties such as size, surface charge, polymer chemistry, and protein corona formation as well as route of administration and species-specific maternal-fetal barriers [7-10]. Despite advances in nanomedicine, in utero biodistribution of NPs is not fully understood. Species-specific differences in placental structure, fetal membrane permeability, and developmental physiology complicate translation across preclinical models, limiting the rational design of targeted fetal therapies [8-9].

Methods:
To address this knowledge gap, we performed a cross-species investigation of polymeric NP biodistribution in murine, ovine, and non-human primates (NHPs). Two clinically relevant administration routes were evaluated: intra-amniotic (IA) and intravenous (IV) delivery. DiI-loaded poly(lactic-co-glycolic acid) (PLGA) NPs were synthesized using a single-emulsion method to enable direct visualization of NP-associated fluorescence in tissues [11]. In mice, laparotomy was performed to visualize the uterine horns and facilitate IA and IV injections (10 mg/mL in PBS). In sheep, ultrasound guided IA injections (12 mg/mL in PBS) were performed. Ultrasound guided IV dosing (300-400 mg/kg) was conducted in both ovine and NHP models. Maternal and fetal tissues were collected at 3 and 24 hours post-injection in murine and ovine models, and 4 hours for the NHP model. Samples were fixed in 4% paraformaldehyde, cryoprotected in PBS sucrose, embedded in OCT, and stored frozen. Cryosections (15 μm) were washed, stained with DAPI, and imaged at 40X magnification using a confocal microscope.

Results:
Imaging in all species revealed that NP biodistribution in utero is strongly influenced by delivery route, with IA delivery favoring localization to amniotic-fluid exposed tissues such as fetal membranes and epithelial surfaces, while IV delivery produced greater signal in vascularized fetal organs.

Conclusion:
As PLGA is an FDA-approved, biocompatible polymer, these findings establish a translational framework for designing in utero nanomedicines with clinically relevant delivery and safety profiles.

Mass-Based Response Testing in Patients with Peritoneal Surface Malignancies: A Single-Center Pilot Study

Princy Gupta, Elizabeth L. Godfrey, Kurt S. Schultz, Kwasi A. Ofori, Justin M. Bader, Kelsey LaBella, Robert J. Kimmerling, Sean Liu, Ava Ospina, Nicole Aguirre, David G. Su, Anup Sharma, Michael Cecchini, Raghav Sundar, Kiran K. Turaga

Introduction:
Peritoneal surface malignancies (PSM) have poor outcomes with limited evidence-based treatment selection strategies. Mass-based response testing (MRT) generates patient-specific drug sensitivity profiles within 48 hours but has not been evaluated in PSM. This pilot study assessed MRT feasibility in PSM samples and provided preliminary assessment of MRT findings in the context of clinical outcomes.

Methods:
Single-center retrospective study of patients with PSM who underwent MRT testing between March 2024 and September 2025. Tumor samples collected during cytoreductive surgery or diagnostic laparoscopy were processed for single-cell mass measurements following ex vivo drug exposure. Technical feasibility, factors affecting success, and preliminary clinical concordance were evaluated.

Results:
Of 99 samples collected, 22 samples were excluded for negative histopathology or QC failure, and 77 samples from 73 patients were analyzed. MRT was successful in 32 samples representing 29 unique patients (40%) with results returned within 48 hours, with insufficient tumor cell yield accounting for 91% of failures. Open surgical approach (50% vs 20%, p=0.02) and progressive disease (75% vs 21-40%, p=0.07) achieved higher MRT success. Among 19 patients with matched neoadjuvant chemotherapy regimens, MRT predicted resistance to the entire regimen or a component thereof in 17 cases (89%). Preliminary clinical correlation was assessable in 3 cases and showed 33% concordance between MRT predictions and outcomes. In one patient with simultaneous sampling from three peritoneal sites, spatial heterogeneity in drug sensitivity was observed.

Conclusion:
This first evaluation of MRT in PSM demonstrates baseline feasibility and reveals intra-patient heterogeneity in drug sensitivity. The 40% success rate, primarily limited by tumor cell yield from paucicellular PSM deposits, identifies key technical barriers requiring optimization.

Integrated CRISPR and Metabolomic Profiling in Gastrointestinal Peritoneal Metastases

Princy Gupta, Kwasi A. Ofori, Justin M. Bader, Nicole Aguirre, Anup Sharma, Michael Cecchini, Raghav Sundar, Kiran K. Turaga

Introduction:
Peritoneal metastases (PM) from gastrointestinal (GI) malignancies represent a clinically distinct entity associated with poor outcomes and limited benefit from conventional systemic therapies. The molecular biology of GI-PM remains poorly understood, hindering the development of effective therapeutic strategies. This study integrates CRISPR-based functional dependency and metabolomic profiling to identify unique molecular dependencies in PM versus non-PM GI cancer cell lines.

Methods:
Cell lines derived from esophageal, gastric, small bowel, and colorectal adenocarcinomas were obtained from the DepMap Public 25Q3 dataset and classified based on site of origin into PM-derived and non-PM-derived groups. Differential gene dependency analysis using CRISPR (DepMap Public 25Q3+ Score, Chronos) identified genes selectively essential in PM cell lines. Gene expression data (Expression Public Q3) were used to assess transcriptional differences, and metabolomic profiles were analyzed to identify distinct metabolic signatures associated with PM.

Results:
Among 172 GI cancer cell lines analyzed, 11 were derived from PM. Differential CRISPR-based dependency profiling identified NAMPT as a significant outlier, with PM cell lines showing greater dependency compared to non-PM cell lines (effect size = –0.896; q = 0.002). Transcriptomic analysis revealed no difference in NAMPTexpression between PM and non-PM groups (effect size = 0.094; q = 0.970). Metabolomic profiling demonstrated reduced kynurenic acid levels in PM-derived cell lines (effect size = –0.662; q = 0.055).

Conclusion:
Integrated CRISPR and metabolomic profiling identified NAMPT as a selective dependency in GI-PM. Lower kynurenic acid levels in PM-derived cell lines suggest reduced activity of the de novo NAD synthesis pathway, potentially explaining their increased reliance on NAMPT-mediated salvage pathway. These findings uncover a metabolic vulnerability unique to GI-PM and support further investigation of NAMPT-targeted therapeutic strategies.

Spatial Transcriptomic Profiling Reveals Compartment-Specific Epithelial-Mesenchymal Divergence in Appendiceal Neoplasms

Sharma Anup, Reddy Biren Thomas*, Good Jennifer, Godfrey Elizabeth, Dhiman Ankit, Gupta Princy, Aguirre Nicole, Bader Justin, Kwasi Ofori, Raghav Sundar, Olino Kelly, Alpert Lindsay; Chowdhury R. Roshni, and Turaga Kiran.(*Co-First)*

Introduction:
Appendiceal neoplasms range from low-grade appendiceal mucinous neoplasm (LAMN) to appendiceal adenocarcinoma (AA). LAMN spreads via peritoneal dissemination, whereas AA invades locally, suggesting fundamentally different molecular programs. No study has characterized their spatially resolved transcriptomic landscape. Defining compartment-specific gene expressions within the tumor microenvironment may identify distinct biological programs and candidate therapeutic targets in these rare tumors.

Methods:
NanoString GeoMx Digital Spatial Profiling (Whole Transcriptome Atlas) was performed on FFPE tissue from a discovery cohort of 4 patients (2 LAMN, 2 AA), selecting 52 regions of interest across epithelial (n=15), T-cell enriched (n=30), B-cell enriched (n=3), and mixed immune (n=4) compartments. Differential expression ($|\log_2 FC|>1$, $Q<0.05$) was assessed as published study. Pathway analysis used GSEA with MSigDB Hallmark gene sets. Findings were orthogonally assessed using a public scRNA-seq dataset (GSE244031; 126,998 cells).

Results:
Global analysis identified 235 differentially expressed genes (DEGs) between LAMN and AA, with compartment-specific analyses revealing the greatest divergence in the epithelial compartment (929 DEGs), followed by T-cell-enriched (211) and mixed immune (205) compartments. LAMN epithelial regions showed upregulation of mucinous differentiation genes (MUC2, MUC5AC, TFF3, SPINK4) and immunoglobulins (IGHG1-4, IGKC), whereas AA was enriched for immune checkpoint molecules, including CD274 (PD-L1). Pathway analysis identified 36 LAMN-enriched pathways dominated by EMT, TNF-α/NF-κB signaling, and complement, vs 3 AA-enriched pathways, an asymmetry potentially reflecting broader transcriptomic reprogramming in mucinous differentiation. Single-cell analysis localized the EMT signal predominantly to stromal populations, suggesting a contribution from cancer-associated fibroblasts. Partial EMT states were enriched in LAMN epithelial cells (24.9%) compared with AA (3.2%), suggesting that hybrid epithelial-mesenchymal programs are a feature of low-grade mucinous neoplasia.

Conclusion:
This first spatial transcriptomic characterization of appendiceal neoplasms provides preliminary evidence of compartment-specific molecular divergence, a partial EMT program distinct from canonical EMT-invasion, and differential expression of immune checkpoints. Given the small discovery cohort, these findings require validation in larger, independent series with functional studies to determine their biological and therapeutic significance.

Radiographic Tumor Regression as a Predictor for Pathologic Response after Neoadjuvant Therapy for Non-Small Cell Lung Cancer

Justin M. Bader; Theresa Ermer; William de Santis; Henna Ragoowansi; Ryan J. Kramer; Emily June Zolfaghari; Elizabeth E. Tremblay; Benjamin J. Resio; Daniel J. Boffa; Justin D. Blasberg; Anna S. Bader; Sanja Dacic; Gavitt A. Woodard

Introduction:
Neoadjuvant chemo-immunotherapy has become standard-of-care for resectable stage II and III non-small cell lung cancer (NSCLC) without EGFR or ALK alterations, and multiple trials have demonstrated improved overall survival in these patients. Preoperative systemic therapy has potential advantages of early control of systemic micrometastatic disease, tumor downstaging, and reduction in size of bulky tumors. However, clinical responses remain heterogeneous with some tumors showing substantial regression while others exhibit limited or no benefit. Accurately assessing treatment efficacy and tumor response during a neoadjuvant course may provide an opportunity to personalize treatment approaches and allow some patients to undergo surveillance rather than surgical resection. This study evaluates correlations between radiographic tumor response and pathologic response to neoadjuvant therapy in NSCLC.

Methods:
All Stage IB-IV NSCLC patients treated with neoadjuvant therapy and surgery between 2015-2025 at Yale New Haven Hospital were included (n=113). Demographics, pathologic, treatment, and radiographic data were collected. Per RECIST 1.1, patients were stratified by radiographic tumor size decrease >30% from baseline (objective radiographic response, ORR) versus decrease <30% (radiographic stable disease). Major pathologic response (MPR) and pathologic complete response (pCR) were determined by pathologist review.

Results:
Among patients with CT scans before neoadjuvant therapy and prior to surgery, 44% (n=35) had ORR. Patients with ORR were more likely to attain pCR (33% vs 10%, p=0.048) and had lower mean percentage residual viable tumor (19% vs 33%, p=0.030). Radiographic size and PET SUVmax decrease demonstrated linear associations with lower percentage of residual viable tumor after neoadjuvant therapy (p=0.0049 and p=0.0025, respectively). Among patients with ORR, 43% (10/23) did not have MPR, reflecting persistent viable tumor in many patients with ORR. PD-L1 status, tumor histology, and specific neoadjuvant treatments were not associated with radiographic or pathologic response.

Conclusion:
Radiographic reduction in tumor size and decreased PET SUVmax were significantly associated with pathologic complete response and lower percentage of residual viable tumor after neoadjuvant therapy in NSCLC. However, viable tumor persisted in some patients with ORR, suggesting predictive performance may be enhanced with additional adjunct biomarkers. Our findings demonstrate that radiographic response can reflect pathologic response and may provide an objective marker for long-term outcomes.

Differential CEACAM5 Expression in Ground-Glass Opacities Versus Other Lung Cancers

de Santis W, Bader JM, Kane E, Jaiswal A, Cho C, Kidacki M, Chen L, Dacic S, Woodard G

Introduction:
Carcinoembryonic antigen-related cell adhesion molecule 5 (CEACAM5) is a cell adhesion molecule implicated in tumor cell migration, invasion, and resistance to apoptosis. Its role as a circulating biomarker in the form of CEA is well-established in some gastrointestinal malignancies. However, CEACAM5 is also overexpressed in approximately 25% of non-small cell lung cancer (NSCLC), particularly lung adenocarcinoma, yet its role as a biomarker and therapeutic target remains unclear. We previously demonstrated elevated CEACAM5 RNA expression in ground-glass opacities (GGO). In this study, using a separate patient cohort, we assess CEACAM5 protein expression as a potential biomarker in GGO compared to other NSCLC tumors.

Methods:
CEACAM5 immunohistochemistry (IHC) was performed in a Clinical Laboratory Improvement Amendments (CLIA) setting on surgically resected GGO and NSCLC. Slides underwent expert thoracic pathologist review and quantification of CEACAM5 expression with standardized H-score. Expression was compared between GGO (n=36) versus solid NSCLC tumors (n=98), and sub-group comparisons were performed based on patient and tumor characteristics. Specimens underwent multiplex immunofluorescence to characterize the immune microenvironment and quantify CD8+ T cell and CD20+ B cell infiltration.

Results:
GGO exhibited significantly higher CEACAM5 expression than the overall NSCLC cohort (H-score: 53 vs 27, $p<0.001$). This increase was also observed when comparing GGO to specific NSCLC subtypes including lung adenocarcinoma (n=57, H-score:53 vs 35, P=0.009), squamous cell (n=20, H-score:53 vs 5, p=0.003), and large cell carcinoma (n=10, H-score: 53 vs 12, p=0.024). Among the adenocarcinoma cohort, stage 1 adenocarcinoma showed lower levels of CEACAM5 compared to stage 2-4 adenocarcinoma (H-score:28 vs 50, p=0.089). Among the GGO cohort, specimens with CEACAM5 H-score ³100 exhibited a higher density of PanCK+ tumor cells (5.5% vs 2.2%, p=0.017). Among patients with ³2 documented preoperative CT scans, all GGO specimens with H-score ³100 (n=6) developed a new radiographic solid component compared to GGO with H-score <100 (100% vs 38%, p=0.035).

Conclusion:
Our findings demonstrate that CEACAM5 is significantly overexpressed in GGO compared to other forms of NSCLC, suggesting its potential utility as a diagnostic biomarker for identifying and monitoring these lesions. Notably, within the GGO cohort, higher CEACAM5 expression was associated with increased tumor cell density and development of a new solid component on imaging. These findings provide insight into the biological significance of CEACAM5 in lung cancer evolution and its possible role in tumor progression. Future studies should explore the clinical utility of CEACAM5-targeted strategies for early detection of invasive lung cancer and lung nodule risk stratification.

YALE SURGERY RESEARCH DAY 2026

CLINICAL SCIENCE ABSTRACTS

Noise Induced Hidden Hearing Loss is a High-Risk Factor to Influence Alzheimer's Disease Development

Tian-Ying Zhai, Chun Liang, Yong Kong, Hong-Bo Zhao

Introduction:
Alzheimer's disease (AD) is a common neurodegenerative disease. Its population has a rapid increase with a trend toward earlier onset in the last decades. However, the underlying mechanisms are unclear. It has been believed that environmental factors may play a major role in this increase. Our previous study demonstrated that noise as a common pollution factor in the modern world could be a high-risk factor to accelerate AD development and progression. In this study, we further explored the underlying mechanisms.

Methods:
5XFAD AD mice were used. Both 5XFAD and littermate wildtype (WT) mice at age of 3-4 months old were exposed to white noise (~98 dB SPL) for 2 hr and one time. ABR, DPOAE, and acoustic-evoked cortical potential (AECP) were recorded to assess hearing function and brain activity. Acoustic startle response (ASR) has been used as behavioral test to assess dementia or cognition decline. The auditory cortex (AC), inferior colliculus (IC), cochlear nucleus (CN), and cochleae were also collected for the bulk Poly(A) RNA Sequencing analyses to assess the genomic changes.

Results:
After noise exposure to induce hidden hearing loss, the noise-exposed 5XFAD mice showed the fast decline in cognition measured by ASR. The decline-speed was 2-3 times faster than that in no-noise-exposed AD mice. RNA-Seq examination showed significant, different immune dysfunctions in the different auditory centers besides the significant downregulation of key synaptic and nerve signaling pathways. Further analysis of the interaction between genotype and noise exposure, i.e., "difference between difference": (noise:5FXAD – control: 5FXAD) – (noise: WT – control: WT), different regions (i.e., AC, IC, CN, and cochlea) of 5FXAD mice demonstrated different reactions to noise. The AC showed exaggerated neuroinflammation, suggesting that AD not only caused baseline neuroinflammation but also appeared hyper-sensitive to noise stress. However, in the IC, noise crippled the immune system and shifted toward a desperate attempt to produce more energy and repair components, suggesting that noise caused the IC in the immuno-compromised state. Like the IC, the CN also showed a suppressed interferon response, but its compensatory mechanism appears to focus on structural changes. Finally, the cochlea showed a combined the metabolic stress observed in other auditory centers with a unique, non-interferon-based inflammatory response. This could lead to different types of synapse/tissue damage and hearing loss.

Conclusion:
Noise can accelerate AD development and progression. AD mice have hyperinflammatory state after noise exposure. The difference between brain and cochlear further indicates that the interaction between AD and noise can trigger diverse, tissue-localized pathologies. This study also reveals that noise could induce widespread immune dysreaction throughout the brain and cochlea and provides important information for noise-induced hearing loss.

Restoration of Hearing in Cx30 (GJB6) Knockout Mice by Compensation of Cx26 (GJB2) Expression in the Cochlea

Hui Zhang, Jin Chen, Tian-Ying Zhai, Zi-Rui Zhao, Chun Liang, Hong-Bo Zhao

Introduction:
Cx30 (GJB6) is another dominant gap junction connexin isoform and co-expressed with Cx26 (GJB2) in the cochlea. Cx30 mutations or knockout (KO) also could induce hearing loss. Previous studies demonstrated that Cx26 expression in the cochlea is reduced in Cx30 KO or mutation. In this study, we tested whether compensation of Cx26 expression in the cochlea could restore hearing function in Cx30 KO mice. This study provides valuable information for gene therapy for Cx30 mutation induced hearing loss.

Methods:
Cx30 KO mice were used and injected with AAV-based GJB2 vectors via the posterior semicircular canal (PSCC) route. Only the right ear in the mouse was injected. Hearing function was assessed by ABR, DPOAE, cochlear microphonics (CM), and acoustic startle response (ASR) behavioral testing. RNA sequencing and digital droplet (dPCR) were also employed to assess gene expression and changes.

Results:
After injection of AAV-based GJB2 vectors (right ear), the hearing function in Cx30 mice could be restored; the ABR thresholds in the right ear were reduced from ~100-110 dB SPL at the untreated Cx30 KO mice to ~30-40 dB SPL in GJB2-injected mice. DEOAE and CM in the injection ear were also recovered. The auditory behavioral rest measured by ASR recording also showed an almost normal response in the treated mice. However, the ABR thresholds in the left untreated ear remained at ~100-110 dB SPL; DPOAE and CM in the left ear were also not significantly improved.

Conclusion:
Compensation of Cx26 expression in the cochlea can rescue hearing loss in Cx30 KO mice.

Extended Reality Augmented Anatomy Education: Qualitative Analysis of a Collaborative Pilot Study

Corsi T, Juggan S, Hill R, Mackay Z, Xu Y, Stewart W, Duncan C, Lapre P, Aboian E.

Introduction:
Mastery of anatomy is foundational to safe and effective surgical intervention. There is growing interest in harnessing anatomy education to optimize patient care, though debate remains over which educational methods are highest yield. Use of extended reality (XR) technology is increasing in anatomy education and has been shown to improve knowledge acquisition, suggesting its possible use as an effective tool. However, significant heterogeneity in previous studies of its use suggest additional inquiry is needed to understand the efficacy, feasibility, and ideal implementation of XR in anatomical education.

Methods:
Twelve first-year medical students enrolled in the Yale School of Medicine Human Anatomy course participated in the Apple Vision Pro (AVP) XR anatomy pilot study. Students participated in traditional cadaveric dissections and classroom didactics, as well as two standardized 45-minute XR sessions facilitated by a teaching assistant. Each session featured headset orientation and 3-dimensional abdominal or pelvic prosections. Timing of the XR sessions relative to dissection and course examination was variable across participants.
Two focus groups were conducted after completion of the pilot. A discussion guide comprised of 6 open-ended questions developed by anatomy and surgical faculty in partnership with the Educational Technology & Innovation Team was utilized.
Focus groups were audio recorded and transcribed, then coded inductively by two independent coders. Codes were discussed in consensus meetings. Themes and sub-themes were identified.

Results:
Six major themes with corresponding sub-themes were developed. AVP technology was favored by participants for interactive spatial learning, system usability with intuitive controls, and improved understanding of complex anatomical concepts. While AVP was considered superior to most other teaching methods, participants emphasized a synergy of the XR tool with traditional dissection for anatomic education. AVP enhanced perceived productivity of dissection and independent study. Participants expressed desire for partner learning with XR and favored an implementation strategy that included facilitated learning. Physical usability limitations such as headset fit and weight were noted, as well as concerns for maintaining hygiene if equipment were to be shared in larger scale implementation.

Conclusion:
The feasibility and efficacy demonstrated in an undergraduate medical education pilot support the use of XR in anatomic education and provide considerations for implementation. Furthermore, our results support future study with surgical trainees in the context of preoperative and operative patient care.

Receipt of Breast Conservation Versus Mastectomy by Breast Cancer Subtype

Hickey AJ, Sun F, Li F, Valero MG, Golshan M, Moses J, Raymond-King L, Morton C, Greenup RA, Berger ER

Introduction:
Breast conserving surgery (BCS) with radiation results in equivalent local recurrence rates and overall survival as mastectomy. The choice of surgical treatment of breast cancer depends on multiple factors such as tumor to breast size ratio, multicentricity, patient anatomy, ability to administer radiation, and patient preference. Meanwhile, the contemporary approach to systemic therapy depends heavily on tumor biology, particularly molecular subtype. We sought to characterize patterns of surgical management based on breast cancer molecular subtype.

Methods:
Women diagnosed with stage I-III invasive breast cancer between 2013 to 2023 were identified in The National Cancer Database (NCDB). Patients were categorized by molecular subtype based on hormone receptor (HR) and HER2 status: HR+/HER2-; HR+/HER2+; HR-/HER2+; and HR–/HER2– (triple negative). The primary outcome was type of definitive breast surgery. Baseline demographic, clinical, and treatment variables were compared across subtypes. The rate of mastectomy was calculated for each receptor subtype. Differences in rate of mastectomy across the four molecular subtypes were compared using chi-square tests, with statistical significance defined as $p<0.05$.

Results:
A total of 6,060,300 women with invasive breast cancer were included. The median age was 62.0 years. Overall, 3,548,861 (58.6%) patients underwent BCS and 2,511,439 (41.4%) underwent mastectomy. The rate of mastectomy differed significantly by receptor subtype ($p<0.001$). Patients with HR–/HER2+ tumors had the highest mastectomy rate (57.8%), followed by those with HR+/HER2+ tumors (50.0%) and triple-negative tumors (49.2%). The lowest mastectomy rate was observed among patients with HR+/HER2– tumors (39.5%).

Conclusion:
Among women with non-metastatic breast cancer, surgery type differs significantly by receptor subtype. HR–/HER2+ tumors are associated with the highest rate of mastectomy, while HR+/HER2– tumors are associated with the lowest. These findings suggest that tumor biology influences patterns of surgical management in breast cancer.

Familial Patterns in Thoracic Aortic Aneurysms and Dissections, Revisited

Harling LC., Changez MIK., Zafar MA., Papanikolaou D., Ellauzi H., Takkou T., Chopra M., Li Y., Eraky MA., Ziganshin BA., Balen A., Elefteriades JA.

Introduction:
The heritable nature of aortic disease is currently well established and as genetic understanding advances, it becomes more important to examine clinical patterns of familial clustering of thoracic aortic aneurysm and dissection (TAAD). Our primary objective was to confirm the familial nature and frequency of TAAD in a large population of affected patients and to characterize familial clustering and phenotype patterns.

Methods:
Patient charts and electronic medical records were retrospectively reviewed for the 3746 patients currently in our Aortic Institute Database. Disease was categorized as syndromic (with extra-aortic manifestations) or non-syndromic (without) for each patient. Family history and status of Whole Genome Sequencing (WES) were assessed.

Results:
From the total 3746 patients in the database, family history of aneurysm or dissection and connective tissue status was determined for 3113 patients, divided into 109 (3.5%) syndromic and 3004 (96.5%) non-syndromic TAAD patients. Our findings were as follows: (I) In the syndromic group, 46 (42.2.6%) patients had a 'proven' family history, 6 (5.5%) had a 'likely' family history, 4 (3.7%) had a 'possible' family history, 35 (32.1%) had 'none'. (II) In the non-syndromic group, 587 (19.5%) patients had 'proven' family history, 147 (4.9%) had 'likely' family history, 210 (7.0%) had 'possible' family history and 1444 (48.1%) had no family history, representing sporadic TAAD patients. (III) There was a significant difference between the rate for 'proven' and 'none' family history between the syndromic and non-syndromic groups (42.2% vs. 19.5% and 16.5% vs. 48.1%, respectively; $p < 0.001$). (IV) Syndromic patients presented at a significantly younger age than non-syndromic or sporadic patients (41.2 vs. 63.3 | 63.6; $p < 0.001$). (V) Overall, 631 patients (25 syndromic, 552 non-syndromic, and 54 with unknown connective tissue status) underwent WES, with 170 disease-causing or suspicious variants [13 pathogenic, 16 likely pathogenic, and 134 Variants of Uncertain Significance (VUS)] found in the exosomes of 141 (22.3%) patients (12 syndromic, 103 non-syndromic TAAD patients). 70 (49.6%) of the patients with disease-causing or suspicious variants had a 'proven' family history, with 83 disease-causing or suspicious genetic variants, as some patients had more than one disease-causing or suspicious variant. (VI) Familial TAAD patients were more likely to have a disease-causing or suspicious variant in their WES result than patients without a family history (70 vs. 26; $p < 0.001$).

Conclusion:
Our study clarifies the family patterns of thoracic aortic disease. We vividly demonstrate the familial nature of TAAD, both clinically and by genetic sequencing. Our findings strongly support vigorous family investigation when a new patient is diagnosed with as well as vigorous application of Whole Exome Sequencing for these families.

Novel Aortic Root Measurement Technique Increases Efficacy of Identifying Patients At-Risk for Type A Dissection

Harling LC., Kalyanasundaram A., Zafar AM., Ellauzi H., Ziganshin BA., Elefteriades JA.

Introduction:
Laplace's law is commonly applied to calculate aortic wall stress via the luminal pressure and the aortic diameter. Wall stress bears on the likelihood of aortic dissection in dilated aortas. However, Laplace's Law applies only to circles and cylinders. It is not applicable for the aortic root, which can be more closely described as a cloverleaf shape, rather than a circle. We have recently developed a mathematically based measuring technique specifically for the aortic root. This "Laplace diameter provides an appropriate means to measure a "diameter" for the cloverleaf shape of the aortic root.

Methods:
In this study, we assess the predictive ability of the Laplace diameter versus the standard sinus-to-commissure measurement in 33 patients who underwent pre-dissection CT scans for unrelated reasons in close temporal proximity to their acute aortic event. 14 chest CT scans of 33 patients that received pre-dissection scans for unrelated reasons were analyzed.

Results:
We observed a 16.1% increase in the mean root diameter utilizing the Laplace diameter. 21.4% of the analyzed pre-dissection scans could have resulted in detection and prevention of the aortic dissection via surgery if the Laplace diameter had been applied.

Conclusion:
We validated the novel method of the Laplace diameter clinically in determining the aortic root diameter in questions of possible dilation and risk of aortic dissection.

Change in Aortic Dimensions at Time of Aortic Dissection: A Multi-Continental Study

Celik NB., Zafar MA., Grewal N., Collins S., Waldron C., Strachan S., Perez Z., Elefteriades J.

Introduction:
Prevention of aortic dissection (AD) remains a central objective in the management of thoracic aortic disease. Previous work has demonstrated that the aorta enlarges abruptly by approximately 7 mm at the moment of dissection, causing overestimation of pre-dissection diameters and suggesting that many dissections occur below current surgical thresholds. This study expands upon these findings by incorporating a larger and an international cohort from the USA and Europe.

Methods:
Databases from two participating aortic centers were retrospectively reviewed to identify patients with acute type-A aortic dissection who incidentally also had a prior CT scan obtained within 5 years before the dissection event. A total of 53 patients were identified at the center in the USA and 17 at the European center. Standardized CT aortic measurements were performed for the ascending and descending thoracic aorta at both centers. Pre- and at-dissection diameters were compared to quantify the acute dimensional change attributable to dissection.

Results:
A total of 70 patients with imaging available both prior to and at the time of acute aortic dissection were included. For the combined cohort, the mean ascending aortic diameter increased from 43.2 ± 6.7 mm prior to dissection to 51.6 ± 9.6 mm at dissection (Δ=8.9 ± 7.2 mm, $p<0.001$). The mean descending aortic diameter increased from 31.1 ± 7.7 mm to 33.1 ± 8.2 mm (Δ=2.5 ± 4.3 mm, $p<0.001$). When analyzed by center, the US center demonstrated an average increase of 8.3 ± 6.5 mm in the ascending and 2.3 ± 4.6 mm in the descending aorta, while the European showed respective increases of 10.9 ± 8.8 mm and 2.9 ± 3.2 mm. The magnitude of enlargement was similar between institutions ($p>0.05$). Overall, 38.1% of ascending aortas are dissected at diameters below the current surgical threshold of 50 mm.

Conclusion:
Across two centers, the aorta consistently demonstrated a smaller diameter CT scan done prior to dissection. These findings confirm that most dissections occur at smaller sizes than previously thought. This study supports the recent left shift in surgical criteria from 55 mm to 50 mm.

Evaluation of radiographic predictors of adverse outcomes in medically managed acute type B aortic dissection patients

M. Ahad Khattak, Mohammad A. Zafar, Asanish Kalyanasundaram, Hesham Ellauzi, Zachary G. Perez, Bulat Ziganshin, John A. Elefteriades

Introduction:
The literature describes several radiographic predictors of adverse outcomes in acute type B aortic dissection patients. We sought to determine the clinical validity of these predictors among patients with medically managed, initially uncomplicated acute type B aortic dissections (free of rupture, ischemia, acute expansion).

Methods:
81 uncomplicated acute type B dissection patients presenting to our institution for management between 1994 and 2021 with a contrast enhanced computerized tomography (CT) scan on file were analyzed. Radiographic features at presentation analyzed for this study included: maximal descending aortic overall diameter, true and false lumen diameters, maximal ascending aortic diameter, dissection origin location (greater vs. lesser curvature), degree of false lumen thrombosis, branch vessel perfusion and true vs false lumen supply of the branch vessels. These factors were reevaluated in serial scans, and descending aortic growth rates were computed. Measurements were done perpendicular to the long axis of the aorta. The two endpoints analyzed in this study included a descending aortic specific endpoint (descending aortic rupture and aorta related mortality), and a composite endpoint (aortic specific endpoint, descending aortic surgery and all-cause mortality). Regression analyses were conducted to determine the factors' association with these endpoints.

Results:
Mean age at presentation was 60 years. 48 (59.3%) patients were males and 33 (40.7%) were females. Mean follow up duration (from presentation to an endpoint as defined above) was 4.7 years. Median descending aortic growth rate was 0.41 mm/year. The area of maximal dilatation was in the proximal descending aorta (T1-T6). For the aortic adverse event endpoint no radiographic factor was a significant predictor on univariate regression or multivariate regression. For the composite endpoint maximal descending aorta diameter ($p<0.001$) and true lumen diameter ($p=0.033$) were significant predictors on univariate analysis whereas multivariate analysis showed no significant predictors. The freedom from an aortic endpoint at 12 years was 75%.

Conclusion:
We do not confirm prior expectations regarding the value of anatomical variables in prediction of adverse aortic events after acute type B aortic dissection. In patients triaged to optimal medical therapy, ultra long term aortic outlook is more benign than previously anticipated, even in the presence of putative radiographic "high risk' indicators.

Autoimmunity and Cancer-Related Lymphedema Development after Axillary Surgery: A Decade of Outcomes from A Tertiary Cancer Center

Brown S, Fargey S, Klimitz F, Noor S, Sureshanand S, Hintz R; Haykal S

Introduction:
Despite emerging evidence implicating immune dysregulation in the pathogenesis of breast-cancer–related lymphedema (BCRL), the contribution of autoimmune comorbidities to lymphedema development remains poorly defined. The purpose of this study was to investigate the association between a broad range of autoimmune and inflammatory conditions and lymphedema development following axillary surgery.

Methods:
All patients who underwent axillary surgery at a tertiary cancer center between 2013 and 2025were included. Demographic and clinical variables, including age, sex, race, body mass index (BMI), chemotherapy and radiation therapy exposure, and comorbid conditions (diabetes, asthma, and autoimmune diseases), were extracted. The primary outcome was postoperative lymphedema. Univariate and multivariable logistic regression analyses were performed to identify factors independently associated with lymphedema development.

Results:
A total of 16,754 patients were included, of whom 2,665 (15.9%) developed lymphedema. On multivariable analysis, established risk factors including obesity (BMI >30; OR 1.35, 95% CI 1.23–1.49), radiation therapy (OR 2.10, 95% CI 1.91–2.31), and chemotherapy (OR 2.35, 95% CI 2.12–2.62) were strongly associated with lymphedema (all $p<0.0001$). Among comorbid conditions, asthma (OR 1.29, 95% CI 1.16–1.43; $p<0.0001$), Hashimoto's thyroiditis (OR 1.32, 95% CI 1.06–1.64; $p=0.0118$), and systemic lupus erythematosus (OR 1.67, 95% CI 1.14–2.40; $p=0.0068$) were independently associated with increased lymphedema risk. Other autoimmune conditions, including atopic dermatitis, celiac disease, psoriasis, rheumatoid arthritis, and scleroderma, were not significantly associated with lymphedema development after adjustment for covariates.

Conclusion:
In this large institutional cohort, select autoimmune and inflammatory conditions were independently associated with an increased risk of lymphedema following axillary surgery. These findings support a potential role for immune-mediated mechanisms in lymphedema development and highlight the importance of incorporating immune comorbidity profiles into postoperative risk stratification.

Defining Modern Candidate Selection for Lymphaticovenous Bypass: Insights from Two Decades of Published Experience

Brown S, Salcedo G, Kukaran R, Shen A, Klimitz F, Haykal S

Introduction:
Lymphaticovenous bypass (LVB) is an established microsurgical treatment for lymphedema, yet selection criteria vary widely across institutions. Appropriate patient selection is critical, as LVB depends on the presence of functional lymphatic vessels and favorable tissue characteristics. We performed a systematic review to characterize contemporary protocols for LVB candidate selection, including imaging modalities, physiologic requirements, disease stage, and clinical criteria.

Methods:
A systematic review was conducted of studies reporting explicit protocols or criteria for LVB selection. Twenty-one studies were included. Extracted variables included imaging modalities used for lymphatic mapping, disease stage inclusion criteria, requirement for conservative therapy failure, physiologic and tissue characteristics, and use of disease duration in selection.

Results:
Indocyanine green (ICG) lymphography was the most commonly used imaging modality, reported in 48% of studies, followed by lymphoscintigraphy (24%), ultrasound (19%), and MR lymphangiography (5%). The presence of patent lymphatic vessels was explicitly required in 38% of studies, although this was likely an implicit prerequisite in most protocols. Early-stage disease was the dominant treatment window: 33% of studies restricted inclusion to ISL stage I–II, and 71% predominantly treated early-stage patients. Failure of conservative therapy was required in 48% of studies, reflecting LVB's role as a second-line intervention. Notably, disease duration was used as a selection criterion in only 5% of studies, indicating that physiologic lymphatic function rather than chronicity determines candidacy. Favorable tissue characteristics, including minimal fibrosis, were rarely explicitly stated but universally reflected in clinical practice.

Conclusion:
Modern LVB selection protocols prioritize physiologic lymphatic function and disease stage over disease duration. The typical candidate is a patient with early-stage (ISL I–II) lymphedema, demonstrable patent lymphatic vessels on ICG lymphography, and persistent symptoms despite conservative therapy. ICG lymphography has emerged as the dominant global selection modality. These findings support a physiology-driven selection paradigm and help define consensus criteria for optimal LVB candidacy, which may improve surgical outcomes and standardize patient selection across centers.

Predicting Lymphedema Following Cervical Lymph Node Dissection for Head and Neck Cancer: A Decade of Outcomes and Risk Modeling

Brown S, Klimitz F, Soundari S, Hintz R, Pomahac B, Haykal S

Introduction:
Cervical lymph node dissection (CLND) remains a cornerstone in the treatment of head and neck malignancies, but it carries a significant risk of lymphedema. The role of autoimmune and metabolic comorbidities in modulating this risk is not well established.

Methods:
We conducted a longitudinal analysis of all patients who underwent CLND for head and neck cancer at a tertiary cancer center between 2013 and 2025. Demographic, oncologic, metabolic, and autoimmune variables were analyzed. A multivariable logistic regression model was developed to identify independent predictors of lymphedema and support the construction of a clinical risk prediction tool.

Results:
Among 4,925 patients, 752 (15.3%) developed lymphedema. Independent predictors of increased risk included radiation therapy (OR = 6.88; 95% CI: 5.66–8.39; p<0.0001), chemotherapy (OR = 1.98; 95% CI: 1.63–2.40; p<0.0001), older age (OR = 1.008 per year; 95% CI: 1.002–1.015; p=0.0096), Hispanic ethnicity (OR = 0.69; 95% CI: 0.49–0.96; p=0.0291), Hashimoto's thyroiditis (OR = 1.71; 95% CI: 1.00–2.85; p=0.0437), and scleroderma (OR = 4.61; 95% CI: 1.14–16.31; p=0.0221). The model demonstrated strong predictive performance, with an area under the ROC curve (AUC) of 0.803 (95% CI: 0.786–0.820; p<0.0001).

Conclusion:
This is the first large-scale study to model lymphedema risk following CLND using autoimmune and treatment-related predictors. The resulting model, with strong discriminative ability, may serve as a clinically useful tool to guide surveillance and early intervention strategies in high-risk patients, taking into account autoimmune conditions in addition to known risk factors.

Clinical Outcomes of Robotic-Assisted Microsurgical Reconstruction

Shen Y; Gao R; Brown S; Nair M; Glaeser-Khan S; Wo L; Addagatla K; Pomahac B; Haykal S

Introduction:
Robotic microsurgery enables submillimetric precision and enhanced dexterity. Although feasibility has been shown in small case series, comparative clinical data remain limited. This study provides the largest controlled analysis comparing robotic-assisted versus manual microsurgical reconstruction across free flap and lymphatic procedures.

Methods:
A prospective controlled cohort study was performed at our center from September 2024–2025. Patients undergoing free flap breast reconstruction, immediate lymphatic reconstruction (ILR), or lymphaticovenous bypass (LVB) were included. Robotic cases used the Symani Surgical System for microvascular anastomosis; manual cases used conventional techniques. Perioperative outcomes, complications, and operative times were compared using nonparametric tests and Fisher's exact test. Predictors of operative duration were evaluated with multivariable linear regression.

Results:
A total of 118 procedures were analyzed (36 robotic, 82 manual). Robotic use was most common for ILR (52.8%), followed by free flap (33.3%), and LVB (13.9%; all robotic). Demographics and treatment histories were similar between groups, although robotic adoption varied by surgeon ($p<0.05$). In free flap reconstruction, operative time trended longer with robotics (median 570.5 vs 537.0 minutes, $p=0.07$), with higher but nonsignificant revision rates (18.2% vs 5.5%, $p=0.06$). For isolated ILR, robotic cases were significantly longer (92.4 ± 23.6 vs 49.4 ± 18.1 minutes, $p<0.01$). Across ILR and LVB, postoperative outcomes and anastomotic complication rates were comparable. Manual approach ($\beta = –42.1$ min, $p=0.01$) and absence of concurrent procedures ($\beta = –39.1$ min, $p=0.02$) predicted shorter operative times. Anastomosis time decreased significantly with experience (–2.36 min/case, $p=0.01$).

Conclusion:
Robotic-assisted microsurgery yields outcomes comparable to manual techniques. Although initially longer, operative times improved rapidly, supporting a favorable learning curve and integration into reconstructive practice.

Predicting Lymphedema After Groin Lymph Node Dissection: A Risk Stratification Model from a Decade of Outcomes at a Tertiary Cancer Center

Brown S; Fargey S; Klimitz FJ; Noor S; Oh J; Sureshanand S; Hintz R; Haykal S

Introduction:
Groin lymph node dissection (GLND) is associated with a substantial risk of lower-extremity lymphedema, yet no clinically applicable model exists to estimate individual risk. This study aimed to identify independent predictors of lymphedema development after GLND and provide a clinically useful prediction algorithm.

Methods:
We conducted a longitudinal-study of patients who underwent GLND at a tertiary-cancer-center from 2013 to 2024. Demographic and clinical data, along with lymphedema onset, were recorded. Two multivariate-regression models were developed to predict 1) risk of lymphedema and 2) time to first diagnosis.

Results:
1644 patients were included with lymphedema occurring in 13.1% of patients (n=217). Significant predictors of lymphedema included male gender (OR = 0.49, 95% CI 0.35–0.68, $p < 0.0001$), BMI > 30 (OR = 1.91, 95% CI 1.38–2.66, $p = 0.0001$), radiation therapy (OR = 2.32, 95% CI 1.61–3.36, $p < 0.0001$), hypertension (OR = 1.53, 95% CI 1.01–2.34, $p = 0.0481$), and peripheral vascular disease (OR = 1.43, 95% CI 1.00–2.03, $p = 0.0478$). The extent of dissection was also significantly associated with increased risk: deep inguinofemoral lymphadenectomy, involving both superficial and deep nodes including Cloquet's node, carried the highest risk (OR = 10.95, 95% CI 6.15–19.67, $p < 0.0001$). Among patients who developed lymphedema, significant predictors of delayed onset included chemotherapy ($\beta = 6.89$ months, 95% CI 0.94–12.84, $p = 0.0234$), diabetes ($\beta = 6.91$ months, 95% CI 0.86–12.95, $p = 0.0254$), and peripheral vascular disease ($\beta = 6.92$ months, 95% CI 1.00–12.84, $p = 0.0222$). In contrast, deep inguinofemoral lymphadenectomy was associated with significantly earlier onset ($\beta = -9.63$ months, 95% CI –17.09 to –2.16, $p = 0.0118$).

Conclusion:
This is the largest study to identify key clinical and surgical predictors of lymphedema following groin lymph node dissection. The findings support the development of individualized risk assessment tools to guide early surveillance and preventative strategies in high-risk patients, with a focus on risk factors uniquely relevant to lower extremity lymphedema—distinct from those associated with axillary dissection and upper extremity disease.

Association of Facility Type and Surgical Outcomes in Early-Onset Gastrointestinal Patients

Wafa Nomani, Samuel Butensky, Can Akpinaroglu, Oladimeji Aladelokun, Baylee Bakkila, Caroline Johnson, Sajid Khan.

Introduction:
With the rising incidence of early-onset (age < 50) gastrointestinal (EO GI) cancers in the United States, disparities in quality of surgical care exist across different hospital facility types. Here, we sought to evaluate whether hospital facility type affects quality of surgical care for patients diagnosed with early-onset gastrointestinal cancers undergoing surgical intervention.

Methods:
Using the National Cancer Database, we identified 193, 262 EO GI cancer patients undergoing surgical resection from 2004-2022. The primary tumor organ sites included the colon, rectum, rectosigmoid junction, anus, esophagus, stomach, small intestine, peritoneum, pancreas, liver, gallbladder, and other biliary. Multivariate logistic regression was used to assess likelihood of surgery, negative resection margins, and adequate lymphadenectomy. Cox regression analysis was used to evaluate overall survival.

Results:
Facility types included Community Cancer Programs (CCP), Comprehensive Community Cancer Programs (CCCP), Academic/Research Programs (ARP), and Integrated Network Cancer Program (INCP). Patients at CCPs were less likely to receive surgery (odds ratio [OR], 0.805; 95% CI, 0.751-0.863) than ARP, whereas patients at INCPs were more likely (odds ratio [OR], 1.209; 95% CI, 1.151-1.270). Compared to ARP, CCCPs were less likely to achieve negative resection margins (odds ratio [OR], 0.908; 95% CI, 0.853-0.966) and adequate lymphadenectomy (odds ratio [OR], 0.867; 95% CI, 0.829-0.907). CCPs were less likely to have adequate lymphadenectomy (odds ratio [OR], 0.728; 95% CI, 0.673-0.788). INCPs were also less likely to achieve negative resection margins (odds ratio [OR], 0.909; 95% CI, 0.844-0.978) and adequate lymphadenectomy (odds ratio [OR], 0.894; 95% CI, 0.848-0.943). There was no difference in survival among facility types in the aggregate cohort, however, when evaluated by primary site, colon, rectum, rectosigmoid junction, pancreas, stomach, esophagus, liver, and small intestine showed significantly better survival in ARP ($p<0.001$).

Conclusion:
Overall, these findings suggest that ARPs are associated with improved quality of surgical care among EO GI cancer patients in terms of achieving negative resection margins, adequate lymphadenectomy, and overall survival. Further studies are needed to evaluate what factors drive these differences among EO GI cancer patients and ways to optimize care for this increasing population.

Frailty in Non-metastatic Pancreatic Ductal Adenocarcinoma and Its Association with Surgical Resection

Lauren Raymond-King, Sean McGrath, Bhramar Mukherjee, Yiran Wang, Harsh Parikh, John Rothen, Pamela R. Soulos, Cary P. Gross, John W. Kunstman

Introduction:
Frailty is associated with worse cancer-related outcomes, but its prevalence and association with curative-intent treatment have not been characterized in pancreatic ductal adenocarcinoma (PDAC). Clarifying how frailty, rather than chronologic age alone, affects receipt of surgery in non-metastatic PDAC addresses a critical gap in real-world evidence, informing treatment decisions for this high-risk population. This study describes the distribution of frailty in patients with non-metastatic PDAC and evaluates its association with curative-intent pancreatectomy.

Methods:
We performed a retrospective cohort analysis of SEER-Medicare data, including Medicare fee-for-service beneficiaries diagnosed with non-metastatic PDAC from 2013-2019. Frailty was categorized as non-frail, pre-frail, mildly frail, or moderately-to-severely frail using the Claims-based Frailty Index over the 12 months preceding diagnosis. We evaluated frailty distributions via kernel density estimation. We assessed the association between frailty category and receipt of surgery via logistic regression.

Results:
We identified 8,237 patients with non-metastatic PDAC (mean age 78, 57.6% female, 77.4% White). Pancreatectomy was performed in 2,486 patients (30.2%). 39.7% of 2,585 non-frail patients underwent surgery, while 30.7% of 4,043 pre-frail patients underwent surgery, with no significant difference after adjustment [aOR = 1.01, 95% CI = (0.89-1.16)]. 15.8% of 1,256 mildly frail and 5.7% of 353 moderately-to-severely frail patients underwent surgery; both groups had significantly lower odds of surgery versus non-frail patients [mildly frail aOR = 0.53, 95% CI = (0.43–0.66); moderately-to-severely frail aOR = 0.18, 95% CI = (0.11–0.30)].

Conclusion:
Frailty is common in patients with non-metastatic PDAC and is strongly associated with decreased receipt of surgery. Fewer than 40% of non-frail patients underwent surgery, suggesting that curative-intent treatment for PDAC remains infrequent, even among lower-risk adults.

Frailty and Home Time Loss After Surgical Resection for Patients with Non-Metastatic Pancreatic Cancer

Lauren Raymond-King, Sean McGrath, Bhramar Mukherjee, Harsh Parikh, John Rothen, Michaela Dinan, Pamela R. Soulos, Cary P. Gross, Natalia Festam, John W. Kunstman

Introduction:
Home time, conceptualized as days alive outside of inpatient medical settings, reflects the preferences of older adults for maximizing independence, and may capture dimensions of the care continuum obscured by traditional measures. For patients with non-metastatic pancreatic ductal adenocarcinoma (PDAC), home time loss is particularly meaningful given the substantial morbidity and mortality associated with pancreatectomy. The relation between preoperative frailty and home time loss in this population has not been evaluated.

Methods:
Using SEER-Medicare data (2013–2022), we identified patients ≥66-years-old undergoing curative-intent pancreatectomy for non-metastatic PDAC. We classified patients preoperatively as non-frail, pre-frail, or frail using the validated Claims-Based Frailty Index. We defined home time loss as cumulative days lost to hospitalization, skilled nursing facility (SNF) admission, or death in the year post-pancreatectomy. We used negative binomial regression to estimate the association between frailty and home time loss, adjusting for sociodemographic and clinical factors, including tumor stage.

Results:
Among 4,553 patients (median age 74), 44.3% were non-frail, 47.9% pre-frail, and 7.8% frail. Mean home time loss was 83.8 days (19.0 for hospitalization, 7.4 for SNF admission, 57.5 for death).Compared with non-frail patients, pre-frail patients experienced 23% greater home time loss (aIRR 1.23, 95% CI 1.10–1.38) and frail patients had 86% greater loss (aIRR 1.86, 95% CI 1.57–2.22); this association persisted across hospitalization, SNF admission, and death.

Conclusion:
Frailty is strongly associated with home time loss in the year after curative-intent pancreatectomy and warrants careful consideration during shared decision-making for patients with non-metastatic PDAC contemplating surgery.

Not All Wounds Are Visible: Association of Sociobehavioral Comorbidities With Outcomes after Major Elective Cancer Operations in a National Veteran Cohort

D'Aquila, ML; Schultz, KS; Trope, WL; O'Leary, KR; Richburg, CE; King Jr, JT; Hall, DE; Golshan, M; Justice, AC; Leeds, IL

Introduction:
Sociobehavioral comorbidities (SBCs) are increasingly recognized as important determinants of surgical outcomes. However, their relationship with postoperative complications in Veterans, who experience a high burden of these risk factors, is unknown. The purpose of this study was to evaluate the association between modifiable SBCs and complications after elective cancer operations in a national United States Veterans cohort.

Methods:
We conducted a retrospective cohort study of major elective thoracic, abdominal, and pelvic cancer operations within the Veterans Health Administration (VHA) from 2009 and 2024, defined as procedures requiring at least one postoperative hospital night. Structured data from the VHA Corporate Data Warehouse were used to identify three behavioral domains (mental health disorder, suicide risk, substance use) and three social domains (social isolation, housing instability, food insecurity) within 90 days before surgery. These data were linked to the Veterans Affairs Surgical Quality Improvement Program (VASQIP) for demographics, biomedical comorbidities, and outcomes. The primary outcome was any 30-day VASQIP-defined postoperative complication. Multilevel logistic regression clustered by VHA station number was used to estimate adjusted associations between the six SBCs and complications.

Results:
Among 34,805 elective cancer operations, 79% were colorectal, 9% were hepato-pancreato-biliary, and 7% were thoracic. Median age of the cohort was 67 years (IQR 61-73); 4% were females, and 32% identified as non-white. Overall, 39% had one or more SBCs, and 18% experienced at least one VASQIP-defined postoperative complication. After adjustment, four SBC domains were independently associated with complications, including mental health disorder (OR 1.30, 95% CI 1.23-1.39), social isolation (OR 1.33, 95% CI 1.18-1.50), suicide risk (OR 1.68, 95% CI 1.00-2.74), and substance use (OR 1.34, 95% CI 1.24-1.45).

Conclusion:
In a national cohort of Veterans undergoing elective cancer operations within the VHA system, multiple potentially modifiable sociobehavioral comorbidities were independently associated with postoperative complications. These findings support routine sociobehavioral risk assessment and the development of targeted perioperative interventions to improve outcomes among high-risk Veterans.

Freedom From Want: A Community-Engaged Qualitative Study of Patient -Generated Solutions To Address Sociobehavioral Comorbidities Around Major Surgery

Richburg CE; Schultz KS; D'Aquila ML; Rodriguez A; Artis M; Vitous CA; Suwanabol PA; Leeds IL.

Introduction:
Sociobehavioral comorbidities (SBCs), including psychological distress and unmet social needs, carry risks of surgical complications at magnitudes comparable to biomedical comorbidities. Patient priorities for interventions to address these comorbidities are not well defined. The purpose of this study was to elicit patient-desired solutions to address SBCs within standard surgical care pathways.

Methods:
We conducted a community-engaged qualitative study as part of a sequential explanatory mixed-methods design at a large academic medical center. In the quantitative arm, patients who underwent major elective surgery (June 2023 - November 2025) completed a 140-item preoperative SBC assessment. In the qualitative arm, eligible patients screened positive for SBCs and either experienced a 90-day complication (core cases) or did not (positive deviants). Participants were selected using purposive sampling. Community-based research fellows (MA, AR) and clinician-researchers (CR, KS) co-designed the interview guide and conducted one-on-one interviews in-person or via videoconference. Transcripts were analyzed using inductive-deductive, team-based coding. Thematic analysis was applied to the code "patient-generated solutions."

Results:
Sixteen patients were interviewed across three surgical services. Interviews lasted 7 to 131 minutes. Four categories of desired support were identified: 1) traditional talk therapy, 2) peer-based psychological support, 3) formal assistance navigating financial burdens, and 4) connection to longer-term safety-net resources during hospitalization. While some patients with psychological distress found traditional talk therapy helpful, others desired a connection with peers who shared their diagnosis or had undergone the same operation. Patients with social needs described the surgical encounter as destabilizing. Missed work, inability to pay rent, increased transportation needs, and reduced independence intensified financial strain and worsened preexisting social challenges. Many relied heavily on personal networks for basic needs but wanted formal assistance navigating a financially burdensome healthcare environment. Patients cited difficulty accessing longer-term safety-net resources during hospitalization. They perceived social work encounters as narrowly focused on discharge logistics rather than on their ongoing needs outside the hospital.

Conclusion:
Patients with SBCs described major surgery as destabilizing to preexisting psychological distress and material insecurity. Patient-identified priorities emphasize the need for perioperative care that supports behavioral health and extends beyond discharge planning to facilitate connection with long-term social support resources.

Who Lives, Who Dies, Who Tells Your Story? Comparing Sociobehavioral Comorbidity Detection by Natural Language Processing Versus Structured Bedside Screening in Major Elective Surgery

D'Aquila, ML; Schultz, KS; Ren, Y; Trope, W; Keloth, V; Leeds, IL

Introduction:
Sociobehavioral comorbidities (SBCs) are associated with more than a 3-fold increase in postoperative complications after major surgery. Although over half of surgical patients report multiple SBCs preoperatively, structured bedside screening is inconsistent and captures <10% of affected patients. We evaluated an externally developed supervised machine learning natural language processing (NLP) algorithm to identify SBCs from unstructured EMR text. We hypothesized that NLP-derived SBCs would demonstrate agreement with structured bedside screening and be associated with postoperative adverse outcomes.

Methods:
Among patients undergoing major elective GI operations at a large academic center (2022-2024), SBCs were ascertained using (1) NLP extraction from unstructured clinical documentation and (2) structured nursing-administered bedside screening. Agreement between modalities was assessed using Cohen's kappa (k). Multivariable hierarchical logistic regression estimated the association between SBCs and 30-day NSQIP-defined postoperative complications, adjusting for RAI (which includes age, sex, cancer, biomedical comorbidities, and functional status), race, and operative approach, with a random intercept for surgeon.

Results:
Of 921 patients, the median age was 66 years (IQR 17); 496 (54%) were male; 121 (13%) were non-white. Overall, 166 patients (18%) experienced ≥1 postoperative complication. Nearly half (47%) of patients were incompletely screened by structured screening. NLP identified ≥1 SBC in 83 patients (9%), whereas structured screening identified ≥1 SBC in 53 patients (6%), with minimal overlap (n=3, <1%). Agreement between the modalities was poor (k= -0.03, p=0.38). Only structured SBCs were independently associated with postoperative complications (aOR 2.03, 95% CI 1.05-3.92). NLP-derived SBCs and a combination of the two modalities were not associated with complications (NLP: aOR 0.52, 95% CI 0.25-1.07; NLP+structured: aOR 1.03, 95% CI 0.98-1.04).

Conclusion:
NLP-derived SBCs showed poor agreement with structured SBCs and failed to identify an association with complications. Both modalities underestimate SBCs compared to historical assessments suggesting construct validity limitations. While structured screening identified SBCs more closely associated with complications, the degree of missingness challenges widespread implementation. NLP detection needs context-specific refinement when used across institutions but still offers a promising opportunity to efficiently capture currently under-identified SBCs associated with postoperative complications.

Actionable Sociobehavioral Comorbidities and Patient Outcomes After Major Elective Surgery

Schultz, KS., D'Aquila, ML., Richburg, CE., Trope, WL., Huang, Y., Blake, BT., Tompkins, EA., Mohli, A., Leeds, IL.

Introduction:
Demographic disparities in surgical outcomes are well described but largely immutable. Sociobehavioral comorbidities (SBCs) (e.g., depression, limited resilience, and unmet social needs) represent actionable risk factors that could inform targeted interventions; however, the relative contribution of specific SBC domains remains unclear. This study examined the associations between preoperative SBCs and 30-day complications after major elective surgery.

Methods:
In this prospective cohort study, adults undergoing major elective surgery within a statewide health system (July 2023–March 2025) completed a 140-item researcher-administered survey assessing 27 SBC domains within two weeks preoperatively. Associations between individual domains and any 30-day NSQIP-defined complication were estimated using multivariable logistic regression, adjusted for age, sex, race, Social Vulnerability Index, modified frailty index, surgical indication, and surgical service. Structural equation modeling (SEM) identified latent constructs that represent shared variance across SBC domains, thereby reducing dimensionality and preserving statistical power.

Results:
Of 778 eligible patients, 394 (51%) completed the survey. The median age was 64 years (IQR 53–71); 47% were female, 13% non-white, the median mFI-5 was 1 (IQR 0–1), and the median Social Vulnerability Index was 0.3 (IQR 0.1-0.5). Procedures included colorectal (57%), thoracic (24%), and surgical oncology (20%), with 72% performed for cancer. For the individual SBC domains, limited resilience was associated with higher odds of complications (aOR 3.4, 95% CI 1.13–10.1, p=0.029), while faith contributing to well-being was protective (aOR 0.41, 95% CI 0.19–0.85, p=0.017). SEM identified four latent constructs— behavioral health burden, relational strain, navigational barriers, and health-related social needs —comprising 14 of the 27 individual domains, with acceptable model fit (RMSEA=0.05, SRMR=0.06, TLI=0.91; Figure). Each standard deviation increase in the behavioral health burden construct was associated with an 11.5 percentage-point (pp) increase in predicted complication probability (95% CI 4.3-18.8, p=0.002). In contrast, the health-related social needs construct demonstrated an inverse association (−9.2 pp; 95% CI -16.6 to -1.8, p=0.015). Relational strain and navigational barriers were not significantly associated with complications.

Conclusion:
Preoperative behavioral health burden emerged as the construct most strongly associated with complications after major elective surgery. Concordant domain-level findings support routine preoperative behavioral health screening, offering actionable insights for targeted perioperative interventions. Causal inference approaches are underway to disentangle the observed inverse relationship between social needs and complications.

NurseGPT: Evaluating Patient Engagement with a Voice-Enabled AI Assistant in Facial Plastic Surgery

Chung A., Muhammad M., Nunez A.

Introduction:
Clinical evaluations of conversational AI in facial plastic surgery have largely relied on simulated, text-based interactions; real-world voice-to-voice studies on implementation of AI in clinic workflow are limited. The objective of the study was to assess patient experience and characterize patient-initiated conversations with a voice-to-voice AI assistant.

Methods:
Rhinoplasty or facial paralysis patients at a tertiary academic medical center interacted with a voice-to-voice AI assistant (GPT-4o) for 5 minutes in English or Spanish during clinic rooming. Participants completed a Likert questionnaire; transcripts were thematically coded. Pre- vs post-operative groups were compared for questionnaire scores.

Results:
Thirty-two patients participated (21 pre-operative; 11 post-operative; 97% rhinoplasty); mean age 37.7 years (SD 15.7) and 50% female. Agreement/strong agreement was 81.3% for clarity/value, preparedness, and natural/easy to understand; 87.5% for feeling listened to; 46.9% for reduced anxiety; 93.8% overall positive; and 84.4% would recommend. Questionnaire scores did not differ significantly by stage. Pre-op themes included recovery timeline (57.1% of patients) and procedure logistics, risks/side effects, pain/discomfort, functional outcomes, and aesthetic outcomes (28.6% each). Post-op themes included recovery timeline and symptom concerns (63.6% each), symptom management (54.5%), and activity restrictions (36.4%). Common decline reasons were concern about AI replacing nursing roles and not having questions.

Conclusion:
Off the shelf voice-enabled AI can meaningfully improve patient experience across several domains in facial plastic clinical care.

Trends in Pregnancy-Associated Bell's Palsy: A National Claims Database Study

Singh N, Denton AJ, Gupta M, Lee YH, Mohan S

Introduction:
Bell's palsy (BP) occurs with greater frequency during pregnancy and puerperium, potentially due to physiological changes affecting blood pressure, immune modulation, and coagulability. Such alterations also contribute to conditions such as pre-eclampsia/eclampsia, gestational diabetes, HELLP syndrome, premature rupture of membranes, and obesity. Despite these associations, treatment patterns and long-term outcomes of pregnancy-associated Bell's palsy (PABP) remain poorly defined. This study aims to examine PABP incidence, management, and associations with pregnancy-related comorbidities, and identify populations at increased risk for PABP and subsequent interventions.

Methods:
The 2015-2022 PearlDiver M170Neurology database was queried, identifying BP patients with ≥1 year of follow-up using ICD-10 codes. Pregnancy-related comorbidities, early corticosteroid +/- antiviral treatment ≤72 hours, and long-term interventions (physical therapy, Botox injections, and surgery) were identified using CPT codes. Procedures that address both static and dynamic aspects of BP were included. Incidence, treatment, and intervention rates were compared using risk ratios (RR) and chi-square analyses ($p < 0.05$)

Results:
Among 4.7 million pregnancies, PABP occurred at a rate of 69 per 100,000, roughly three times higher than general population estimates. Preeclampsia (RR=1.61, $p<0.001$) and gestational diabetes (RR=1.72, $p<0.001$) were significantly associated with PABP. Pregnant patients were more likely to receive early combination therapy than nonpregnant patients (RR=1.88, $p<0.001$). Early therapy did not alter long-term intervention rates among pregnant patients (RR=1.05, $p=0.85$). Conversely, nonpregnant patients demonstrated reduced long-term intervention rates following early therapy (RR=0.73, $p<0.001$). Pregnancy comorbidities were associated with higher long-term intervention rates (RR=1.78, $p<0.001$)

Conclusion:
This is the first large-scale, claims-based study of PABP. PABP occurs more frequently among pregnant patients with preeclampsia or gestational diabetes. Pregnant individuals were not undertreated relative to nonpregnant individuals; however, they demonstrated less responsiveness to early therapy regarding long-term interventions, particularly among those with gestational diabetes or preeclampsia. Comorbidities, rather than treatment or pregnancy alone, were the strongest predictors of intervention needed, suggesting targeted monitoring in high-risk pregnancies may be warranted.

Convolutional Long Short-Term Memory to Enhance AI-Based Anatomical Recognition in Robotic Cardiac Surgery

Christina Waldron, Mina Zaky, Danial Ahmad, Viswajit Kandula, Marc Pelletier, Arnar Geirsson, Makoto Mori

Introduction:
Artificial intelligence–based anatomy recognition and segmentation is a foundation to computerized augmentation of operative tasks. We developed a model specific to the entry phase of robotic mitral valve repair, integrating temporal context to improve the reliability of intraoperative object identification.

Methods:
We used intraoperative recordings of 9 patients undergoing robotic mitral repair performed at a single center for model training/validation. We extracted 1098 frames from chest entry to aortic endoballoon inflation by temporal down sampling and manually annotated to delineate the borders of seven relevant structures: ascending aorta, right atrium, pericardium, lung, diaphragm, sutures, and robotic instruments. A Mask R-CNN model was trained and validated on 80:20 split of an augmented dataset of 5,490 labeled images. We then incorporated a convolutional long short-term memory (convLSTM) module, enabling frame-to-frame context recognition for temporal awareness. Model performance was evaluated on a 20% hold-out validation set using object-level average precision (AP, range 0-1), which integrates detection confidence across varying thresholds. We compared object-level AP in Mask R-CNN and Mask R-CNN+ConvLSTM models to quantify the potential gain related to adding temporal awareness.

Results:
Baseline Mask R-CNN achieved strong accuracy for consistently visible structures such as the aorta (AP 0.81) and robot-arm (AP 0.82) but lagged in deformable or intermittently visible targets like sutures (AP 0.24) and pericardium (AP 0.51). The ConvLSTM-enhanced model improved true AP in all seven evaluated categories, most notably for the pericardium (AP 0.92, Δ +0.41), sutures (AP 0.74, Δ +0.50), and right atrium (AP 0.83, Δ +0.14). Gains were also observed for the aorta (AP 0.84, Δ +0.03), diaphragm (AP 0.61, Δ +0.03), lung (AP 0.68, Δ +0.03), and robot-arm (AP 0.99, Δ +0.17) (Figure A). Overall, mean true AP increased by +0.19, with qualitative improvements in temporal consistency, object boundary continuity, and robustness to occlusion.

Conclusion:
Incorporating temporal awareness through ConvLSTM substantially improved object segmentation of key anatomical targets during robotic mitral surgery. The greatest gains occurred in dynamically deforming or intermittently visible structures, establishing the feasibility of time-aware AI models as a foundation for real-time, phase-specific guidance in complex cardiac operations.

Trends in Retractions of Peer-Reviewed Surgical Articles

Ahmad D, Lei Y, Khosla P, Pelletier M, Mori M

Introduction:
Retraction of manuscripts due to research misconduct is being increasingly observed in medical literature. In 2023 and 2024, large-scale retraction of published research articles occurred related to the discovery of papermill, potentially undermining the public's trust in the scientific publication process. The magnitude of this event relative to historical surgical literature retraction remains unknown. Therefore, we characterized retraction trend in surgical literature.

Methods:
The retraction watch database was queried for all surgery-related retractions. Total volume of yearly surgery-related publications was quantified via PubMed search. Yearly retraction rates as well as common reasons for retractions were summarized. A linear regression model was fitted to assess the association between year and retraction rate. Data were analyzed using R v4.5.1 (R Foundation for Statistical Computing, Vienna, Austria).

Results:
Between 1983 and 2025, there were 2563 retractions of surgery-related article. After excluding duplicates and those related to ophthalmology or dental surgery, we analyzed a total of 1883 retractions. These retractions occurred in 493 journals and 143 publishers. The median time from publication to retraction was 17.6 months (Interquartile Range (IQR) 9.7-47.8).Among the subspecialties, orthopedics and spine surgery had the highest number of retractions (388, 20.6%), followed by general surgery (307, 16.3%) and cardiac surgery (247, 13.1%). Hindawi was the leading publisher of retracted publications (426, 22.6%, Table).
Leading reasons for retractions included investigation by Journal/Publisher (in 871/1883 retractions, 46.3%), data-related issues/concerns (860, 45.7%), issues/concerns with results and/or conclusions (797, 42.3%), and issues/concerns with peer review (673, 35.7%).

Between 1983-2020, the rate of retraction increased steadily by 0.0031% yearly, with 2020 having 0.17% (N=74) retractions. The rate of increase deviated in 2021, peaking in 2022 (390, 20.7% of all surgical retractions), representing a 13-fold increase over the mean rate of 0.13% in the preceding decade (2011-2020). From 2020 to 2024, the top publishers driving retractions (N=898) were Wiley/Hindawi (414, 46.1%), Wiley (213, 23.7%), Springer (90, 10%), and Elsevier (42, 4.7%).

Conclusion:
Surge in retraction across multiple publishers in recent years was observed in the surgical literature as well, highlighting the vulnerability of current peer-review publishing model against large-scale research misconduct.

Characterizing Non-Utilization of Suitable Donor Hearts Following 2018 Allocation Changes: A UNOS Analysis

Wilson, EM., Dankwa, S., Cassady, C., Wang, KM., Khosla, P., Ahmad, D., Talapaneni, S., Miller, PE., Notarianni, AP., Sen, S., Clark, K., Pelletier, MP., Ahmad, T., Mullan, CW.

Introduction:
In 2018, the UNOS heart allocation system changed, including changes to candidate stratification and a transition from Donation Service Areas to distance from donor hospital. We sought to examine the implications of these changes on donor organ utilization (1, 2).

Methods:
The United Network for Organ Sharing Standard Transplant Analysis and Research (UNOS STAR) donor registry was queried for donors between October 18, 2018 – September 30, 2024 with seemingly suitable hearts defined as: age < 50 years, ejection fraction > 55%, without history of coronary artery disease (CAD), HIV, chest trauma, or structural abnormalities. Transplanted versus non-transplanted organs were compared. Utilization within Organ Procurement and Transplant Network (OPTN) region (by donor state) and trends over time were evaluated. Predictors of non-use were evaluated by multivariable logistic regression analysis. Significance was defined as two-tailed $p<0.05$.

Results:
Of 84,431 donors in the study period, 24,096 (28.5%) hearts were transplanted, and 60,335 (71.5%) hearts were not transplanted, of which 7,099 (11.8%) met suitability criteria. Suitable non-transplanted hearts were more often donation after circulatory death (DCD; 38% vs. 7.8%, $p <0.001$) and were more likely to have died of a cardiovascular event (19% vs. 9.8%, $p<0.001$) or stroke (27% vs. 12%, $p<0.001$). Age, BMI, DCD status, hypertension, malignancy, hepatitis C virus (HCV) infection, and COVID infection were each associated with non-use of a suitable heart (Figure 1).

Interestingly, a majority (73%; 5,211/7,099) of suitable hearts were consented but not transplanted, while 23% (1,650/7,099) were recovered for reasons other than transplant (Table 1). Among suitable non-transplanted hearts, regional non-use ranged from 2.4% to 18% ($p<0.001$). Temporal evaluation identified a peak in non-use in 2021 (28%; 1,473/5,334) followed by a decline through 2024.

Conclusion:
A majority of referred donors did not have their hearts recovered for transplantation. Over 10% of these appear suitable for use. Regional disparities in non-use exist, though utilization improved from 2021 to 2024. Donor characteristics associated with non-use should be carefully evaluated to improve organ utilization.

Outcomes of infrainguinal bypass with spliced veins in patients with chronic limb threatening ischemia

Brandon A. Creisher, Liuqian Bao, Warren Carter, Edouard Aboian, David Strosberg , Isibor Arhuidese, Britt Tonnessen, Jonathan Cardella, Raul J Guzman, Cassius Iyad Ochoa Chaar.

Introduction:
Single segment greater saphenous vein (ssGSV) is the gold standard conduit for infrainguinal bypass for patients with chronic limb-threatening ischemia (CLTI). Spliced vein bypass (SVB) is an alternative conduit, but its outcomes have not been well characterized. Moreover, the impact of the number of spliced segments on outcomes remains unclear. This study examines the outcomes of SVB with 2 vein segments (2sSVB) and 3 vein segments or more (3sSVB) compared to ssGSV for infrainguinal bypass.

Methods:
The Infrainguinal Bypass Vascular Quality Initiative (VQI) module (2003-2025) was reviewed for patients treated for CLTI with ssGSV, 2sSVB, and 3sSVB. Propensity matching (3:1) was performed to compare 2sSVB (cohort 1) and 3sSVB (cohort 2) separately to ssGSV adjusting for baseline characteristics including indication, urgency, medical management, and bypass configuration. Perioperative and long-term outcomes were reported, and the primary outcome was major adverse limb events (MALE)-free survival.

Results:
A total of 46,945 infrainguinal bypass procedures (51.5% ssGSV N = 24,185; 4.1% 2sSVB N = 1,906; 0.42% 3sSVB N = 198) were analyzed. There were significant baseline differences in characteristics. After matching, there were 2 comparison groups (cohort 1: 5,017 ssGSV vs 1,681 2sSVB and cohort 2: 525 ssGSV vs 175 3sSVB) with similar characteristics in each cohort. Splicing veins incrementally increased operating time by 64 min (2sSVB) and 84 min (3sSVB). Estimated blood loss also incrementally increased by 91ml (2sSVB) and 114ml (3sSVB) as well as corresponding mean number of pRBC transfusions. There was a trend towards higher cardiac complications that reached statistical significance only for 2sSVB. Perioperatively, 2sSVB had higher rates of return to OR for thrombosis (4.9% vs 3.7%, p = 0.031) compared to ssGSV and a similar trend was noted for 3sSVB. Patients undergoing 3sSVB had a 3-fold increase in inpatient mortality (3.4% vs 1.0%, p = 0.033) compared to ssGSV. Over the mean follow-up of 406 days, 2sSVB patients had statistically significant higher cumulative rates of major amputation, reintervention, and mortality with outcomes of patients treated with 3sSVB showing similar trends. KM curve shows significantly lower MALE-free survival for 2sSVB ($p<0.001$) and 3sSVB (p = 0.04) compared to ssGSV. The 1-year estimates of MALE or death were 29.1%-31.2% (ssGSV-cohorts 1, 2), 38.0% (2sSVB) and 49.3% (3sSVB).

Conclusion:
Splicing veins for infrainguinal bypass to treat CLTI is associated with incremental increase in operative time, blood loss, and perioperative complications compared to ssGSV. MALE-free survival decreased with increasing number of spliced vein segments. Comparison of SVB to other alternative conduits is needed to better define its role in limb salvage.

PCSK9 Inhibitors are Associated with Improved Amputation-Free Survival After Lower Extremity Revascularization

Nicholas Wells, James Cross, Priscilla Oluwakemi Badusi, Warren Carter, Stephen Possick, Britt Tonnessen, Jonathan Cardella, Raul J Guzman, Nihar Desai, Cassius Iyad Ochoa Chaar

Introduction:
Elevated low-density lipoprotein cholesterol (LDL-C) is a well-established risk factor for peripheral arterial disease (PAD) and is associated with adverse cardiovascular and limb-related outcomes. While statins remain first-line therapy for LDL reduction, many patients fail to achieve adequate lipid control or experience progressive disease despite treatment. Proprotein convertase subtilisin/kexin type 9 inhibitors (PCSK9i) provide potent LDL lowering and have demonstrated cardiovascular benefit in high-risk populations, however, their impact on outcomes following lower extremity revascularization (LER) for PAD remains incompletely characterized. This study evaluates long-term cardiovascular and limb outcomes associated with PCSK9i therapy following LER for PAD.

Methods:
A single center retrospective analysis of all patients undergoing LER for PAD was performed (2013-2024). Patients treated with PCSK9 inhibitors were identified and matched 1:4 to patients who did not receive PCSK9i therapy. The index procedure was defined as the LER performed closest in time to PCSK9i initiation for treated patients. Baseline characteristics, perioperative outcomes, and long-term cardiovascular and limb-related outcomes were compared. Kaplan–Meier analysis was used to evaluate amputation-free survival (AFS).

Results:
A total of 2,710 patients were reviewed and only 3.10% (N=84) were treated with PCSK9i. Among PCSK9i-treated patients, 44 (52.38%) initiated therapy prior to the index intervention. After matching, baseline characteristics were comparable between groups, with 37.7% treated for chronic limb-threatening ischemia and 90.3% undergoing endovascular revascularization. Patients receiving PCSK9i had higher baseline LDL-C compared with controls (105.38 vs 85.98 mg/dL, $P<0.001$) and were less likely to be treated with statin prior to index procedure. Perioperative outcomes were similar, with perioperative mortality close to 1% in both groups. After a mean follow up of 4 years, LDL-C levels decreased with no significant difference remaining between the treatment groups. Although patients treated with PCSK9i had higher cumulative rates of myocardial infarction, percutaneous coronary intervention, and overall MACE, they had significantly lower mortality on long-term follow up. There were trends towards lower frequency of reinterventions and major amputation with PCSK9i therapy that did not reach statistical significance. Kaplan–Meier analysis demonstrated improved amputation-free survival among PCSK9i-treated patients that was sustained for up to 8 years of follow up which persisted in patients treated for CLTI only.

Conclusion:
PCSK9i inhibitor therapy is associated with improved amputation-free survival after LER. The benefits of PCSK9i are sustained despite cardiovascular events and seem disproportionate to the target LDL-C reached in this study. Larger prospective studies in patients with advanced PAD undergoing LER are needed to confirm the findings.

Drivers and patterns of disease progression as a novel schema for risk stratification in metastatic non-small cell lung cancer

Gabriela R. Esnaola, Mengru Wang, Jeffrey J. Ishizuka, Benjamin J. Resio, Alexander Pan, Daniel Lee, Aaron Cohen, Madeleine Schmitter, Kelly L. Olino

Introduction:
Targeted therapy (TT) and immunotherapy (IO) have transformed the systemic therapy (ST) landscape for non-small cell lung cancer (NSCLC), but overall prognosis remains poor. Select organ metastases may be predictive of decreased survival; however, the fundamental drivers and patterns of metastatic progression are not well established, and the site-specific effects of ST are poorly understood. We leveraged a large-scale, real-world database containing metastatic site, genomic, and treatment information to characterize and assess the prognostic value of patterns of metastasis and genomic correlates on real-world overall survival (rwOS) in patients with metastatic NSCLC receiving ST.

Methods:
This retrospective study utilized the Flatiron Health-Foundation Medicine Clinico-Genomic Database of patients with metastatic NSCLC treated with first-line (1L) ST. Patient, tumor, and treatment variables were compared with chi-squared tests. rwOS was estimated via Kaplan Meier method and compared with logrank test; adjusted hazard ratios were computed with multivariable Cox regression. Bernoulli mixture models were used to cluster patients by metastatic sites at 1L therapy start using the R package “flexmix”.

Results:
Sites of disease were evaluated for 10,571 patients. Patients with spleen, skin, liver, kidney, and bone metastases had worse OS. Data from 18 metastatic sites revealed 8 clusters: high metastatic burden (HMB, ≥3 sites with frequency ≥0.5, n = 933), bone (n = 2,889), pleura (n = 2,469), lung (n = 1,710), liver (n = 1,345), brain (n = 1,163), lymph node (LN, n = 748), and adrenal avid (n = 659). While HMB (8.4 months) and liver mets (8.9 months) are known to be associated with poor median OS, we also found that bone (11.9 months), adrenal (13.4 months), pleura (14.0 months), and LN (14.4 months) clusters had worse median OS compared to lung (17.7 months) and brain (16.5 months, $p<0.001$). Certain mutations had increased odds ($OR>1.5$ and $p < 0.05$) in site-specific clusters, including: adrenal (SRC, ARID1A, BCL2L1, ATR, EPHA3, CCND3, KEAP1), liver (AXL, AKT1, AKT2, EPHB1), brain (MAP2K4, GLI1, PIK3CB, KDR), and bone (ERBB3). Interestingly, EP300, EPHB4, and PBRM1 mutations were associated with HMB, but no individual sites. Adrenal and brain clusters had the highest tissue tumor mutational burden of the clusters. TT was associated with greater OS compared to other ST in lung, pleura, and bone clusters (HR 0.68-0.80, $p < 0.01$).

Conclusion:
Definable patterns of metastasis predict survival and treatment response in lung cancer. Genomic patterns of mutation predict site-specific metastatic spread. This study is the most comprehensive evaluation of the impact of sites of metastasis and genetic markers on survival outcomes in patients with NSCLC to date. Our proposed clusters may represent a novel framework for mechanistic inquiry and risk stratification in advanced NSCLC.

Development of an AI-Powered Platform for Object Detection and Spatial Quantification of Anatomical Structures during Robotic-Assisted Surgery

Bader J., Ramirez-Hardy A., Sun X., Rosenfelt T., Vitchutripop T., Srinivasan A., Pantel H., Khanna A., Rakita D.

Introduction:
Critical operative steps in robotic surgery have not been quantified on an instrument/tissue relationship level. Establishing and optimizing these metrics can improve surgical precision, teaching, and outcomes. In collaboration with Yale's Departments of Computer Science and Colorectal Surgery, we developed an AI-powered object detection and spatial quantification model which measures features of anatomical structures in robotic surgery.To demonstrate this technology, our model analyzed robotic colorectal surgery videos of Inferior Mesenteric Artery (IMA) division. The IMA lies in a high-risk area which requires meticulous dissection and instrument positioning. Incomplete or poorly performed IMA division can lead to devastating consequences like bleeding and tissue ischemia. However, there are no established guidelines for optimal retraction and relative tissue/instrument angles during IMA exposure and division.

Methods:
Our AI-model was built with Python and designed with a front-end interface using PyQt6 technology. Videos of robotic low anterior resections (n=13) and sigmoid colectomies (n=11) from 2 surgeons at Yale were annotated for the moments before IMA division. Videos were sectioned at 30 frames/second. The first 3-5 frames had manual selection of IMA and stapler followed by application of zero-shot SAM2 technology which precisely delineated and tracked the IMA and stapler for the remaining hundreds of frames. Deep learning algorithms and 3D mesh modeling allowed for quantification of intraoperative structures including 3D and 2D angles of stapler and IMA, surface area and width of IMA, and visualized area under IMA during tissue exposure.

Results:
The model successfully derived 2D angles in 81% of videos (mean 2D IMA angle 58.4° [95%CI 48.6–68.6°]; stapler angle 29.6° [95% CI 20.0–38.0°]; and intersection angle 91.0° [95%CI 82.8–98.0°]) with consistent measurements for angles despite variations in operative fields and surgeon technique. The model successfully measured 3D stapler angle, IMA tissue width, visualized IMA surface area, and exposure area under the IMA prior to division. Exploratory application utilized support vector machine and principal component analysis of 3D vectors to define the spatial relationship of the stapler and IMA associated with higher bleeding rates after IMA division.

Conclusion:
We demonstrate the feasibility of our AI-powered model to quantify intraoperative anatomy during robotic surgery. This work provides the first AI-defined metrics for vessel exposure and division. After multicenter validation, our model has potential for optimizing intraoperative maneuvers, real-time teaching, retrospective review/surgeon credentialing, complication prevention, and improving patient outcomes with applicability to a wide range of robotic surgeries.

Prognostic Impact of Tumor Suppressor and DNA Damage Repair Gene Mutations in Oral Cavity Squamous Cell Carcinoma: A Clinico-Genomic Analysis from a Real-World Database

Parisa Abedi, Andrew George, Benjamin Schiff, Soraya Fereydooni, Andres Aguirre, Saral Mehra, Benjamin Judson, Curtis Pickering.

Introduction:
Oral cavity squamous cell carcinoma (OCSCC) is a distinct head and neck squamous cell carcinoma (HNSCC) subtype with unique genomics and clinical behavior. Although pembrolizumab-based regimens are standard first-line therapy for recurrent/metastatic HNSCC, prognostic and predictive biomarkers remain incompletely defined in OCSCC. Prior surgical series and TCGA analyses link TP53 mutations to worse survival (HR ~1.4–1.7) and TERT promoter mutations to adverse outcomes (HR ~2). Emerging data also suggest DNA damage response (DDR) genes (e.g., BRCA1/2, PRKDC) may influence immunotherapy response, but real-world clinico-genomic evidence with linked treatment and survival outcomes is limited. We characterized the prognostic impact of key genomic alterations in OCSCC using a large real-world clinico-genomic database.

Methods:
We identified 381 patients with OCSCC in the Flatiron Health–Foundation Medicine Clinico-Genomic Database, linking comprehensive genomic profiling (~300 genes) with longitudinal outcomes. Mutation frequencies were benchmarked to TCGA and AACR GENIE. We evaluated TP53, CDKN2A, TERT promoter, PIK3CA, and DDR pathway genes. Inverse probability of treatment weighting (IPTW) balanced mutation groups for age, sex, stage IV, smoking, and advanced disease, and a 90-day landmark minimized immortal time bias. Immunotherapy (IO) was received by 213 patients (56%), predominantly pembrolizumab (80%) or nivolumab (19%). TMB-high was defined as ≥10 mut/Mb. Endpoints were overall survival (OS) from diagnosis (primary) and OS from IO initiation (secondary).

Results:
Stage IV was the strongest clinical prognostic factor for OS from diagnosis (HR 1.64, 95% CI 1.29–2.08, p<0.0001). In IO-treated patients, TMB-high trended toward improved OS (HR 0.54, 95% CI 0.30–0.96, p=0.0349). Genomic alterations were prognostically informative: DDR pathway mutations (BRCA1/BRCA2/PRKDC) were associated with inferior OS from IO initiation (HR 2.34, 95% CI 1.00–5.49, p=0.049; median OS 5.7 vs 13.8 months; 12-month OS 17.4% vs 50.4%). TP53+CDKN2A co-mutation showed worse outcomes versus TP53 mutation alone (HR 1.50, 95% CI 0.99–2.27, p=0.056; median OS 9.8 vs 12.8 months; 12-month OS 34.7% vs 51.5%).

Conclusion:
Overall, TP53 was associated with worse OS, and TP53+CDKN2A defined a higher-risk subset with substantially shorter survival versus wild-type (median 20.9 vs 44.5 months); CDKN2A alterations co-occurred with TP53 in 95%. TERT promoter mutations, enriched in oral cavity tumors, confirmed an adverse prognostic role. In contrast, PIK3CA mutations were associated with favorable prognosis (HR 0.59). DDR alterations predicted particularly poor outcomes after IO, suggesting potential resistance mechanisms. These findings support prospective validation and may inform molecular risk stratification and genomically guided therapeutic strategies in OCSCC.

Clinicogenomic Determinants of Survival and Immunotherapy Response in Advanced Head and Neck Cancer

Parisa Abedi , Andrew George , Ben Schiff , Soraya Fereydooni , Andres Aguirre , Benjamin Judson , Saral Mehra , Curtis Pickering

Introduction:
Somatic mutations drive cancer progression and guide targeted therapy selection in many tumor types. Although genomic alterations in head and neck squamous cell carcinoma (HNSCC) have been characterized by The Cancer Genome Atlas and other sequencing projects, the association between specific mutations and real-world treatment response remains incompletely understood.

Methods:
This study analyzed real-world data from the Flatiron Health-Foundation Medicine HNSCC Clinicogenomic Database (CGDB), focusing on how clinical variables and disease characteristics correlate with treatment responses and overall survival. We characterized mutation frequencies across clinically relevant subgroups to understand their impact on disease trajectory.

Results:
The CGDB cohort includes 1,531 HNSCC patients, with 52% of tumors originating from the oropharynx and nearly 70% being HPV-positive. Clinical heterogeneity is evident: median OS varies by tumor site (oral cavity: 32.2 months; oropharynx: 45.8 months) and treatment pattern (metastatic at diagnosis or untreated: 30 months; secondary locoregional recurrence after treatment: 103.6 months). Primary site influenced AJCC progression patterns—oral cavity tumors frequently presented as not cured at diagnosis (37.8%), while oropharyngeal cancers more often progressed to distant metastasis (40.8%).

In advanced disease, mutations were dominated by TP53, followed by MLL2 and NOTCH1. HPV-positive oropharyngeal tumors harbored PIK3CA, MLL2, and EP300 mutations. TP53 mutations associated with worse outcomes in high-stage oropharyngeal tumors treated with immunotherapy. High CPS scores and high TMB improved immunotherapy survival. In HPV-positive oropharyngeal patients, mutations in KRAS pathway genes (NF1, HRAS, KRAS, NRAS), DNA damage repair genes (BRCA1, BRCA2, PRKDC), and PI3K/AKT/mTOR signaling associated with better immunotherapy outcomes.

Conclusion:
Integrating genomic biomarkers into treatment selection addresses HNSCC's clinical and molecular heterogeneity. Specific alterations like TP53 mark poor prognosis, while pathway-level alterations in KRAS signaling, DNA repair, and PI3K/AKT/mTOR may predict immunotherapy benefit. Tailoring treatment by anatomic site, disease stage, and somatic mutations has potential to advance precision medicine in HNSCC.

Racial Disparities in Surgical Outcomes after Hernia Repair in 708,654 Patients – A Multi-Institutional Data Analysis

Moritz Milewski; Felix J. Klimitz; Leonard Knoedler; Samuel Knoedle; Stav Brown; Frederik J Hansen; John R DiBello; Michael Alfertshofer; Paul David; Fortunay Diatta; Omar Allam; Georg F Weber; Paris D Butler; Siba Haykal; Bohdan Pomahac; Martin Kauke-Nav

Introduction:
Racial disparities in surgical outcomes have been widely reported across multiple surgical disciplines; however, comprehensive analyses in hernia repair remain limited. This study aimed to evaluate racial disparities in perioperative characteristics and postoperative outcomes following hernia repair using a large multi-institutional database.

Methods:
Adult patients undergoing hernia repair between 2008 and 2021 were identified from the American College of Surgeons National Surgical Quality Improvement Program database. Demographic, clinical, perioperative, and 30-day postoperative outcomes were analyzed. Univariable analyses were performed using chi-squared and Kruskal-Wallis tests. A Bayesian multinomial logistic regression model adjusted for confounders to assess independent associations between race and outcomes.

Results:
A total of 708,654 patients were included, predominantly White (86.3%), followed by Black (11.0%), Asian (1.9%), American Indian/Alaska Native (0.6%), and Native Hawaiian/Pacific Islander (0.3%) patients. Significant baseline differences existed across racial groups, including BMI, comorbidities, and hernia types. Black patients had higher rates of hypertension, diabetes, dialysis dependence, longer operative times, and were less likely to undergo laparoscopic repair. They also experienced higher rates of postoperative complications, including reintubation, transfusion, and return to the operating room. In contrast, Asian patients demonstrated lower rates of postoperative complications, including wound infections, pneumonia, and reoperation, despite higher rates of renal comorbidities. American Indian patients showed the highest rates of wound infections. Length of stay was significantly associated with race, with prolonged hospitalization more common among Black patients.

Conclusion:
Significant racial disparities exist in clinical characteristics, surgical management, and postoperative outcomes following hernia repair. Black and American Indian patients experience disproportionately worse outcomes, whereas Asian patients demonstrate comparatively favorable postoperative courses. These findings highlight the need for targeted interventions to reduce inequities and improve surgical outcomes across diverse populations.

From Inflammation to Fibrosis: The Molecular Basis of Breast Implant Capsular Contracture – A Systematic Review

Moritz Milewski; Yizhuo Shen; Felix J. Klimitz; Renee Gao; Stav Brown; Jen-Yeu Wang; Samira Glaeser-Khan; Martin Kauke-Navarro; Justin M. Broyles; Siba Haykal; Bohdan Pomahac

Introduction:
Capsular contracture remains one of the most common and challenging complications following cosmetic breast augmentation, yet its biological pathogenesis is incompletely defined. Emerging evidence implicates a multifactorial interplay between silicone exposure, microbial signals, immune activation, and extracellular matrix (ECM) remodeling. This systematic review synthesizes human mechanistic studies to define a unified biologic framework for capsular contracture.

Methods:
A PRISMA-compliant search of PubMed/MEDLINE, Embase, and Cochrane CENTRAL identified human studies investigating histologic, cellular, molecular, or microbiologic mechanisms of capsular contracture specifically in cosmetic augmentation patients.

Results:
Of 1,732 records, 19 studies met inclusion criteria. Progressive fibrosis was characterized by increased capsule thickness, altered collagen architecture, and enhanced ECM crosslinking, associated with elevated lysyl oxidase activity and MMP/TIMP imbalance. Early tension-mediated contractility was driven by fibroblast proliferation and α-SMA–positive myofibroblasts, whereas mature capsules exhibited matrix-dominant stiffness. Silicone particulate deposition was consistently observed and associated with foreign-body giant cells, chronic macrophage activation, and granulomatous inflammation. Microbiologic analyses identified increased biofilm burden and staphylococcal-dominant dysbiosis, though with study-to-study variability. Transcriptomic studies demonstrated pervasive innate and adaptive immune activation, including Th1/Th17 polarization, cytotoxic $CD8^+$ signaling, reduced regulatory T-cell suppression, and oligoclonal T-cell expansion, along with upregulation of B-cell activation receptor pathways.

Conclusion:
Human mechanistic evidence supports capsular contracture as a chronic immune-mediated foreign body response initiated by surgical injury and perpetuated by silicone particulate exposure, biofilm-associated dysbiosis, and sustained macrophage, T-cell, and B-cell activation. These immune cues drive progressive ECM deposition, collagen crosslinking, and long-term matrix stiffening. This integrated framework highlights potential therapeutic and implant-design targets—including macrophage polarization, B-cell activation pathways, and LOX inhibition—to mitigate capsular fibrosis.

Frailty Independently Predicts Postoperative Complications After Elective Surgery for Diabetic Foot Ulcers

Klimitz, FJ; Knoedler, S; Brown, S; Milewski, M; Pomahac, A; Kauke-Navarro, M; Panayi, AC; Haykal, S; Pomahac, B

Introduction:
Diabetic foot ulcers (DFUs) represent a major cause of morbidity, hospitalization, and limb loss. Despite high perioperative risk, current stratification models inadequately capture cumulative physiologic vulnerability. Frailty has emerged as a multidimensional predictor of adverse surgical outcomes. We evaluated whether frailty, quantified by the Five-Item Modified Frailty Index (mFI-5), independently predicts postoperative complications in patients undergoing elective DFU surgery.

Methods:
We performed a retrospective cohort study using the American College of Surgeons National Surgical Quality Improvement Program (ACS-NSQIP) database (2015–2021). Adults with type 2 diabetes and ICD-10–coded DFUs (E11.621) undergoing elective surgical management were included. Patients were stratified as prefrail (mFI-5 ≤2) or frail (mFI-5 >2). Primary outcome was any 30-day postoperative complication (composite of mortality, reoperation, readmission, surgical and medical complications). Multivariable logistic regression assessed the independent association between frailty and outcomes, adjusting for clinically relevant confounders.

Results:
Among 2,819 patients, 714 (25.3%) were classified as frail. Frail patients were older and exhibited higher rates of insulin-treated diabetes, COPD, CHF, dialysis dependence, dyspnea, bleeding disorders, and functional dependence (all $p<0.05$). Overall complications occurred more frequently in frail versus prefrail patients (50.6% vs. 32.9%, $p<0.001$), as did mortality (4.1% vs. 1.6%, $p=0.003$). In adjusted models, frailty independently predicted any postoperative complication (OR 1.34, 95% CI 1.05–1.70, $p=0.02$) and medical complications (OR 1.53, 95% CI 1.12–2.07, $p=0.007$), though not surgical complications alone. Frail patients were more frequently discharged to nonhome facilities (40.8% vs. 35.4%, $p=0.02$).

Conclusion:
Frailty, as measured by the mFI-5, independently predicts postoperative morbidity and mortality after elective DFU surgery. Integrating preoperative frailty screening into multidisciplinary perioperative workflows may improve shared decision-making, optimize resource allocation, and guide targeted perioperative optimization strategies in this high-risk population.

Cancer-related Lymphedema and Alzheimer's Disease Development after ALND

Brown S, Klimitz FJ, Kauke-Navarro M, Noel O, Knoedler S, Wo L, Haykal S, Pomahac P

Introduction:
Emerging evidence suggests that impaired cervical lymphatic drainage contributes to the accumulation of amyloid-beta and the pathogenesis of Alzheimer's disease (AD). While axillary lymph node dissection (ALND) is a common cause of cancer-related lymphedema, its potential relationship to AD has not been previously explored.

Methods:
We analyzed all female patients who underwent ALND at a tertiary cancer center from 2013 to 2024. Demographic and clinical data were collected, including lymphedema diagnosis and AD onset. A multivariate regression analysis and Propensity Score Matching were used to assess risk factors for AD after ALND and evaluate the relationship between lymphedema and AD development.

Results:
Of the 15,666 patients, 2,535 (16.2%) developed lymphedema, with a mean onset of 20.5 months post-ALND. Among the 8,095 patients aged 60 or older, 243 (3.0%) were diagnosed with AD. Significant independent predictors of AD included older age at ALND ($OR = 1.11$, $p < 0.001$), cerebrovascular disease ($OR = 1.63$, $p = 0.002$), and preexisting depression ($OR = 3.56$, $p < 0.001$). African American race was associated with increased risk ($OR = 1.87$, $p = 0.005$), as was Hispanic/Latino ethnicity ($OR = 2.20$, $p = 0.002$). Importantly, a diagnosis of lymphedema was associated with a significantly lower risk of developing AD ($OR = 0.34$, $p = 0.001$).

Conclusion:
This is the first and largest study to investigate the relationship between lymphedema and AD following ALND. Further research is warranted to explore whether therapeutic interventions for lymphedema or compensatory enhancements in central lymphatic drainage caused by extremity lymphedema may enhance clearance and contribute to reduced AD risk.

Patterns of Risk-Reducing Surgery in Genetic Mutation Carriers: A Claims Based Analysis

Proussaloglou EM, Moore MS, Berger ER, Valero M, Giri VN, Schneider E, Greenup RA

Introduction:
As genetic testing becomes more accessible and prevalent, evidence-based care for hereditary breast and ovarian cancer (HBOC) risk is critical. We performed a claims-based analysis to assess national patterns of risk-reducing surgery and patient-level differences using administrative claims data from the Merative MarketScan Database (2017-2022) to determine the current rates of risk-reducing surgery amongst unaffected high-risk genetic variant carriers.

Methods:
Women aged 18-64 who had undergone RRM and/or RRO with one or more diagnostic code for HBOC (Z15.01, Z15.02) were included; 6 months of pre-surgery enrollment was required. Patients with acquired absence of breast or ovaries and those with diagnosis of breast/ovarian malignancy were excluded. Surgery was identified by ICD-10-PCS and CPT codes. Demographics and data on index and secondary surgery were collected and assessed using t-test, ANOVA, and Pearson's chi-square tests.

Results:
1,797 female enrollees underwent risk-reducing surgery and met inclusion criteria. Mean age at time of index surgery was 44.1 years. Most enrollees underwent RRO as their index surgery (58.0%, n= 1043), with 40.5% (n =727) having index RRM and 1.5% (n=27) having same-day RRM and RRO. Patients undergoing RRM were significantly younger (mean 40.3, median 40) than those undergoing RRO (mean 46.7, median 46) and those undergoing concomitant surgery (mean 44.1, median 43). Family history (FH) of cancer influenced patterns of risk-reducing surgery; FH of breast cancer was significantly higher in the RRM patients (88.2% vs 62.8% and 81.5% respectively, $p < 0.001$) while. Rates of FH of ovarian cancer was significantly higher among women undergoing RRO first or concomitant RRM/RRO when compared to RRM (37.5% vs 44.4% vs 19.1% respectively, $p<0.001$). No statistically significant difference was identified between groups in employment status or insurance type, though more dependents (<26yo) underwent mastectomy as index surgery (6.1% vs 0.6% RRO and 0% both surgeries, $p < 0.001$). The overwhelming majority underwent age-indicated RRO according to national guidelines, with only a small minority (7.3%, n = 53) having RRO prior to age 35. Among women undergoing both RRM and RRO (n = 150), younger patients were more likely to undergo RRM first. Patients with initial RRM were more likely to have their second surgery within the same calendar year (64.4%, $p < 0.001$) than patients getting initial RRO (44.9%). Of patients that had both surgeries during the study period, 60.7% of them had surgery within a calendar year.

Conclusion:
This is the first modern assessment of surgical risk-reduction patterns in genetic carriers unaffected by cancer.We found excellent compliance for age-indicated RRO and many women undergoing sequential risk-reducing surgeries within one calendar year. FH of breast vs ovarian cancer and age are both associated with timing of risk reducing surgery and may be major motivators of surgical decision making.

The Modern Endocrine Surgery Job Market (2005–2025): Analysis of Hiring Pathways, Practice Composition, and Predictors of Success

Syed F Haider, Courtney Gibson, Jennifer Ogilvie, Adriana G Ramirez

Introduction:
Twenty years into its dedicated fellowship, endocrine surgery has matured into a distinct subspecialty. Data guiding graduates navigating the modern job market remain limited. This study defines contemporary employment trends and determinants of early career success among American Association of Endocrine Surgeons (AAES) fellowship graduates.

Methods:
A national survey of AAES fellowship graduates (n=87) assessed demographics, job timing, practice type, recruitment pathways, and perceived success factors. Descriptive statistics and regression modeling evaluated temporal trends and predictors of employment outcomes and early career success.

Results:
Among respondents (57.5% female), academic positions declined from 90% to 45% over two decades (−2.4%/yr, p=0.016). Early hiring increased modestly (26%→38%, p=0.31). Pure endocrine-only (20–30%) remained stable, while endocrine-heavy practices (≥50% endocrine volume) rose from 39%to 70% (+1.8%/yr, p=0.14), driven by nonacademic surgeons (+4.6%/yr, p=0.013).

Top hiring resources were trainee faculty (64%), peer colleagues (41%), and the AAES job board (40%). Valued skills included high-volume fellowship experience (82%), minimally invasive adrenal surgery (38%), and research productivity (33%). Key success factors included high clinical volume (88%), mentorship/senior partner access (67%), office-based procedure proficiency (43%), and intraoperative adjunct familiarity (43%).
Digital recruitment expanded significantly: AAES job board awareness increased from 64% to 91% (p=0.007), online job searches from 21% to 47% (p=0.046), and hybrid/remote interviews from 14%→56% (p=0.001). Only 6% reported Endocrine Surgery University as helpful for job acquisition.

Multivariable analysis linked academic placement with research productivity (OR 4.5, $p<0.05$). Community placement correlated with later graduation (OR 21.4, p=0.0003), compensation (OR 6.8, p=0.010), and mixed-practice flexibility (OR 3.2, p=0.038). Early hiring was associated with mentorship and faculty involvement (OR 4.8, p=0.025), while early career success correlated with mentorship access (OR 5.2, p=0.001) and high-volume training (OR 3.0, p=0.018).

Conclusion:
The modern endocrine surgery job market is increasingly structured, digital, and mentorship-driven. While academic positions have declined, community practices have expanded. Mentorship access and operative volume remain the strongest predictors of early success. Enhanced mentorship and career-development resources may better prepare fellows for the evolving workforce.

Overtreatment of Minimally Invasive Oncocytic Carcinoma Relative to 2025 American Thyroid Association Guidelines

Gabriel JM., Haynes CV., Gabriel TJ., Haider SF., Mahoney FS., Rome C., Gibson C., Ogilvie J., Ladenheim A., Ramirez AG.

Introduction:
Oncocytic Thyroid Carcinoma (OC), previously called Hürthle Cell Carcinoma, is a rare type of thyroid cancer with aggressive characteristics and high rates of radioactive iodine (RAI) resistance. Broadly, oncocytic neoplasms can be categorized as oncocytic adenoma (OA), minimally invasive OC (MIOC), or widely invasive OC (WIOC) based on degree of invasion and presence of aggressive characteristics. The 2022 World Health Organization reclassification and 2025 American Thyroid Association (ATA) guidelines have refined the definition and management of OC. The new guidelines conditionally recommend lobectomy without completion thyroidectomy or radioactive iodine (RAI) for oncocytic neoplasms in the absence of high-risk features. We investigated whether recent management of OC is consistent with new ATA guidelines and identified factors to risk stratify tumors.

Methods:
A retrospective review identified all patients who underwent thyroid surgery for oncocytic neoplasms at a tertiary center from 2012–2022. Tumors were classified as OA, MIOC, or WIOC according to the ATA guidelines. Demographic, pathologic, and treatment variables were compared using chi-square, Fisher's Exact, and ANOVA tests, with multivariable analysis comparing OA vs MIOC and OA vs WIOC.

Results:
Among 309 patients, 224 had OA, 46 MIOC, and 39 WIOC. Mean age at diagnosis rose from 54.9 years in OA to 58.9 in MIOC and 62.3 in WIOC ($p = 0.004$). Average tumor size was correlated with aggressive pathology (2.25 cm OA, 2.88 cm MIOC, 5.63 cm WIOC; $p < 0.001$), with tumors ≥ 4 cm observed in 15%, 35%, and 87%, respectively. Multivariate logistic regression showed that compared to OA, OR for MIOC increased by 25% per cm increase in tumor size ($p = 0.024$), and OR for WIOC more than doubled per cm increase in tumor size (OR =2 .44, $p < 0.001$). Initial total thyroidectomy was performed in 44% of MIOC versus 46% of WIOC. Among lobectomy cases, 54% of MIOC and 86% of WIOC underwent completion thyroidectomy ($p = 0.056$). Tumor size was not associated with extent of surgery decision-making as 36% of tumors < 4cm underwent upfront total thyroidectomy compared with 39% of tumors ≥ 4cm ($p = 0.75$). 48% of MIOC versus 74% of WIOC had RAI ($p = 0.023$). Recurrence was only observed in 13% of WIOC ($p = 0.018$).

Conclusion:
In this study, WIOC demonstrated a distinct high-risk phenotype, characterized by older age at diagnosis, larger tumor size, and a measurable risk of recurrence. In contrast, MIOC exhibited indolent behavior with no observed recurrences consistent with the ATA's recommendation to manage similarly to low-risk differentiated thyroid cancers. However, approximately half of MIOC patients received completion thyroidectomies and RAI highlighting persistent overtreatment. Adherence to ATA recommendations favoring lobectomy without RAI for MIOC is supported and should inform more conservative, risk-adapted practice.

Clinicopathologic and Therapeutic Insights Into Early Recurrence of Widely Invasive Oncocytic Thyroid Carcinoma

Gabriel JM., Haider SF., Haynes CV., Gabriel TJ., Mahoney FS., Rome C., Gibson C., Ogilvie J., Ladenheim A., Ramirez AG.

Introduction:
Widely invasive oncocytic carcinoma (WIOC) represents the most aggressive phenotype within the oncocytic neoplasm of the thyroid, as defined by the 2022 WHO and 2025 ATA classifications. Despite standardized diagnostic criteria, the timing, pattern, and management outcomes of recurrence in WIOC remain poorly defined. This study characterizes the clinicopathologic features and treatment strategies associated with the early-recurrence phenotype of WIOC.

Methods:
A retrospective review was conducted of all oncocytic thyroid neoplasms managed at a tertiary endocrine surgery center between 2012 and 2022. Cases meeting histopathologic criteria for widely invasive oncocytic carcinoma were identified, and those with postoperative recurrence were analyzed to characterize recurrence timing, anatomic distribution, adjuvant radioiodine use, and management strategies.

Results:
A total of 309 oncocytic thyroid neoplasms were identified, comprising 224 oncocytic adenomas, 46 minimally invasive oncocytic carcinomas, and 39 widely invasive oncocytic carcinomas (WIOC). Recurrence was observed exclusively within the WIOC subset, reinforcing its biologically aggressive nature. Among patients with WIOC, five developed disease recurrence (12.8%). The recurrent cohort demonstrated a trend toward older age (64.8 ± 18.0 vs 61.3 ± 16.8 years, p = 0.73) and larger primary tumors (7.5 ± 3.5 vs 5.6 ± 2.2 cm, p = 0.28) compared with nonrecurrent WIOC. All patients with recurrence had undergone total or completion thyroidectomy, with four undergoing concurrent central and/or lateral neck dissection. Adjuvant RAI was administered in 4 of 5 patients (80%), with an average dose of 164.2 ± 33.4 mCi (range 142–214). The mean time to recurrence was 14.4 ± 21.7 months (range 3–53), and four of five (80%) recurred within the first postoperative year. Sites of recurrence included the lateral neck (n=1), central neck (n=2), tracheal/laryngeal invasion (n=1), and lung metastasis (n=1). Following recurrence, surgical re-intervention was performed in three patients. Lenvatinib was initiated in one patient and radiation therapy was delivered in two. No disease-specific mortalities were observed.

Conclusion:
Recurrence within the oncocytic spectrum occurred exclusively in WIOC and predominantly within the first postoperative year. Early and comprehensive surgery combined with adjuvant RAI and selective reintervention provides durable control, underscoring the need for vigilant early surveillance in this high-risk subset.

Neighborhood Deprivation and Outcomes Following Parathyroidectomy for Uremic Hyperparathyroidism

Syed F Haider, Courtney Gibson, Jennifer Ogilvie, Adriana G Ramirez

Introduction:
Secondary hyperparathyroidism (SHPT) is a common complication of end-stage renal disease (ESRD) associated with substantial morbidity. Parathyroidectomy (PTX) improves biochemical control, yet socioeconomic disparities may influence longitudinal outcomes. The Area Deprivation Index (ADI) is a validated measure of neighborhood disadvantage. We evaluated whether ADI influences surgical outcomes and kidney transplant access following PTX for SHPT.

Methods:
We conducted a retrospective single-institution cohort study of ESRD patients undergoing PTX for SHPT with follow-up through last contact or death. ADI percentiles were categorized as Low (0–33), Moderate (34–66), and High (67–100). Demographics, disease severity, operative characteristics, postoperative outcomes, transplant candidacy, transplant conversion, and survival were compared using ANOVA and chi-square testing.

Results:
Among 149 patients, demographics differed significantly by ADI, including race distribution and non-English language prevalence (p=0.005), while comorbidities and disease severity were similar. Referral pathways and disease severity did not differ, including dialysis duration (5.2 vs 5.9 vs 5.5 years; p=0.795), preoperative PTH (1,568 vs 1,703 vs 1,819 pg/mL; p=0.746), calcium, phosphate, and cinacalcet. Operative management was comparable across groups, with subtotal PTX performed in >93% for all subgroups (p=0.733). Postoperative outcomes did not differ, including length of stay, readmission, calcium infusion requirement, mortality, or biochemical success (dcPTH <300 pg/mL achieved in 66.7%, 80.9%, and 86.0%; p=0.292). Overall transplant rates were similar (p=0.627). However, transplant candidacy differed by ADI (50.0% vs 44.7% vs 67.4%; p=0.047), and conversion from candidacy to transplantation declined with increasing deprivation (83.3% vs 64.3% vs 41.4%; p=0.040).

Conclusion:
Neighborhood deprivation was not associated with operative or biochemical outcomes after PTX suggesting equitable surgical care. However, higher deprivation was associated with reduced progression from transplant candidacy to transplantation highlighting persistent socioeconomic barriers in longitudinal ESRD care

The Prognostic Value of Metastatic Sites in Single-site Synchronous Oligometastatic Non-Small Cell Lung Cancer in the Era of Immunotherapy

Gabriela R. Esnaola, Maureen Canavan, Giorgio Caturegli, Abigail Lynch, Benjamin J. Resio

Introduction:
Systemic immunotherapy (IO) has been shown to improve survival in patients with non-small cell lung cancer (NSCLC). Single metastatic sites have a more favorable prognosis than multiple sites, and patients with single-site metastatic NSCLC have historically been considered candidates for local therapy (LT) in the form of radiation or surgery. However, most studies demonstrating a possible benefit to local therapy originated prior to widespread IO adoption, and a recent randomized trial has shown no advantage for LT in patients who received IO with less than three metastatic sites. National survival outcomes for patients receiving LT and systemic therapy (ST) for lung cancer with single metastatic sites in the era of immunotherapy remain poorly described. We used the National Cancer Database (NCDB) to assess how site of metastasis and the use of LT in combination with systemic IO is associated with prognosis of patients with single-site metastatic NSCLC in the United States (US).

Methods:
The NCDB (2018–2023) was used to retrospectively evaluate patients with single-site synchronous oligometastatic NSCLC (clinical stage IVA) treated with IO. Patients were stratified based on metastatic site and treatment type: systemic IO with or without LT (IO+LT or IO). All patients could have additionally received chemotherapy (CTX). Prognosis was evaluated using Kaplan-Meier survival analysis landmarked at the median time from diagnosis to LT initiation.

Results:
Among included patients (N=4,159), sites of oligometastatic disease included bone in 16.2% (N=1,059), brain in 26.9% (N=1,763), distant LN in 5.4% (N=354), liver in 3.3% (N=216), lung in 26.0% (N=1,699), and other sites in 22.2% (N=1,455) of patients. 992 patients (23.9%) were treated with IO and 3,157 (76.1%) with IO+LT (79.4% of all patients received CTX, 62.9% radiation, and 14.2% surgery). Poor OS was associated with bone (median survival 22.6 months, 25.5% 5-year survival) and liver (median survival 16.7 months, 12.0% 5-year survival) metastases compared to brain, lung, or nodal metastases (median survival 28.4 months, 31.5% 5-year survival). Significantly longer survival was associated with patients selected for LT.

Conclusion:
The addition of local therapy to a systemic regimen containing immunotherapy was common for patients with single metastatic sites in the US. Patients selected for local therapy had a favorable prognosis, which varied by metastatic location.

Long-term Prognosis of Thymic Neuroendocrine Tumors in the National Cancer Database

Caturegli G, Patil J, Lynch A, Canavan M, Jernigan E, Boffa D, Resio B

Introduction:
Primary thymic neuroendocrine tumors (TNETs) are rare and understudied. There is little data to inform clinical care and prognosis of these tumors. The purpose of this study was to assess tumor characteristics, treatment patterns, and prognosis of TNET in the United States

Methods:
All TNETs diagnosed between 2004 and 2023 in the National Cancer Database were identified. Patient, treatment, and tumor characteristics were compared to patients with thymic carcinoma and thymoma by Chi-squared and Wilcoxon rank-sum tests. Stage was abstracted into the TNM AJCC 8th edition using available variables. Survival was modeled by Kaplan-Meier analysis, and multivariable Cox proportional hazards regression models were performed to assess prognostic factors.

Results:
In total, 1029 TNET cases were identified, compared to 14641 thymoma and 5100 thymic carcinoma cases. Patients with TNET were younger (median age 58) and more likely to be male (67%). 579 (56%) TNETs were managed surgically, while only 398 (39%) received chemotherapy and 57 (6%) radiation. TNETs were more likely to present with localized stage [379 (37%)] compared to thymic carcinoma [1386 (27%), $p<0.001$], but less likely than thymoma [7798 (53%), $p<0.001$]. Five-year survival of surgically resected TNET was 77% vs. 86% for thymoma and 66% for thymic carcinoma ($p<0.001$). Five-year survival was similar for surgically managed thymic typical and atypical carcinoids (84% vs 82%). Carcinoid histology was associated with increased five-year survival compared to neuroendocrine carcinoma (67%) or small cell (63%, $p<0.001$). Definitive surgical management was the strongest prognostic factor for both localized and advanced tumors (HR 4.42, 95% CI 2.50-7.83, $p<0.001$, localized; HR 2.62, 95% CI 1.74 -3.95, $p<0.001$, advanced)

Conclusion:
TNETs have an intermediate prognosis compared to thymoma and thymic carcinoma that is variable based on a spectrum of histology and achievement of complete resection. Surgical resection is the most prognosis-determining treatment in both localized and advanced stages.

Malnutrition as a Predictive Indicator of Discharge Home after Carotid Revascularization

Stephanie Carter, David Strosberg, Alan Dardik, Ronnie Rosenthal, Cassius Iyad Ochoa Chaar, Eric B. Schneider

Introduction:
Carotid endarterectomy (CEA) and transcarotid artery revascularization (TCAR), are widely used to prevent ischemic stroke in patients with carotid artery stenosis. Although these procedures are considered relatively low risk, postoperative outcomes are strongly influenced by factors such as nutritional status and frailty. Malnutrition is known to impair wound healing, immune function, and physiologic response to surgical stress. Prior studies have shown associations between poor nutritional markers and increased morbidity. There is limited research on how nutritional reserve and frailty affect outcomes specifically in carotid revascularization in veteran populations.

Methods:
This retrospective study evaluated elective carotid revascularization patients at West Haven Veterans Affairs Hospital over a three-year period (2021-2024). Clinical demographics, preoperative and postoperative Nutritional Risk Index (NRI) and Clinical Frailty Scale (CFS) scores were calculated and collected. Primary endpoints included wound infection, pneumonia, acute renal failure, myocardial ischemia, limb ischemia and stroke.

Results:
117 patients in total were included (Not Frail: 11; Frail: 106). Demographics, comorbidities and nutritional parameters were comparable between groups. Higher NRI was a significant predictor of discharge home (NRIpre=2.49, SE= .05, p= .013) increasing the odds ratio of discharge home by 1.12% (OR= 1.12, 95% CI [1.02, 1.23]).

Conclusion:
This study contributes novel insight into an understudied population by integrating personalized, longitudinal nutritional and frailty assessments within a geriatric-focused surgical care framework. The results highlight opportunities for routine nutritional screening and targeted preoperative optimization into carotid revascularization pathways. Enhancing nutritional reserve—even before lower-risk procedures—may improve postoperative recovery, reduce complications, and support better functional outcomes in frail veteran patients.

Associations of Autoimmune Diseases with Appendiceal Cancer in a Population-Based Study

Ofori KA., Bader JM., Reddy B., Aguirre N., Gupta P., Sharma A., Godfrey EL., Ong CS., Cecchini M., Sundar R., Turaga K

Introduction:
Appendiceal cancer incidence is rising rapidly, particularly among younger adults, yet its causal determinants remain poorly understood. Emerging data suggest immune dysregulation in appendiceal malignancies, which is notable given the appendix's role in mucosal immune regulation. We hypothesized that autoimmune diseases and thyroid disorders, including potentially under-recognized autoimmune thyroiditis, are associated with appendiceal cancer.

Methods:
Using the All of Us Research Program (v8), a large and diverse U.S. cohort integrating electronic health record and survey data, we conducted a population-based study comparing adults with appendiceal adenocarcinoma to cancer-free controls. Autoimmune diseases were identified using ICD codes, and thyroid disorders were classified as autoimmune (Graves' disease, Hashimoto's thyroiditis) or benign (non-autoimmune thyroid disorders). Controls were adult participants with available electronic health record and demographic data and no history of primary malignancy. Age- and sex-adjusted logistic regression models estimated odds ratios (ORs).

Results:
Among 203 appendiceal cancer cases and 327,591 cancer-free controls, cases had a higher prevalence of any autoimmune disease (18.7% vs 10.2%, $p<0.001$) and benign thyroid disorders (32.5% vs 11.2%, $p<0.001$). In age- and sex-adjusted analyses, appendiceal cancer was significantly associated with inflammatory bowel disease (adjusted OR 3.82, 95% CI 1.95-6.67), benign thyroid disorders (OR 3.47, 95% CI 2.54-4.72), rheumatoid arthritis (OR 2.40, 95% CI 1.29-4.07), autoimmune thyroid disease (OR 2.37, 95% CI 1.17-4.27), type 1 diabetes (OR 2.24, 95% CI 1.01-4.25), and any autoimmune disease overall (OR 1.92, 95% CI 1.33-2.71) (all $p<0.05$).

Conclusion:
Autoimmune diseases and thyroid disorders are associated with appendiceal cancer in this large, population-based cohort. These findings support a potential role for immune-mediated and thyroid-related pathways in appendiceal tumorigenesis and warrant further mechanistic and temporally ordered investigations, particularly in the context of the rising incidence of both appendiceal malignancies and immune-mediated conditions.

Germline Mutation Profiles in Patients with Peritoneal Surface Malignancies of Appendiceal Origin

Aguirre N, Sharma A, Gupta P, Bader JM, Gustafson AM, Ofori KA, Turaga K

Introduction:
Peritoneal surface malignancies (PSM) of appendiceal origin are rare and biologically heterogeneous. While somatic alterations have been described, germline predisposition remains poorly characterized. Characterizing germline variants may identify biologically distinct subgroups and inform genetic counseling and therapeutic strategies.

Methods:
Forty-six patients with peritoneal surface malignancies of appendiceal primaries underwent germline mutation testing (Invitae 70-gene hereditary cancer panel) using saliva swabs. Variants were classified as pathogenic or variants of uncertain significance (VUS). Genes were grouped into DNA repair, tumor suppressor, and RTK/oncogenic signaling pathways. Clinicopathologic correlations with tumor grade, histology, peritoneal cancer index (PCI), and overall survival (OS) from time of PSM diagnosis were assessed.

Results:
Seventeen of 46 patients (37%) harbored germline variants, including 4 (9%) with pathogenic mutations and 13 (28%) with variants of unknown significance (VUS). Five patients had multiple alterations.Most frequently altered genes: BRCA1 (n=2), MUTYH (n=2), RET (n=2). There was aggregation at the gene and pathway level within DNA repair, tumor suppressor, and RTK/oncogenic signaling pathways. All pathogenic variants occurred in DNA Damage Repair genes (BRCA1, BRCA2, ATM, MUTYH, NTHL1).

No significant association was found between mutation status and tumor grade ($p = 0.81$), histology ($p=0.09$), or PCI (>20 vs ≤20, $p= 0.3$). Mutation prevalence was highest in goblet cell adenocarcinoma (5/10, 50%) compared with mucinous (0/2, 0%), colonic-type (3/11, 27%), and low-grade appendiceal mucinous neoplasms (5/15, 33%).Patients with DNA repair mutations tended to have higher PCI scores (>20).
Median overall survival (OS) was 35.2 months for mutation-positive patients and not reached for mutation-negative patients ($p = 0.76$). OS did not differ significantly among mutation subgroups.

Conclusion:
Germline variants were present in one-third of patients with appendiceal peritoneal metastases, most frequently affecting DNA repair genes. Although most alterations were variants of uncertain significance, the prevalence exceeded that reported in broader cancer populations (9–28%). Absence of survival difference suggests variants reflect inherited susceptibility rather than acquired driver events. These findings suggest underlying biologic heterogeneity and reinforce the value of routine germline testing to uncover hereditary risk and inform patient counseling.

Comprehensive Molecular Profiling Predicts Survival Among North American Patients with Mesothelioma

Bader JM, Dhiman A, Aguirre N, Ofori KA, Gupta P, Quin H, Sharma A, Mitchell O, Tjota MY, Husain AN, Drazer M, Churpek J, Kindler H, Turaga K

Introduction:
Mesothelioma is a rare cancer with poor prognosis and variable treatment response. Somatic mutations in mesothelioma are vastly understudied due to the rarity of mesothelioma and lack of large patient cohorts. In collaboration with University of Chicago, we gathered one of the largest cohorts of mesothelioma patients in North America and identified clinically actionable, prognostic signatures that can refine risk stratification, treatment planning, and clinical trial eligibility.

Methods:
Sequential patients with mutational profiling and mesothelioma diagnosis between 2010-2022 at a large health system were enrolled in a registry and biorepository. Mutations, treatments, and tumor characteristics were compared among pleural versus peritoneal mesothelioma, histologic subtypes, and patients with shortened versus extended survival. Kaplan-Meier method and multivariate analysis compared overall survival (OS) among groups.

Results:
Among 195 patients, 70% (n=137) had pleural mesothelioma: 30% (n=58) had peritoneal mesothelioma. NF2 mutations were independently associated with worse OS in pleural mesothelioma (HR: 1.95, 95%CI=1.14-3.34, p=0.015). NF2 variants, including non-sense and frameshift mutants with premature stop codon, had significantly worse OS in pleural mesothelioma (log-rank p<0.001). Loss-of-function/structural NF2 variants, including large chromosomal deletions/rearrangements, were not associated with worse OS. Patients with NF2 truncating variants had significantly higher mortality at 1-year (44% vs 7.7%, p=0.044) and 18-months (69% vs 17%, p=0.006) compared to patients with other NF2 pathogenic variants. This challenges broadly grouping all NF2 pathogenic variants in mesothelioma into one category.

Conclusion:
With one of the largest mesothelioma patient cohorts in North America we demonstrated the potential of tumor sequencing to improve prognostication and patient selection for biomarker-enriched clinical trials, especially for trials targeting the NF2 pathway. These NF2-targeted trials have consistently demonstrated unsuccessful results. We showed that the drastic variability historically observed may be due to distinct differences among NF2-specific variants, specifically our discovery of NF2 truncating variants, which previously had not been accounted for. These findings reiterate the need to obtain somatic testing for patients with mesothelioma to improve prognostication, guide clinical-trial enrollment, and ultimately, to develop targeted-treatment approaches.

Racial and Ethnic Differences in Breast-Conserving Surgery After Neoadjuvant Chemotherapy for HER2-Positive and Triple-Negative Breast Cancer

Hickey AJ, Sun F, Li F, Proussaloglou EM, Berger ER, Greenup RA, Valero MG

Introduction:
Neoadjuvant chemotherapy (NACT) increases eligibility for breast-conserving surgery (BCS) among patients with stage II–III breast cancer, particularly those with HER2-positive and triple-negative breast cancer (TNBC). Despite equivalent oncologic outcomes between BCS and mastectomy, racial and ethnic disparities in surgical management persist. Data examining racial and ethnic differences in receipt of BCS following NACT remains limited. We examined the association between race and ethnicity and the odds of undergoing BCS after NACT.

Methods:
The National Cancer Database was used to identify female patients with stage II or III HER2-positive or TNBC diagnosed between 2013 to 2022 who received NACT followed by surgery. Patients were categorized by race and ethnicity, and the primary outcome was receipt of BCS versus mastectomy. Demographic and clinical variables were compared using Chi-square tests and one-way ANOVA, as appropriate. Multivariable logistic regression was used to examine the association between race/ ethnicity and the odds of undergoing BCS, adjusting for age, year of diagnosis, clinical stage, subtype, insurance status, geographic region, facility type, and comorbidity score.

Results:
Among 255,735 women who met inclusion criteria, 65.4% were non-Hispanic White, 19.5% Black, 9.3% Hispanic, 5.3% Asian or Pacific Islander, and 0.4% American Indian or Alaskan Native. Following NACT, 60.1% underwent mastectomy and 39.9% underwent BCS. Compared with Non-Hispanic White women, Black (OR 1.26, 95% CI 1.15-1.38) and Hispanic (OR 1.23, 95% CI 1.04-1.46) women had higher odds of receiving BCS, whereas Asian and Pacific Islanders had lower odds (OR 0.73, 95% CI 0.56-0.94) (Table 1). Older age, stage II disease, lower comorbidity score, treatment in New England, and more recent diagnosis year were independently associated with significantly higher odds of receiving BCS. On moderation analysis, clinical stage did not modify the association between race/ ethnicity and receipt of BCS.

Conclusion:
Patterns of surgical management following NACT vary by race and ethnicity. Black and Hispanic women had higher odds of undergoing BCS compared with Non-Hispanic White women, whereas Asian and Pacific Islander women had lower odds, independent of key covariates. Further research is needed to elucidate the underlying factors contributing to these differences.

Association between Genetic Variants of Unknown Significance for Thoracic Aortic Disease and Outcomes Following Aortic Surgery.

Sedem Dankwa, Tuan Anh Phu, Ely Erez, Irbaz Hameed, Adrian R. Acuna Higaki, Michela Cupo, Chanseo Lee, Yona Lei, Shiv Verma, Fabrizio Darby, Kristina Wang, Sem Asmelash, Sriharsha Talapaneni, Kwasi Ansere Ofori, Pavan Khosla, Titilayo Oden Shobayo, Roland

Introduction:
Genetic testing increasingly identifies variants of unknown significance (VUS) in patients with thoracic aortic disease (TAD). Treated as non-mutations, VUS impact on outcomes remains unclear. We evaluated associations between patients' genetic variants for genes strongly associated with heritable TAD.

Methods:
This single-center retrospective study evaluated adults with thoracic aortic aneurysm or dissection who underwent genetic testing between 2012–2023. Patients were classified as having pathogenic, VUS, or no mutation in the 11 primary ACC/AHA and ClinGen-validated TAD genes. The primary outcome was death or reoperation. Cox regression assessed genetic status with no mutation as reference, adjusting for age, sex, bicuspid aortic valve, dissection type, and aneurysm type.

Results:
Among 1,004 patients, 866 (86.3%) had no mutation, 107 (10.7%) had VUS, and 31 (3.1%) had pathogenic variants. Overall, there were 713 surgical patients with median follow-up of 57.4 months (IQR 39.5–82.0). VUS mutations were independently associated with a twofold increased risk of death or reoperation compared with no mutation (HR 2.13, 95% CI 1.35–3.37, p=0.001). Pathogenic variants showed no significant association (HR 0.99, 95% CI 0.38–2.58, p=0.99). Other significant predictors included type A dissection (HR 3.37), type B dissection (HR 4.06), descending aneurysm (HR 2.04), arch aneurysm (HR 1.92), and greater age at surgery (HR 1.04).

Conclusion:
Patients with VUS mutations in validated TAD genes conferred twofold increased risk of death or reoperation outcomes, suggesting current management treating these variants as benign may be inadequate. Further prospective studies are needed to refine risk stratification for patients with VUS mutations.

Left Ventricular remodeling following zone 0 thoracic endovascular aortic repair versus ascending hemiarch replacement for ascending thoracic aortic aneurysm

Talapaneni S., Hameed I*., Fatima M., Cangut B., Best C., Berry G., Acuna Higaki A., Ahmad H., Assi R., Ma W.G., Akintoye E., Reinhardt S.W., Vallabhajosyula P (*Equal Contribution)*

Introduction:
Thoracic endovascular aortic repair (TEVAR) is increasingly utilized for ascending aortic pathologies, yet long-term cardiac remodeling data remain limited. We evaluated long term left ventricular (LV) remodeling following zone 0 TEVAR or ascending hemiarch replacement in patients with ascending thoracic aortic aneurysms.

Methods:
All patients presenting with ascending thoracic aortic aneurysms from October 2019 to August 2024 at a large, academic aortic center were retrospectively reviewed. Patient demographics, comorbidities, clinical outcomes, and serial echocardiographic parameters were extracted for patients who underwent zone 0 TEVAR or ascending hemiarch replacement. Among 240 patients with complete echocardiographic data, 36 underwent TEVAR and 204 underwent hemiarch replacement. Nearest-neighbor propensity score matching was then performed, yielding the final matched cohort of 58 patients. Echocardiographic parameters of LV remodeling were analyzed at three time points: pre-treatment, short-term follow-up of 6 (±2) months, and long-term follow-up 2 (±0.6) years. Mean changes in various echocardiographic parameters were calculated and paired sample t-tests were used to compare means.

Results:
A total of 240 patients were studied. Mean age was 61 ± 12 years, and 190 (79.2%) were male. 66.3% had hypertension, 50.4% had dyslipidemia, and 20.4% had diabetes. Overall mortality rates were 2.7% (1/36) with TEVAR and 2% (4/204) with ascending hemiarch replacement (P = 0.35). Following nearest-neighbor propensity matching, a total of 58 patients were studied (29 per group). 55.2% had a history of smoking in both groups (P = 1.000), 51.7% vs. 44.8% had dyslipidemia (P = 0.793), and 34.5% vs. 24.1% had diabetes (P = 0.564). At initial follow-up, zone 0 TEVAR patients demonstrated no significant changes in echocardiographic parameters compared to pretreatment. In contrast, hemiarch replacement patients demonstrated significant reductions in LVEDD (mean Δ = −0.38 cm (−0.78, 0.02), P = 0.050), and LVESD (mean Δ = −0.30 cm (−0.59, −0.01), P = 0.050), and a near-significant increase in AoV Mn gradient (mean Δ = 2.00 mmHg (−3.35, 2.57), P = 0.050). At long-term follow-up, zone 0 TEVAR patients demonstrated a significant decrease in LVEDV compared to initial follow-up (mean Δ = −28.35 ml (−49.72, −6.98), P = 0.019) while all other parameters remained stable. In contrast, hemiarch replacement patients at long-term follow-up showed significant changes in Aov Pk velocity (mean Δ = 0.16 m/s (−0.18, 0.2), P = 0.043), and AoV Mn gradient (mean Δ = −0.29 mmHg (−0.77, 0.77), P = 0.50).

Conclusion:
In patients with ascending thoracic aortic aneurysms, both zone 0 TEVAR and ascending hemiarch replacement are associated with preserved LV remodeling at initial and long term follow up.

Predicting response to neoadjuvant tyrosine kinase inhibitors (TKI): a trial meta-analysis

Ryan J. Kramer, MD; Giorgio Caturegli, MD; Justin Bader, MD; Sanja Dacic, MD, PhD; Vignesh Raman, MD, MHS; Emily J. Zolfaghari, MD; Benjamin Resio, MD; Justin Blasberg, MD, MPH; Collin Blakely MD, PhD; Katerina Politi, PhD; Roy S. Herbst, MD, PhD; Daniel

Introduction:
Adjuvant tyrosine kinase inhibitor (TKI) therapy has had success in lung cancer with actionable driver alterations including EGFR and ALK. Neoadjuvant use of TKIs appeals for tumor downstaging and control of micro-metastatic disease. Multi-center neoadjuvant TKI trials are underway with encouraging results. However, pathologic response rates are variable, survival data remain immature, and it is unclear which patients benefit from these regimens. To address this, a meta-analysis was performed to evaluate predictors of radiographic and pathologic response to neoadjuvant TKI therapy.

Methods:
Systematic review identified 45 trials submitted to the FDA to study neoadjuvant TKI therapy. A total of 4 trials with published data using modern TKIs were identified, as well as the 2 preliminary reports of NeoADAURA and ALNEO. Patient-level data were abstracted, and Fisher's exact tests identified factors associated with radiographic and pathologic response. Analyses were stratified by EGFR and ALK; ALK data not shown as it included 2 trials only.

Results:
Among the 235 patients extracted from 6 neoadjuvant TKI monotherapy trials, 82% (192/235) of patients had EGFR mutations and 18% (43/235) had ALK rearrangements. For those with EGFR mutations, 43% (82/192) of individuals had both pathologic and RECIST radiographic outcome data. Positive radiographic response was significantly associated with larger T stage; 79% (11/14) T3+ tumors had partial radiographic response (PRR) versus 38% (6/16) of T1 and 37% (7/19) of T2 tumors (p=0.03). Similarly, clinical stage was associated with radiographic response, with 69% (29/42) of stage III tumors and 69% (11/16) of stage II tumors achieving PRR versus 30% (7/23) stage I tumors (p=0.03 for stage I vs II, p=0.004 for stage I vs III). Tumor size- and stage-dependent responses were not observed with respect to major pathologic response (MPR). There was no association between PRR and MPR rates (p=1.0). These results were recapitulated in the ALK cohort.

Conclusion:
Larger tumors were more likely to have a positive radiographic response among patients undergoing modern neoadjuvant TKI therapy. Importantly, major pathologic response did not correlate with radiographic response. While survival data from larger trials is still needed, this meta-analysis demonstrates that neoadjuvant TKIs may serve a practical role in downstaging larger tumors, which may aid in local control with improved resectability.

Postoperative Outcomes of Ventral Hernia Repair in Patients With Heart Failure: A Multicenter Analysis

Flom, E., Ying, Lee., Huang, L., Farinas Lugo, D., Butensky, S., Duffy, A., Zhou, R

Introduction:
Abdominal wall reconstruction in patients with heart failure can be extremely challenging but is often medically necessary. This study investigates 30-day complications after complex ventral hernia repair in patients with and without a history of heart failure.

Methods:
A retrospective cohort study was conducted using the Abdominal Core Health Quality Collaborative (ACHQC) database, a multi-institutional registry that collects health information including clinical and outcomes data for abdominal wall reconstruction. The study analyzed 30-day complications after ventral hernia repair from 2018-2024. Patients undergoing ventral hernia repair with myofascial release classified as clean or clean/contaminated settings were included.

Results:
A total of 5,580 patients were included, of whom 163 had heart failure. Heart failure patients tended to be older, more likely to be male, and had more medical comorbidities. After propensity score matching, heart failure patients were associated with increased postoperative morbidity. Surgical site occurrences were significantly more common in heart failure patients compared with matched controls (24% versus 15%, p=0.01), higher rates of surgical site occurrences requiring procedural intervention (12% versus 3%, p=0.04), and overall complication rates (35% versus 27%, p=0.04).

A secondary analysis was conducted in heart failure patients alone. There was no statistically significance difference in operative time (p=0.7), HerQLes or PROMIS pain up to 5 years (p=0.3, p=0.5), recurrence up to 5 years (p=0.5), or intra-operative complications (p=0.4) between robotic and open approaches. Robotic repair was associated with a shorter length of stay (1 versus 5 days open, p<0.001) and lower 30-day surgical site infection rates (0% versus 8% open, p=0.02). Although seroma formation at 30 days was more frequently reported after robotic repair (84% versus 53% open, p=0.04), none were infected.

Conclusion:
Complex abdominal wall reconstruction in heart failure patients is challenging but often medically necessary. In this large, multicenter analysis, heart failure was independently associated with increased short-term morbidity, including higher rates of surgical site occurrences, procedural interventions, and overall complications. Within the heart failure cohort, robotic repair was associated with a significantly shorter length of stay and fewer infectious complications, suggesting that minimally invasive approaches may help mitigate select postoperative risks in appropriately selected patients. These findings highlight the need for enhanced patient selection, perioperative management, and optimization of heart failure patients as well as careful operative planning in heart failure patients undergoing abdominal wall reconstruction.

Prehabilitation and Postoperative Outcomes After Ventral Hernia Repair: A Multicenter Registry Study

Emily Flom; Lee Ying; Cassie Hennessy; Andrew Duffy; Randal Zhou

Introduction:
Increased preoperative exercise and functionality improves patient outcomes. Smoking cessation also decreases surgical complications. This study aims to further elucidate whether improved preoperative activity level and smoking cessation decreases surgical complications and improves outcomes for high-risk patients after ventral hernia repair.

Methods:
Utilizing the Abdominal Core Health Quality Collaborative (ACHQC), we analyzed adult patients who participated in smoking cessation within 1 year of surgery or increased physical activity with subsequent ventral hernia repair with at least 30 day follow up. Patients were stratified by American Society of Anesthesiologists (ASA) Physical Status Classification System. Multi-variate logistic regression analyses were used to assess how preoperative exercise and smoking cessation affected primary outcomes including length of stay, 30-day readmission, surgical site infection (SSI), surgical site occurrences (SSO), and surgical site occurrence requiring procedural intervention (SSOPI).

Results:
A total of 17819 patients were included in the analysis. Patients were stratified by ASA class and reported preoperative exercise level (none (no reported exercise), sporadic (once a month), moderate (once per week), and intense (more than once per week)). In patients with ASA class 2 or above, any level of preoperative exercise regimen improved outcomes. Specifically, patients with ASA 2 or above benefited significantly from sporadic, moderate, or intense preoperative exercise, as sporadic had 0.535 times the odds of a 30-day readmission, moderate 0.860 times the odds of, and intense 0.421 times the odds compared to those with no exercise, adjusting for other potential confounders. Furthermore, ASA class 3 individuals with a moderate to intense exercise also had decreased rates of surgical site infections ($p=0.04$; ASA 3 with 0.431 moderate, 0.546 intense compared to no exercise). ASA 3 individuals also had improved length of stay with increased exercise and smoking cessation, as moderate exercise decreased hospital duration by 1.8 days and intense exercise decreased by 2.24 days compared with no exercise; smoking cessation also decreased length of stay, as ASA class 3 with smoking pre-habilitation noticed a decrease of 2.2 days for length of stay compared to continued smoking, adjusting for other potential confounders.

Conclusion:
Patients with greater exercise frequency before surgery demonstrated improved outcomes including decreased odds of 30-day readmission, surgical site infections, and hospital length of stay. Smoking cessation also decreased length of stay for patients with higher co-morbidities. Further analysis is needed to target which subset of patients would benefit from these pre-habilitation programs to improve outcomes.

YALE SURGERY RESEARCH DAY 2026

QUALITY IMPROVEMENT ABSTRACTS

Utility of abdominal aortic aneurysm detection software for quality improvement at a tertiary referral center.

BA. Creisher, C. Dandu, U. Fischer, CI. Ochoa Chaar, H. Mojibian, E. Aboian

Introduction:
Abdominal aortic aneurysm (AAA) is often diagnosed incidentally on imaging modalities. Patients and primary care providers (PCP) may be occupied by other health problems and the opportunity for patient education and referral to a vascular specialist can be missed. Emergence of artificial intelligence and natural language processing provide a new opportunity to detect and refer patients to an aortic specialist. We report our experience with a quality improvement program leveraging AAA detection software and its impact on patient outcomes.

Methods:
A quality improvement project was implemented utilizing the AIDOC platform to detect AAA in a health care network. The software generated alerts and a list of patients with AAA ≥ 4 cm. A team of vascular surgeons, nurse navigators, and a radiologist analyzed AIDOC for accuracy of AAA detection and appropriateness for referral to vascular surgery. Patients deemed unfit for repair, found to have an external provider, or with advanced cancer were excluded. After initial review, a nurse navigator communicated with the PCP regarding the AAA using a standardized letter. The first six months of implementation were retrospectively analyzed for number of aortic referrals, AAA repairs, AAA ruptures, and long-term surveillance.

Results:
A total of 264 patients were identified in the six-month period, and after filtration with exclusion criteria, 47 (17.8%) letters were sent to the corresponding PCP. The average age was 75.8 and 68% (N=32) were males with an average AAA diameter of 4.5 cm. A total of 25 appointments were made (53.2%), and 24 (51.1%) patients were seen by a vascular surgeon. An additional 9 patients made appointments with their PCP or cardiologist, for a total of 34 patients enrolled in subsequent AAA surveillance. Over the follow-up period, 6 patients underwent repair, and 1 had an aortic rupture. The system captured 24 new consults (CPT 99203/4, $180/ea), 30 AAA surveillance ultrasounds ($150/ea), and 6 endovascular repairs (DRG 268/269, $30,000/ea) for a total estimated annualized revenue of $377,000.

Conclusion:
An AAA detection and notification system utilizing commercial software significantly improved the quality of AAA care. Specifically, the program resulted in early referral to an aortic specialist, AAAs under surveillance, timely repairs, and a positive financial benefit. Further prospective evaluation of the program is needed to determine the impact on prevention of AAA mortality.

Stopping Reflux Induced Aspiration Injury by Neuromodulation

Paul Ayodele, Nishant Gupta, Kurt Gerhardt Frederic, Sodiq Ajose, Thomas Neiderhauser, Rigu Gupta, Pramod Bonde

Introduction:
Pulmonary macro/micro aspiration of gastric contents is implicated in the pathogenesis of lung injury in intubated/ventilated patients and associated mortality. Anesthetic agents, sedatives and opiates relax lower esophageal sphincter (LES) leading to acute gastroesophageal reflux (AGER), anti- acids lead to bacterial overgrowth and these are often found as causative organisms in these patients. CDC guidelines recommend using gravity (head elevation) as a central strategy to mitigate this risk, but compliance remains variable. We present neuromodulation of LES which potentially could prevent AGER and lung injury in intubated patients.

Methods:
Polyurethane tubes (10 Fr diameter) incorporating 46, 200 micron gold electrodes, MEMS pressure sensor and radio-opaque markings were used for stimulation (biphasic square wave with 200 us pulse width) at 2-30 mAmp controlled by a custom stimulator. Extensive in-vitro tests were conducted to standardize pulse wave duration. Four domestic pigs intubated and ventilated, in supine position underwent placement of 10 Fr catheters under vision orally and the electrodes were positioned under X-ray guidance in the vicinity of the LES. Aim was to effect >10 cm of water (H2O) pressure increases over the baseline (pre-stimulation) pressure by increasing the simulation current, to assure closed status of LES and stop AGER.

Results:
LES pressures: Pre-stimulation: 20±2 cm of H2O, post-stimulation: 40±4 cm of H20, on average was obtained with 20mA stimulation. No adverse events in terms of arrythmia or diaphragmatic contractions observed for the duration of experiment. Minimum current to increase LES pressure was 14 mA and the response saturated for stimulation strength above 20 mA. The results could be repeated for a continuous stimulation lasting half an hour (4 hrs/each animal).

Conclusion:
An esophageal pressure differential over gastric pressure can be achieved using neuromodulation for maintaining LES tone and possibly stop reflux of gastric contents. This has the potential to prevent and address one of the important elements in the causation of acute lung injury in intubated patients.

Successful Manuscript Publication of Southern Thoracic Surgical Association Annual Meeting Abstracts

Wang KM, Ramdeen SL, Bilgili A, Huggins LKL, Abu-Mowis Z, Wilson JT, Danielson MD, Purlee M, Higaki AA, Papageorge MV, Woodard GA, Ailawadi G, Romano JC, Jacobs JP, Lee ME

Introduction:
The Southern Thoracic Surgical Association (STSA) is one of the largest North American regional cardiothoracic surgical societies. Recent studies have reported publication rates of abstracts presented at national and international cardiothoracic surgical conferences to be over 75%. However, no studies have reviewed the publication rates of abstracts accepted at regional cardiothoracic surgery conferences. This study aims to assess the publication rate and characteristics of abstracts presented at STSA meetings.

Methods:
STSA meeting program books from 2015 to 2019 were reviewed for all oral presentation abstracts. Abstract title, authors, presentation category, study design, projection, and measured outcomes were collected. Abstracts were searched online with a standardized protocol to assess whether they were converted to manuscripts and subsequently published in peer-reviewed journals as of March 2025. Characteristics of published and non-published abstracts were compared using Pearson's Chi-squared or Fisher's exact tests, as appropriate.

Results:
A total of 410 abstracts were presented as oral presentations at the STSA annual meetings from 2015 to 2019, with a median of 83 abstracts presented yearly. Presented work were primarily cohort studies (71.2%). Most had a retrospective design (84.4%), had human subjects (95.6%), and/or measured clinical outcomes (92.7%). There were 318 (77.6%) abstracts that had a corresponding publication; median time from presentation to publication of 205 days (IQR 133-345). There was no temporal trend in publishing rates by year of abstract presentation ($p=0.42$). Publication status differed significantly by study design; cohort studies were more likely to be published ($p<0.001$), and case reports were less likely to be published ($p<0.001$). There was no difference between clinical and experimental studies in publication rates ($p=0.10$) and no difference in publication rates across presentation categories (adult cardiac, general thoracic, congenital, historical/educational) ($p=0.29$). The highest rate of publication was among abstracts presented within the adult cardiac surgery category (80.6% [150 out of 186]). Publications were primarily in cardiothoracic surgery journals, the most common being The Annals of Thoracic Surgery (75.5%). Published studies were cited a median of 8 times (IQR 3.3-13.0).

Conclusion:
Abstracts presented at the STSA annual meetings demonstrate a high rate of subsequent publication in peer-reviewed journals, comparable to rates reported for national and international cardiothoracic surgery conferences. These findings highlight the STSA meeting as a robust venue for disseminating high-quality research. Continued participation in and support of regional meetings such as STSA may play an important role in fostering scholarly productivity and advancing cardiothoracic surgery literature.

Gender Analysis of The Southern Thoracic Surgical Association Annual Meeting Presentations Achieving Manuscript Publication

Wang KM, Ramdeen SL, Bilgili A, Huggins LKL, Abu-Mowis Z, Wilson JT, Danielson MD, Purlee M, Higaki AA, Papageorge MV, Woodard GA, Ailawadi G, Romano JC, Jacobs JP, Lee ME

Introduction:
The Southern Thoracic Surgical Association (STSA) annual meetings are an important regional contributor to the field of cardiothoracic surgery. Though there has been an increase in the number of women presenters at the STSA, it is unclear if author gender is correlated with successful publication. This study aims to assess trends in gender representation at the STSA meeting and whether author gender is associated with subsequent publication in peer-reviewed journals.

Methods:
STSA annual meeting program books from 2015 to 2019 were reviewed for all oral presentation abstracts. Validated software (Genderize.io) was used to classify the gender of presenters based on author names. Abstracts were searched online with a standardized protocol to assess whether they were converted to manuscripts and subsequently published in peer-reviewed journals as of March 2025. Characteristics of abstracts with women first authors and men first authors were compared using Pearson's Chi-squared or Fisher's exact tests, as appropriate.

Results:
Of 410 abstracts, 26.1% (n=107) had women first authors and 9.0% (n=37) had women senior authors. Abstracts with women first authors were more likely to have a woman senior author than those with men first authors ($p<0.001$). The yearly proportion of abstracts with women first authors ranged from 14.4% to 32.4%, and there was no temporal trend in the proportion of women first-author abstracts ($p=0.25$). Among all abstracts with women first authors, the most common presentation category was general thoracic surgery (42.1%), followed by adult cardiac (41.1%) and congenital (14.0%). In contrast, presentations by men were mostly in the adult cardiac category (46.9%), followed by general thoracic (32.7%) and congenital (19.1%). There was no significant association between first author gender and presentation topic ($p=0.18$). There were 318 abstracts that were subsequently published in peer-reviewed journals, most (75.5%) of which were in The Annals of Thoracic Surgery. There was no difference in publication rates of presented abstracts between women and men first authors (73.8% vs. 78.9%, $p=0.35$) or senior authors (70.3% vs. 78.3%, $p=0.36$).

Conclusion:
Despite being a regional conference, the STSA demonstrates a high abstract-to-publication conversion rate comparable to national and international cardiothoracic surgery meetings. Author gender was not associated with subsequent publication, suggesting equitable dissemination of scholarly work once presented. However, abstracts with women first authors were significantly more likely to have women senior authors, highlighting the importance of same-gender mentorship and sponsorship. Continued efforts to promote inclusive mentorship may further enhance gender representation and academic advancement within cardiothoracic surgery.

Standardizing Cervical Collar Management with a Care Signature Pathway

Seddio AE, Miller SM, Johnson J, Alok K, Mendel E, Aydin A, Sangal RB, Maung AA, Gilmore EJ, Maerz LL

Introduction:
Cervical collars stabilize, immobilize, and support patients with confirmed or suspected cervical spine injuries. Patients with physical trauma are often precautionarily placed in cervical collars while undergoing evaluation for injury. This quality improvement project implemented with the use a Care Signature Pathway aims to standardize cervical collar management, increase collar clearance efficiency, decrease collar complications from prolonged use, and minimize the rate of missed injuries.

Methods:
An interdisciplinary team, including representatives from nursing, emergency medicine, neurocritical care, trauma surgery, orthopaedic/neurosurgery spine services, and urgent care, was assembled to create the Cervical Spine Management Care Signature Pathway. Over the course of five months, we built and refined the pathway which now defines the standard of care for our health system. We have conducted a descriptive analysis of the patients for whom the pathway has been applied. We plan to perform a pre- and post-pathway cohort analysis to evaluate the pathway impact on patient care and outcomes.

Results:
The Cervical Spine Management Care Signature Pathway went live on February 6, 2026. This pathway describes cervical collar placement and associated management across a wide range of clinical scenarios from patients who are alert and asymptomatic, alert and symptomatic, or obtunded. Key pathway features include:
Additional guidance for evaluating and managing patients experiencing an in-hospital fallA revised algorithm for close follow up in urgent care for patients who present to the emergency department with neck pain but have negative imaging and can discharge safelyA linked video detailing the physical exam required for clinical collar clearance (forthcoming)

In its first week since being live, the pathway was used for by 18 providers for 14 patients. Users included nurses, advanced practice providers, students, junior and senior trainees, and attending physicians at hospitals across our network including York Street, Bridgeport, Greenwich, L&M, and Westerly. It has been used in emergency departments, SICU, MICU, and hospital floors.

Importantly, five patients were managed in the ICU setting. Among this subgroup, pathway utilization was associated with cervical collar clearance in four patients (80%), with no subsequent collar replacement or delayed identification of cervical spine injury thereafter. The median time from ED arrival to collar clearance was 1.33 days (IQR 1.01 – 1.61).

Conclusion:
With interdisciplinary collaboration, the Cervical Spine Management Care Signature Pathway was created and launched to standardize management practice within the Yale New Haven Health System. Ongoing work will evaluate the impact of this pathway on patient care and patient outcomes.

Validation and Establishment of the Contrast Volume Prediction Model: For Optimizing Renal Efficiency in EVAR (the FORE-EVAR calculator)

Justin M. Bader; Yining Qian; Anh Phu; Edouard Aboian, MD; Hannah Zwibelman; David P. Kuwayama; Raul J Guzman; Martin Slade; Yuan Huang; Cassius Iyad Ochoa Chaar

Introduction:
Post-contrast acute kidney injury (PC-AKI) is a serious complication associated with volume of contrast administered during endovascular abdominal aortic aneurysm repair (EVAR). Using a 49,417-patient dataset, we previously published a prediction model, “For Optimizing Renal Efficiency in EVAR” (FORE-EVAR), which utilizes 13 patient-specific variables to generate a recommended contrast volume to prevent PC-AKI after elective EVAR. Current objectives include (1) evaluating FORE-EVAR’s performance compared to AI-based models; (2) validating FORE-EVAR with an external dataset; and (3) designing FORE-EVAR’s user-interface and establishing it for national use.

Methods:
To ensure optimization of FORE-EVAR, our data-science team applied 8 machine-learning algorithms to the 49,417-patient VQI-EVAR dataset (2003–July 2024). After demonstrating equivalence of FORE-EVAR to machine-learning models, an updated VQI EVAR dataset (Aug 2024–Oct 2025) of 7,112 new patients was used for external validation.

Results:
Using split-sample approach of the 49,417-patient dataset, FORE-EVAR demonstrated a strong AUC=0.753 (similar to machine-learning models [range=0.712-0.759]). FORE-EVAR had equivalent, and often superior, accuracy, precision, sensitivity, and specificity. Importantly, FORE-EVAR requires input of only 13 patient variables which is significantly less than the 50+ variables required by machine-learning models. The high prediction metrics, along with simplicity of variables, positioned FORE-EVAR as the best model for clinical implementation. Furthermore, external validation with the 7,112-patient dataset, showed AUC=0.706, emphasizing FORE-EVAR’s predictability even across smaller cohorts.

FORE-EVAR’s user-interface displays personalized recommendations, including 3 key outputs: (1) FORE-EVAR determines each patient’s PC-AKI risk category based on the VQI dataset population. (2) FORE-EVAR utilizes the patient’s risk category to determine an appropriate risk threshold (2% for Low/Moderate and 5% for High/Very High-Risk categories–demonstrated in our previous work). FORE-EVAR then generates a contrast volume ensuring PC-AKI risk is below the risk threshold. (3) Lastly, FORE-EVAR provides the patient’s PC-AKI risk compared to the population at set volumes of 50mL/100mL.

Conclusion:
FORE-EVAR is a validated prediction tool invented by Yale surgeons and computer scientists which utilizes 13 patient-specific variables to generate a recommended contrast volume threshold to prevent PC-AKI after EVAR. FORE-EVAR provides valuable contrast volume recommendations and can identify high-risk patients to ensure close monitoring and faster PC-AKI recognition postoperatively. FORE-EVAR is being released for national use, and prospective studies will evaluate FORE-EVAR’s impact on patient outcomes.

Bridging the Gap: Integrating Undergraduate Talent in Surgical Clinical Trials

Liu S., Ospina A., Bader J.M., Belperron A., Turaga K.K.

Introduction:
Surgical clinical trials remain the gold standard of evidence-based medicine, yet they account for less than 10% of published articles in surgical journals (1,2). In addition to methodological challenges, limited funding prioritization and workforce capacity continue to constrain trial development and execution (3,4,5). Academic medical centers may address these barriers by leveraging an underutilized and accessible resource: undergraduate students.

Methods:
We examine existing models of undergraduate research engagement and propose a structured framework for integrating undergraduate students into surgical clinical trial teams. Drawing on institutional experience and established educational models, we outline key tenets for onboarding, training, mentorship, and role delineation, while identifying foreseeable barriers such as mentor time burden, uncertainty of commitment, and regulatory constraints. Strategies to mitigate these challenges—including structured communication, collaborative supervision, artificial intelligence-assisted onboarding, and a credit-based course pipeline—are described.

Results:
Key challenges to integrating undergraduates into surgical clinical trials include the significant upfront investment required from oftentimes overextended surgical researchers, difficulties in assessing student intent and research fit, and limited clinical exposure opportunities due to hospital regulatory policies and patient safety concerns. These barriers may deter faculty and student engagement. To this end, structured communication around expectations and goals, coupled with regular feedback, may reduce uncertainty and improve alignment between mentors and students (6). Artificial intelligence-assisted onboarding can help students acquire foundational knowledge prior to direct research involvement, thereby reducing mentor time burden. Additionally, a credit-based, course-centered pipeline may provide a standardized mechanism for training, matching, and sustaining undergraduate participation without imposing additional financial costs on research teams (7).

Conclusion:
Integrating undergraduate students into surgical clinical trials offers a mutually beneficial and scalable approach to addressing persistent barriers in surgical research. While upfront investment and logistical challenges exist, targeted solutions such as structured mentorship, AI-supported training, and course-based research models may facilitate implementation. Investing in undergraduate engagement represents a long-term investment in the future of surgical innovation and the sustainability of surgical clinical trials research.