YALE SURGERY RESEARCH DAY 2024

KEYNOTE SPEAKER

Robert Montgomery, MD, DPhil, FACS
NYU Langone Health

Dr. Robert A. Montgomery is the Chairman and Professor of Surgery at NYU Langone Health and the Director of the NYU Langone Transplant Institute. He received his Doctor of Medicine with Honor from the University of Rochester School of Medicine. He received his Doctor of Philosophy from Balliol College, The University of Oxford, England in Molecular Immunology. Montgomery completed his general surgical training, multi-organ transplantation fellowship, and postdoctoral fellowship in Human Molecular Genetics at Johns Hopkins. For over a decade he served as the Chief of Transplant Surgery and the Director of the Comprehensive Transplant Center at Johns Hopkins.

Dr. Montgomery was part of the team that developed the laparoscopic procedure for live kidney donation, a procedure that has become the standard throughout the world. He and the Hopkins team conceived the idea of the Domino Paired Donation (kidney swaps), the Hopkins protocol for desensitization of incompatible kidney transplant patients, and performed the first chain of transplants started by an altruistic donor. He led the team that performed the first 2-way domino paired donation, 3-way paired donation, 3-way domino paired donation, 8-way multi-institutional domino paired donation, and co-led the first 10-way open chain. He is credited in the 2010 Guinness Book of World Records with the most kidney transplants performed in 1 day. He is considered a world expert on kidney transplantation for highly sensitized and ABO incompatible patients and is referred the most complex patients from around the globe.

Dr. Montgomery has had clinical and basic science research supported by the NIH throughout his career. He has authored over 300 peer reviewed articles, cited more than 33,000 times and has an h-index of 99. His academic interests include HLA sensitization, tolerance protocols including simultaneous solid organ and bone marrow transplantation, bioartificial organs and xenotransplantation. He has received important awards and distinctions including a Fulbright Scholarship and a Thomas J. Watson Fellowship and memberships in the Phi Beta Kappa and Alpha Omega Alpha academic honor societies. He has been awarded multiple scholarships from The American College of Surgeons and The American Society of Transplant Surgeons.

The National Kidney Foundation of Maryland has recognized his contributions to the field of transplantation with the Champion of Hope Award, the National Kidney Registry with the Terasaki Medical Innovation Award and The Greater New York Hospital Association with the Profile in Courage Award. Newsweek Magazine featured him as one of America's Greatest Disruptors in December 2021. He received the Liberty Science Center's 2022 Genius Award. Modern Healthcare named him one of the Top 25 Innovators in Healthcare for 2022. Also in 2022, he was recognized by Crain's New York Business as a Notable Health Care Leader. He received the 2022 American Association of Kidney Patients Medal of Excellence Award. The American Society for Histocompatibility and Immunogenetics named him the winner of the 2022 Paul I. Terasaki Clinical Science Award. Dr. Montgomery became the recipient of a heart transplant in 2018 and has become known for his advocacy for transplant patients. He is a Chevalier of the Order of Merit having received the Order of Merit (Ukraine) awarded by Volodymyr Zelenskyy on September 21, 2023 at the National Archives in Washington for his surgical care of Ukrainian patients during the war. He is a member of the National Academy of Medicine.

Department of Surgery

AGENDA

Keynote Presentation will be in-person AND via Zoom. All other portions of Research Day are IN-PERSON only.

7:00AM Breakfast (on-site)

7:30AM Opening Remarks: Nita Ahuja, MD, MBA

7:35AM Introduction of Keynote Speaker: Peter J. Gruber, MD, PhD

7:40AM Grand Rounds Keynote Presentation –
"The Story of An Unlikely Personal and Professional Transplant Odyssey"
Robert A. Montgomery, MD, PhD
H. Leon Pachter Chair and Professor of Surgery
Director, NYU Langone Transplant Institute

Zoom Participation Link:
https://yale.zoom.us/j/95637640365?pwd=d01ydnpSUzVWTHc4L1A5TDJXTnJwQT09&from=addon

8:45AM Quick Shots
3 Speakers:

- Sara Pai, MD, PhD: "Novel Immunotherapeutics for Head and Neck Cancers"
- Robert Becher, MD: "Building the Evidence for Frailty-Guided Geriatric Surgical Care"
- Jason Sheltzer, PhD: "A Mis-characterized Compound that Selectively Targets Drug-Resistant Cancer Cells"

9:45AM Break

10:00AM Highlighted Abstracts

1. Presenting: Leanne Brown, MD
   "An Elevated Rate of Whole-Genome Duplication In Cancers From Black Patients"

   Brown L, Hagenson R, Sheltzer J

2. Presenting: Viola A. Stögner, MD
   "A Nationwide Analysis on Major Upper Extremity Amputations and Replantations"

   Viola A. Stögner, MD1, Sacha C. Hauc, BS, BA*, Helia Hosseini, MS, Mica C.G. Williams, BA, Sam Boroumand, BS, Lioba Huelsboemer, MD, Martin Kauke-Navarro, MD, Bohdan Pomahac, MD, David Colen, MD*

3. Presenting: David Weiss
   "Artificial Intelligence-Based Morpho-Volumetric Analysis of Pre- and Post-Evar Infrarenal Abdominal Aortic Aneurysms Characterized on Computed Tomography Angiography"

   Weiss D, Hager T, Aboian M, Lin M, Renninghoff D, Holler W, Fischer U, Deuschl C, Aneja S, Aboian E.

11:00AM Panel Discussion
Moderator: Rachel Greenup, MD
"Managing Risk and Innovation in Surgical Research"
Panelists:

- Robert Montgomery, MD, PhD
- Sanjay Kulkarni, MD
- Jordan Pober, MD, PhD

11:55AM Closing Remarks: Peter J. Gruber, MD, PhD

12:00PM Abstract Poster Session with lunch provided (on-site)

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BASIC SCIENCE ABSTRACTS

PHOSPHODIESTERASE 10A REGULATES MEDIAL ARTERIAL CALCIFICATION THROUGH P38/MAPK-MMP3 SIGNALING

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

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, and pivotal in a variety of cardiovascular events. However, the role of PDE10A involved in the medial artery calcification remains unclear.

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.

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 controlling p38 MAPK signaling and MMP-3 activity through cGMP/PKG signaling.

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.

SMOOTH MUSCLE CELL-SPECIFIC MMP-3 DELETION REDUCES OSTEOGENIC TRANSFORMATION AND MEDIAL ARTERY CALCIFICATION

Xie Y, Lin T, Berezowitzi AG, Wang X, Lu J, Cai Y, Guzman RJ.

Vascular calcification is highly prevalent in atherosclerosis, diabetes, and chronic kidney disease. It is associated with increased morbidity and mortality in patients with cardiovascular disease. Matrix metalloproteinase 3 (MMP-3), also known as stromelysin-1, is part of the large matrix metalloproteinase family. It can degrade extracellular matrix components of the arterial wall including elastin, which plays a central role in medial calcification. In this study, we sought to determine the role of MMP-3 in medial calcification.

Using calcium assay, siRNA knockdown, and transgenic mice.

We found that MMP-3 expression was increased in vascular smooth muscle cells (SMCs) cultured in a phosphate calcification medium. It was also highly expressed in calcified tibial arteries from patients with peripheral arterial disease (PAD). Knockdown and inhibition of MMP-3 suppressed phosphate-induced SMC osteogenic transformation and calcification, whereas the addition of a recombinant MMP-3 protein facilitated SMC calcification. In an ex vivo organ culture model and a rodent model of medial calcification induced by vitamin D3, we found that MMP-3 deficiency significantly suppressed aortic medial calcification, suggesting that MMP-3 in SMCs is crucial for medial calcification.

These findings suggest that MMP-3 expression in vascular SMCs is an important regulator of medial calcification and that targeting MMP-3 could provide a therapeutic strategy to reduce it and address its consequences in patients with PAD.

DIGITAL SPATIAL PROTEOMIC PROFILING REVEALS IMMUNE CHECKPOINTS AS BIOMARKERS IN LYMPHOID AGGREGATES AND TUMOR MICROENVIRONMENT OF DESMOPLASTIC MELANOMA

Su DG, Schoenfeld DA, Ibrahim W, Cabrejo R, Djureinovic, D, Baumann R, Rimm DL, Khan SA, Halaban R, Kluger HM, Olino K, Galan A, Clune J

Desmoplastic melanoma (DM) is a rare melanoma subtype characterized by dense fibrous stroma, a propensity for local recurrence, and a high response rate to PD-1 blockade. Occult sentinel lymph node positivity is significantly lower in both pure and mixed DM than conventional melanoma, underscoring the need for better prognostic biomarkers to inform therapeutic strategies.

We assembled a tissue microarray comprising various cores of tumor, stroma, and lymphoid aggregates from 45 patients with histologically confirmed DM diagnosed between 1989 and 2018. Using a panel of 62 validated immune-oncology markers, we performed digital spatial profiling using the Nanostring GeoMx platform and quantified expression in three tissue compartments defined by fluorescence colocalization [tumor (S100+/PMEL+/SYTO+), leukocytes (CD45+/SYTO+), and nonimmune stroma (S100-/PMEL-/CD45-/SYTO+)].

We observed higher expression of immune checkpoints (LAG-3 and CTLA-4) and cancer- associated fibroblast (CAF) markers (smooth muscle actin [SMA]) in the tumor compartments of pure DMs than mixed DMs. When comparing lymphoid aggregates (LA) to non-LA tumor cores, LAs were more enriched with CD20+ B-cells, but non-LA intratumoral leukocytes were more enriched with macrophage/monocytic markers (CD163, CD68, CD14) and had higher LAG-3 and CTLA-4 expression levels. Higher intratumoral PD-1 and LA-based LAG-3 expression appear to be associated with worse survival.

Our proteomic analysis reveals an intra-tumoral population of SMA+ CAFs enriched in pure DM. Additionally, increased expressions of immune checkpoints (LAG-3 and PD-1) in lymphoid aggregates and within tumor were associated with poorer prognosis. These findings might have therapeutic implications and help guide treatment selection in addition to informing potential prognostic significance.

CCR4 MEDIATES VENOUS WALL REMODELING FOLLOWING AVF CREATION

Thaxton C, Matsubara Y, Gonzalez L, Zhang W, Ohashi Y, Bai H, Ayoyagi Y, Li Z, Kano M, Yatsula B, Pober J, Dardik A

The high rate of arteriovenous fistula (AVF) failure reflects our poor understanding of the mechanisms underlying fistula failure. Although the innate immune response regulates venous remodeling, the role of the adaptive immune response remains poorly understood. CCR4 is a chemokine receptor found on Th2 and regulatory T cells that regulates lymph node trafficking. Since T cells can regulate venous remodeling, we hypothesized that inhibition of CCR4 leads to increased venous wall thickening and worse fistula outcomes.

Aortocaval fistulae were created in male C57B6 mice. A CCR4 inhibitor (AF-399/42018025) or vehicle was administered by intraperitoneal injection daily for 21 days. Ultrasound was used to measure vessel diameter and flow on the day of surgery and serially thereafter. Aortocaval specimens were harvested on day 21 and analyzed using conventional histology with EVG staining.

AVF in mice treated with the CCR4 inhibitor had more relative venous wall thickening compared to mice that received vehicle alone (18.53x vs. 8.52x, p < 0.0001). There were no statistically significant differences in vessel size or hemodynamic parameters. There was no significant difference in patency between treatment groups (day 21); however, the only occluded fistula occurred in the CCR4 inhibitor group.

Mice treated with the CCR4 inhibitor had increased wall thickening following fistula creation compared to vehicle alone. This data suggests Th2 and regulatory T cells may have a role in limiting neointimal hyperplasia following fistula creation, suggesting a role for the adaptive immune response during AVF maturation.

SOMATIC VARIANTS ACQUIRED LATER IN LIFE IMPLICATED IN CAUSATION OF THORACIC AORTIC ANEURYSMS: JAK2 V617F

Waldron C, Zafar MA, Ma D, Zhang H, Ziganshin BA, Popa A, Jha A, Kwan J, Elefteriades JA.

Due to the devastating morbidity and mortality associated with ascending thoracic aortic aneurysms (ATAA) and dissections, medical science has long sought to identify genetic etiologies of ATAA to improve identification of asymptomatic patients and management of aortic disease on a gene-by-gene basis. Historically, syndromic connective tissue diseases were among the first recognized drivers of ATAAs. Later, non-syndromic familial etiologies explained an additional 20% of ATAAs. Despite these advances, two-thirds of ATAAs occur without known genetic etiology or explanation. Population-scale genomic sequencing continues to deepen our understanding of germ line and somatic variants and their roles in cardiovascular disease. In particular, JAK2 V617F is a somatic variant frequently identified as a driver in adult-onset myeloproliferative neoplasms and is increasingly being associated with vascular complications. Herein, we report JAK2 V617F somatic variants which may contribute to the development of ATAA.

We conducted a retrospective study of patients identified by Yale DNA Diagnostics Lab to have documented somatic JAK2 V617F variants and ATAA. The genotype-first approach was utilized to investigate possible associations between JAK2 V617F variants and ATAA. An in-house exome database, containing 4350 clinical-grade patients exomes from a broad phenotypic spectrum, was interrogated. 492 patients (11.3%) were referred for genetic evaluation of ATAA or connective tissue disorders. We identified four patients with a JAK2 V617F variant diagnosed on whole exome sequencing of peripheral blood and a concurrent ATAA, with variant allele fractions (VAF) ranging from 11.2%-36%. Electronic medical records were queried to investigate patient demographics, medical and surgical histories, and relevant imaging studies.

75% of the patients were female, and the average age at time of diagnosis was 63. The mean height and weight were 1.75 m and 90.6 kg. One patient had a documented family history of aortic aneurysms. Every patient harbored an ATAA, and the mean ascending aneurysm size was 5.1 cm. Three patients had undergone surgical ascending aortic aneurysm repair. For all 4 patients, the thoracic ascending aneurysms were discovered on CT chest imaging. Three patients had a history of hypertension, and two had a history of atrial fibrillation. Of the 4 patients, one had undergone prior coronary artery bypass graft surgery and one an aortic valve replacement.

The acquired JAK2 V617F mutation was documented in four ATAA patients. This novel observation warrants further investigation among ATAA patients. Such acquired somatic mutations of later life may contribute a meaningful aliquot of aneurysm patients, above and beyond the standard known genetic causes acquired from the time of conception. Furthermore, the cadre of patients with somatic JAK2 V617F variants and ATAA may not be trivial, especially in older patients subject to acquired hematologic variants later in life. With genetic sequencing becoming commonplace, other mosaicisms may be uncovered, and somatic variants may be investigated more regularly. Importantly, this novel genetic mechanism offers the potential for utilizing hematopoietic JAK-STAT signaling as a target of therapy for ATAA.

IDENTIFICATION OF NOVEL CANDIDATE RISK GENES CAUSING THORACIC AORTIC DISEASE VIA EXOME SEQUENCING

Ziganshin BA, LeDuc CA, Zafar MA, Shen Y, Chung WK, Elefteriades JA

One in five cases of thoracic aortic aneurysm and dissection (TAAD) are familial. Although more than 60 genes (with varying degrees of evidence) have been implicated in causing TAAD, suspicious variants are found in only one-third of patients. Via exome sequencing of DNA samples from patients with thoracic aortic disease, we applied advanced gene searching techniques in an effort to identify novel risk genes for TAAD.

Genomic data on 1278 unrelated TAAD patients of European ancestry were analyzed for enrichment in a case-control model for rare (allele frequency <10-4) deleterious missense and likely gene disrupting variants. For the control group, we used 145,103 unrelated individuals of European ancestry from the UK BioBank. The fundamental principle of our gene search technique was to identify, via advanced genomic statistical methods, genes substantially “enriched” in our TAAD patients compared to controls.

First, we analyzed the genomic data to identify deleterious variants in known TAAD risk genes, which were then classified according to the ACMG criteria. We identified 52 pathogenic or likely pathogenic variants in the currently known TAAD risk genes, signifying that these genes can explain only 4.1% of all TAAD cases.

Next, three potential novel candidate genes emerged from the unbiased case-control analysis:

1) VPS8, a gene involved in endosomal vesicle fusion ($p=8.8\times10^{-9}$ for the β-propeller domain only)

2) STAG2, a member of the cohesion complex ($p=3.9 \times 10^{-8}$)

3) UTP11, a component of the small subunit processome ($p=3.9 \times 10^{-8}$)

In a case-control association analysis, we have identified three promising novel candidate risk genes for TAAD (VPS8, STAG2, and UTP11), which merit further investigation and confirmation in other cohorts of patients with aortopathy. With each newly identified TAAD gene, a progressively greater proportion of TAAD cases are “explained” by underlying genetic causes.

DEFINING THE GENETIC LANDSCAPE OF CONSERVED NON-CODING ELEMENTS THAT REGULATE EMBRYONIC CARDIAC lncRNAs IN CONGENITAL HEART DISEASE

Pickell Z, Wolfsohn M, Kuebler S, DePalma S, Ng K, Brueckner M, Laugwitz KL, Moretti A, Grote P, and Gruber PJ

Although significant progress identifying coding regions associated with congenital heart disease (CHD), the genetic landscape of non-coding regions contributing to CHD is poorly understood, with over half the genetic risk unexplained. Long noncoding RNAs (lncRNA) are transcribed during cardiogenesis, and several lncRNAs are essential to normal cardiac development. We hypothesized that mutations within regulatory elements of lncRNAs expressed during cardiac development contribute to CHD.

We interrogated mutations in transcription factor binding sites (TFBS) upstream of 545 lncRNAs expressed in cardiac development in nearly 3,000 whole genome sequences (WGS) of patients with CHD from the Pediatric Cardiac Genomics Consortium. We employed a custom GATK pipeline filtering by allele quality, Gnomad minor allele frequency, and CADD score to select rare, damaging mutations. TFBS-specific predicted significant gain-of- function (GOF) and loss-of-function (LOF) mutations were identified using position weight matrices (PWMs) from JASPAR's 2023 TFBS database and FABIAN Variant analysis software.

Our analysis identified 12 GOF and 36 LOF mutations in TFBS essential for cardiogenesis such as (GATA4, NKX2.5, and HAND2). Subsequent analysis revealed a greater number of GOF (53) and LOF (47) TFBS mutations in basal transcriptional regulatory factors (RNA-Pol2, TFIID, and TFIIB).

We identified damaging mutations surrounding developmentally regulated cardiac lncRNAs in patients with CHD. These mutations significantly affect the TFBS of both important cardiac TFs and basal transcription machinery that may affect cardiac lncRNA function. This provides a broad new set of targets to help explain the gap in genetic information and requires further study to determine the effects on cardiac development.

SINGLE NUCLEAR GENOMIC ANALYSIS REVEALS DYNAMIC REGENERATION BY DISTINCT CELL TYPES USING A GROWTH-ADAPTIVE ACELLULAR EXTRACELLULAR MATRIX FOR TRICUSPID VALVE REPLACEMENTS

Pickell Z, Mortlock R, Raredon S, Luna E, Wolfsohn M, Best C, and Gruber PJ

Currently, there are no growth-adaptive pediatric valve replacements other than pulmonary autografts. Recently, an acellular extracellular matrix (ECM) derived from a porcine small intestinal submucosa (SIS) has been employed to successfully replace the tricuspid valve (TV). Despite some clinical success, there are limitations. Our objective is to understand the biology of ECM valve remodeling.

Sheep underwent SIS-ECM TV replacement with sacrifice at 3, 4, 5, and 10 months. Valves were analyzed for longitudinal function using TTE and subsequently harvested and divided for histological analysis using light microscopy and single nuclei RNA sequencing.

Functionally, TTEs demonstrated excellent leaflet coaptation and trace tricuspid regurgitation. Histology demonstrated a dynamic flux of discrete cell types: first an infiltration of inflammatory cells followed by a reduction of inflammatory cells that begin at the annulus and spread towards the leaflets. Genomic analysis revealed distinct cell clusters that are consistent with an initial hypercellular inflammatory immune response, initially displaying large clusters of macrophages, and inflammatory fibroblasts which subsequently decreased while clusters of B-cells, T-cells, and endothelial cells emerged more prominently. Dynamic immune cell changes appeared to mediate valvular maturation and key formation of valvular endothelial cells and interstitial cells.

T-cell and B-cell emergence may represent a critical shift from an initial inflammatory response to immune cell-mediated tissue repair, driving valvular maturation. Acellular SIS- ECMs may become a promising approach to growth adaptive valve replacements. Understanding the basic biology is required to design rational therapies to enhance valve maturation and prevent valve degradation.

AN INJECTABLE FIBROBLAST-ENCAPSULATED HYDROGEL AND ITS CROSSTALK WITH M1 MACROPHAGES

Gao D, Shipman WD, Beraki, L, Hsia HC

Fibroblasts are introduced to differentiate into myofibroblasts by signaling and physical factors to facilitate wound healing. But dysfunctional fibroblasts in diabetic wound have shown approximately 10 days of delayed differentiation compared to that in non-diabetic wound in a rat model, persisting myofibroblasts in late stage of wound healing has inhibited the skin regeneration. Jeong et al. have transplanted human dermal fibroblasts into a full- thickness wound model of rat via a hydrogel, showing the accelerated wound closure and the improved epithelialization and skin appendage formation, due to the fibroblast encapsulation device producing combination of cytokines and providing ECM components. In addition, some commercial skin substitute products, such as Apligraf® and Dermagraft® have loaded fibroblasts into scaffolds for treatment of chronic wounds. Overall, transplantation healthy fibroblasts or their subsets to the diabetic wound sites can be a strategy to rescue the communications with dysfunctional fibroblasts and surrounding environments of diabetic wound. But it is essential to understand the interactions between encapsulated fibroblasts and native cells.

In this study, we aimed to increase the understanding of the functions of primary human dermal fibroblasts encapsulated within an injectable hydrogel with interpenetrating polymer network (IPN) synthesized by alginate/collagen/fibronectin and study their cellular and molecular interactions with pro-inflammatory M1 macrophages. In addition to direct communication between fibroblasts and macrophages, the function of the hydrogel in the interactions was investigated. A simplified coculture in vitro model was engineered by analyzing the cytokines secretion, reactive oxygen species (ROS) and macrophage polarization. This fibroblast transplantation hydrogel has potential to be a future feasible cell therapy approach for chronic wounds via pathological communications with native dysfunctional macrophages.

In this study, we engineered an injectable composite hydrogel of alginate/collagen/fibronectin with interpenetrating polymer network can provide better cellular microenvironment compared to alginate hydrogel and showed the potential to promote angiogenesis. Based on the hydrogel and M1 macrophage, an ELABORATE platform had been constructed to mimic the hydrogel rescuing a proinflammatory environment on a cellular level, demonstrating decreased pro-inflammatory cytokine secretion (IL-8 and IL-6), reduced ROS production and increased anti-inflammatory cytokine secretion (TGF-β, TIMP1 and SDF1α) in the coculture groups with the presence of the hydrogel relative to the M1 monoculture. In addition, the secretion of MMP2, VEGF and PDGF-AA of fibroblasts in the hydrogel were maintained, indicating its potential to promote ECM deposition and angiogenesis.

In conclusion, this design represented an attractive model for mimicking the process of cell therapy for diabetic wound.

EXOSOME-MEDIATED FIBROBLAST-ENDOTHELIAL CELL CROSSTALK IS DYSFUNCTIONAL IN DIABETIC FIBROBLASTS IN VITRO

Shipman WD, Gao D, Hsia HC

Impaired wound healing in type 2 diabetes involves inflammation, hypoxia, neuropathy, and vascular dysfunction leading to chronic, non-healing wounds such as diabetic foot ulcers (DFUs). Dermal fibroblasts (DFs) critically contribute to wound healing by cytokine and growth factor secretion, inflammatory cell recruitment, and granulation tissue formation. Healing-enriched fibroblasts (HEFs), a subset of DFs, are localized to the wound bed, a key site of angiogenesis, and are reduced in diabetic skin and non-healing DFUs.

Therefore, we explored endothelial cell support by human DFs and possible dysfunctional crosstalk in human diabetic DFs via flow cytometry and ELISA analysis of human DFs and examination of human DF-endothelial cell co-cultures.

Prior single-cell RNA sequencing data demonstrates a pro-angiogenic signature in non- diabetic HEFs. In vitro, diabetic DFs exhibited decreased VEGF-A expression and secretion along with altered secretion of other wound repair cytokines. In addition, in vitro diabetic DFs consisted of decreased HEFs and displayed a myofibroblast-like phenotype, indicating an altered state. In 3D DF-endothelial cell co-cultures, diabetic DF co-cultures generated reduced endothelial cell numbers, suggesting decreased support. Endothelial cells also displayed reduced proliferation, adherence, and angiogenesis when cultured with diabetic DF-conditioned media compared to non-diabetic DF conditioned media. Exosomes are crucial mediators of intercellular communication. Diabetic DFs produced decreased exosomal protein and non-diabetic DF exosomes rescued impaired diabetic DF-endothelial cell proliferation, implicating exosomes in dysfunctional diabetic DF-endothelial cell crosstalk.

These findings deepen our understanding of DFs, underscore the significance of HEFs, and highlight the importance of exosomes in intercellular communication. Furthermore, these data suggest a dysfunctional DF-endothelial cell axis in diabetes, proposing HEFs or their byproducts as potential therapeutic targets for chronic, non-healing wounds.

IDENTIFICATION OF NOVEL SALIVA AND SERUM MIRNA AND MRNA SIGNATURES FOR ORAL CANCER DETECTION USING WHOLE TRANSCRIPTOME AND SMALL NON-CODING RNA SEQUENCING: PREDICTION OF THEIR ASSOCIATION WITH THE PI3K/AKT PATHWAY.

Vangeli DP, Doukas PG, Townsend JP, Pickering C, Judson BL

Identification of molecular biomarkers in the saliva and serum of oral cavity cancer patients represents a first step in the development of essential and efficient clinical tools for early detection and post-treatment monitoring. Molecular analyses of paired saliva and serum samples from an individual patient will likely yield better results than analyses of either serum or saliva alone.

We performed whole-transcriptome and small non-coding RNA sequencing analyses on sixteen paired saliva and serum samples from patients with oral squamous cell carcinoma (OSCC) and healthy controls (HC).

We identified twelve novel saliva and serum miRNAs and a panel of unique miRNA and mRNA signatures, significantly differentially expressed in saliva and serum of OSCC patients versus HC (log2foldchange: 2.6–26.8; DE 0.02–0.000001). We utilized a panel of the 10 top- deregulated miRNA and mRNA markers (hsa-miR-7704, hsa-miR-3648-5p, TNC, MMP10, TP63 in saliva; and hsa-miR-23a-5p, hsa-miR-499a-5p, hsa-miR-556-5p, RELA(p65), and TCAIM in serum) and evaluated its putative diagnostic potential (87% sensitivity; 100% specificity). Functional and pathway analyses based on the discovered miRNAs and mRNAs and their targets indicated interactions with canonical pathways, including PI3K/AKT signaling.

We have identified a panel of miRNA and mRNA markers exhibiting promise as non-invasive biomarkers for oral cavity cancer detection and recommend further clinical testing.

ORAL PREMALIGNANT LESIONS-ASSOCIATED SALIVA AND SERUM MRNA AND MIRNA PROFILES BY NEXT- GENERATION SEQUENCING: A PILOT STUDY

Vangeli DP, Schiff B, Roche A, Doukas PG, Pickering C, Judson BL

Oral premalignant lesions (OPML) with dysplastic features can turn into malignancy. The utility of less invasive approaches to detect molecular signatures associated with OPML and distinguish those at low risk from others at high risk for malignancy could enable rapid and accurate screening of patients with OPML, and risk stratify them for cancer development and their follow-up.

We performed whole transcriptome (mRNA-seq) and small non-coding RNA sequencing (smRNA-seq) analyses, including miRNAs, in serum from 10 patients with OPML [5 mild dysplasia; 5 moderate/severe dysplasia/CIS] and 10 healthy controls (HC).

We identified 981 miRNAs expressed in the serum of OPML patients and HC, 25 of those significantly differentially expressed (1.0 log2foldchange; P= 0.05; by DESeq2). The 3 top-deregulated miRNAs (3-8.2 log2foldchange; DE: 0.00024-0.000000035; by DESeq2) demonstrated a biological role associated with NOTCH1 regulation, EMT, or oral premalignancy. We identified 745 deregulated genes in OPML serum vs. HC, 44 of those with high alterations (24 log2foldchange; DE: = 0.0000000000001; by DESeq2), including a set of 9 top-deregulated genes with an oncogenic function, 2 of those linked with oral malignancy. This combined set of 9-top deregulated serum mRNAs and miRNAs showed high sensitivity and specificity (100%) for OMPL, while 6 of those were associated with low-grade dysplasia (mild vs. moderate to severe/CIS: 4.5 foldchange; P=0.05; by t-test).

We identified novel serum mRNAs and miRNAs as promising non-invasive molecular biomarkers for oral premalignant and early malignancy detection, prognosis, and monitoring.

MULTI-INSTITUTIONAL LANDSCAPE OF SOMATIC VARIANTS IN PANCREATIC NEUROENDOCRINE TUMORS

Brown L, Hagenson R, Sheltzer J, Kunz P, Kunstman J

Pancreatic neuroendocrine tumors (PNETs) are rare neoplasms, resulting in a paucity of molecular data. Existing genomic studies remain limited. Aggregation of genomic repositories to define the somatic mutational landscape may facilitate our understanding of PNETs.

Mutational and clinical data of all PNETs in cBioPortal were analyzed. A 5% mutational frequency threshold excluded infrequently mutated genes. Significance testing was done by Chi-squared and Fischer's exact for association, Wald for logistic regression, and logrank for survival.

452 PNET cases (313 primaries and 139 metastases) were analyzed. Metastases demonstrated a higher tumor mutational burden than primaries (2.59 vs 0.86 mutations/megabase, respectively; $p<0.01$). 6,208 nonsynonymous variants were identified of which 33.4%, 32.5%, 21.1%, and 8.6% were missense, frameshift, nonsense, and splice site mutations, respectively. Frequently mutated genes amongst all lesions were MEN1 (41.3%), DAXX (23.4%), ATRX (15.2%), SETD2 (8.5%), PTEN (6.7%). Metastases displayed increased TP53 (16.6% vs 3.2%), TSC2 (13.7% vs 5.1%), ARID1A (3.2% vs 7.9%), and KRAS (7.2% vs 0.3%) mutations compared to primaries. TP53 and TSC2 mutations correlated with metastasis ($p<0.01$, both). TP53 and KRAS mutations were associated with worse prognoses ($p<0.01$, both), whereas ATRX and DAXX mutations demonstrated improved survival ($p<0.01$, both). ATRX and DAXX variants were mutually exclusive in primaries (z-score=4.16) and correlated with nodal metastasis ($p<0.01$, both).

This study represents the largest landscape of PNET somatic mutations utilizing publicly available datasets. Frequent mutations of MEN1, ATRX, and DAXX illustrate the importance of chromatin remodeling. Mutations in TP53, KRAS, and TSC2 were associated with aggressive disease.

DEVELOPMENT OF AN MRNA THERAPEUTIC VACCINE FOR VIRALLY DRIVEN MERKEL CELL CARCINOMA

Frey A, Perry C, Olino K, Ishizuka J

Merkel Cell Carcinoma (MCC) is a neuroendocrine skin cancer associated with integration of Merkel Cell Polyomavirus Large T Antigen (LTA). LTA is immunogenic, and its expression is required for proliferation of MCC, rendering it an ideal vaccine target.

B16-F10 murine melanoma cells that express LTA were used as an MCC model. In vitro transcription was used to create an LTA mRNA. Mice bearing LTA expressing tumors were treated with LTA mRNA or placebo +/- anti-PD1. MCC patient PBMCs were used as a model for human in vitro vaccination. Monocyte derived dendritic cells were transfected with LTA mRNA or placebo and used to stimulate the remainder of the PBMC pool.

LTA mRNA suppressed tumor growth compared to placebo (day 21 mean volume 47.28mm3 vs. 575.12mm3 $p<0.01$) and prolonged median survival (46 vs. 24 days $p<0.01$). Combination treatment with anti-PD1 resulted in 100% tumor regression. Flow cytometry of tumors revealed increased immune infiltration (mean CD45+ 11.56% vs. 7.81% P=.037), increased CD3+ cells (mean 69.74% vs. 57.36% P=.0013), and CD8+ cells with increased cytotoxic markers (MFI GZMB 26785 vs. 13607 P=.0026). In vitro vaccination of patient PBMCs resulted in expansion of LTA tetramer specific CD8+ T cells (0.3% vs. 0.077%), increased IFNg release (21.78ng/mL vs. 5.35ng/mL $p<0.01$).

LTA mRNA suppresses tumor growth and prolongs survival by increasing infiltration of cytotoxic immune populations. In vitro human vaccination increases the proportion LTA specific CD8+ T cells, IFNg release, and specific killing of MCC cells.

INTERLEUKIN-1 ENABLES ENDOTHELIAL SURFACE EXPRESSION AND TRANS-PRESENTATION OF INTERLEUKIN -15 BY RELIEVING LET-7C-3P SUPPRESSION OF PROTEIN TRANSLATION

Mullan CW, Summer L, Lopez F, Tobiasova Z, Manes T, Yasothan S, Song G, Jane-Wit D, Saltzman WM, Pober JS

Expression of interleukin-15 (IL-15) on the surface of human graft endothelial cells (ECs) bound to the IL-15 receptor alpha (IL-15Ralpha) subunit can increase the activation of cytotoxic T lymphocytes (CTLs), potentiating allograft rejection. Previous work showed that surface expression of this protein complex could be induced by alloantibody-mediated complement activation, through increased IL-1beta synthesis, secretion, and autocrine/paracrine IL-1-mediated activation of NF-kappaB.

We treated cultured primary human endothelial cells with cytokines, small molecule inhibitors, siRNA, and antimir and performed deep RNA sequencing, qRTPCR, immunofluorescence, and small RNA sequencing, and we performed co-cultures with CD8 memory T cells for evaluation of downstream IL-15 signaling.

Cultured human ECs were found to constitutively express 8 differently spliced IL-15 transcripts. Remarkably, IL-1β does not alter the expression level of any IL-15 transcript but induces surface expression independently of RNA Polymerase II-mediated transcription while requiring new protein translation. Mechanistically, IL-1β causes an NF-kappaB- mediated reduction in the level of microRNA Let-7c-3p, thereby relieving a block of translation of IL-15 surface protein. Let7c-3p antimir can induce EC surface expression of IL- 15/IL-15Ralpha in the absence of complement activation or of IL-1beta, enabling IL-15 trans- presentation to boost CD8 T cell activation.

Endothelial IL-15 is regulated post-transcriptionally by let-7c-3p. The complexity of IL-15 regulation requires caution in interpreting increased total IL-15 mRNA or protein levels as a surrogate for trans-presentation.

ABLATION OF FIBROBLAST ACTIVATION PROTEIN (FAP+) CELLS RESULTS IN THINNER ADHESIONS WHICH LACK CELLS OF MESOTHELIAL ORIGIN

Blackburn HN, Roulis M, Lewis W, Qu R, Kluger Y, Flavell RA

Fibrosis evolved as a fundamental property of multicellular life and, as such, fibrotic diseases and complications affect every organ system. Despite this, there are limited effective anti-fibrotic therapies. Intra-abdominal adhesions are a common and severe fibrotic complication of abdominal surgery, and the underlying cells and mechanisms driving adhesion development remain unclear. Here, we sought to understand the role of mesothelial-to-mesenchymal transition (MMT) and FAP+ cells in the development and cellular origin of intra-abdominal adhesions.

First, we employed the creER-loxP genetic tool to selectively label cell types within the abdomen. These mice underwent either adhesion-promoting or sham procedures and tissue was evaluated for cellular origins. Lineage-tracing results demonstrated that mesothelial cells are a primary source of cells within adhesions through MMT. To further interrogate our hypothesis of MMT, we performed high resolution single cell RNA sequencing of sorted mesothelial and mesenchymal cells from lineage-traced adhesions. These analyses identified distinct clusters of transitioning cells—unique to adhesions—that were lineage-traced to mesothelial origin, and defined by a combination of known mesothelial, mesenchymal, and pro-fibrotic markers.

Next, we selectively ablated proliferating FAP+ cells prior to adhesion induction and found that without FAP+ cells, mice develop fewer adhesions and thinner adhesions. To interrogate the cellular origin of adhesions which lack FAP+ cells, we ablated proliferating FAP+ cells within lineage tracing mice. Here we found that ablation of FAP+ cells results in the complete absence of mesothelial origin cells within adhesions.

In conclusion, we found that cells of mesothelial origin are the major contributor of cells within adhesions, where they express markers of mesothelium and mesenchyme, as well as pro-fibrotic markers such as myofibroblast markers, extracellular matrix proteins, and extracellular matrix modifiers. And second, that ablation of FAP+ cells results in thinner adhesions, which lack cells of mesothelial origin, suggesting that treatments to target FAP+ cells could be valuable in decreasing the burden of adhesions in humans.

TARGETING CREBBP/EP300 MUTATIONS CREATES A SYNTHETIC LETHALITY WITH PARP INHIBITION AND MAY BE A NEW GENOMICALLY-TARGETED THERAPEUTIC APPROACH FOR HEAD AND NECK SQUAMOUS CELL CARCINOMA

P. Abedi, L. Qu, B. Leibowitz, H. Skinner, C. Pickering

Head and neck squamous cell carcinoma (HNSCC) present significant treatment challenges, with limited targeted therapy options. Our preliminary findings suggest that mutations in CREBBP or EP300 are associated with enhanced homologous recombination (HR) DNA damage repair (DDR) pathways, contributing to radiation therapy (RT) resistance. Inhibition of these mutations with the histone acetyltransferase inhibitor (HATi) A-485 reduces HR repair and increases cell death post-RT. We hypothesize that reduced HR activity may also sensitize to PARP inhibition similar to what occurs with BRCA1 mutation in other tumor types.

This study aims to investigate the therapeutic potential of combining histone acetyltransferase inhibitors (HATi) with PARP inhibitors to target CREBBP/EP300 mutant tumors in HNSCC. Additionally, we will assess the activity of PROTAC-based HATi. To test our hypothesis, HNSCC cell lines with CREBBP mutations will be treated with A485, PROTACs, radiation, and/or PARP inhibitors, and cell viability will be measured.

Our data indicate that co-treatment with A-485 and PARP inhibitors significantly increases cell death in CREBBP/EP300 mutant HNSCC cells. Furthermore, the PROTAC dCBP effectively mimics A-485's sensitization to radiation and induction of cell death while degrading CBP and suppressing acetylation.

Targeting CREBBP/EP300 mutations with small molecule or PROTAC-based HATi combined with PARP inhibitors shows promise as a therapeutic strategy in HNSCC. This approach has the potential to become a genomically-targeted treatment option for HNSCC.

UNDERSTANDING THE ROLE OF HISTONE ACETYLATION DURING THE RESPONSE TO RADIATION TREATMENT IN HNSCC

Pickering C.

Head and neck squamous cell carcinoma (HNSCC) are the seventh most common type of cancer globally. Radiation therapy (RT) is one of the most effective treatments for HNSCC. Its efficacy hinges not only on its ability to cause direct DNA damage but also on the ability of the cells to repair that damage. We have found that CREBBP mutations in HNSCC that increase acetylation activity also increase homologous recombination (HR) DNA repair activity. We hypothesize that changes in histone acetylation following RT are impacted by CREBBP activity and may be targets for radiosensitization. Our study employed ChIP-seq to investigate the epigenetic alterations mediated by H3K27Ac, H3K56ac, H4K16ac, and H2BK20ac, as well as the DNA repair protein BRCA1 in HNSCC cells after radiation treatment. Our findings indicate a distinctive epigenetic signature associated with radiation, wherein H3K27Ac, was prominently enriched at transcription starting site (TSS) of genes involved in the DNA damage response. H4K16ac and H2BK20ac (transcriptional activation) showed dynamic changes at 30mins and 12h after irradiation, suggesting a role in gene expression reprogramming during DNA repair. H3K56ac (open chromatin) exhibited transient enrichment at sites of DNA repair. Lastly, the presence of BRCA1 in promoter regions and near TSSs suggests it may have a regulatory role in gene expression. Our data provide valuable insights into the epigenetic reorganization induced by radiation therapy and identify potential targets for enhancing therapeutic efficacy in HNC.

ULTRASONIC CHARACTERISTICS OF PRESTIN COMPLEX NONLINEAR CAPACITANCE (CNLC) IN THE MOUSE: MUTATION AND MOLECULAR DYNAMICS (MD)

Santos-Sacchi J, Bai J-P, Zhang C, Oliver D, Beckstein O, Navaratnam, D.

We measured ultrasonic frequency responses of prestin's cNLC under voltage clamp in guinea pig (GP) OHC membrane patches where cellular loads are absent (Santos-Sacchi et al., J Neuro, 2023). Real and imaginary components of cNLC report on prestin's influence on cochlear amplification, since prestin's charge movements drive electromotility. The frequency where the imaginary component intersects the real component (Fis), reveals this cut-off, near 20 kHz for GP. Fis depends on prestin's kinetics, which is influenced by intracellular chloride levels (Santos-Sacchi and Song, BJ, 2016) and membrane fluidity (Santos-Sacchi et al., BJ, 2022). In the mouse, we test a knock-in prestin mutation that may alter chloride binding influence on ultrasonic conformational switching. We also use MD to probe the potential influence of phospholipids on cNLC.

cNLC was measured (4-120 kHz) as described for GP membrane macro-patches, using admittance-based techniques (Santos-Sacchi et al., J Neuro, 2023). Control OHCs and knock- in mouse OHCs with the prestin chloride binding site mutation (S396E) were compared. For MD we used the structure we determined by cryo-EM (Butan et al., BioRxiv, 2021; Butan et al., Nature Comm., 2022). Simulations were run on Anton2 at 296K and 333K, ranging up to 12 ls.

On average, Fis for both control and S396E OHCs (n=4-5 patches) have similar cut-offs, namely 27.8 and 25.8 kHz. These values are greater than for GP (20 kHz), possibly resulting from differing membrane characteristics between species. To evaluate phospholipid influence on prestin charge movement we employed MD, where we monitored the separation (center of mass of 3 end terminal residues) of TM12 and TM6 over time. After about 2 ls following imposition of a negative potential across the membrane, these TM helices separated near the inner leaflet, permitting the intercalation of two phospholipids from the bilayer into prestin. At higher temperatures, the intercalation occurred sooner. Those helices possess charged residues that we suggested to contribute to prestin's voltage sensor (Bai et al., BJ, 2009). Thus, unusually intimate interactions between protein and lipid may impact on prestin's complex charge movements.

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 cNLC. We show that chloride binding, absent in the S396E mouse, has little effect on cNLC high frequency response. Lower frequency activity could be impacted to a greater extent since we found that salicylate blocks low frequency components of NLC (Santos-Sacchi and Tan, iScience, 2019). We suggest that the stretched-exponential nature of prestin's NLC results from viscoelastic interaction with membrane components, whereby the evolution of the imaginary component may correspond to phospholipid intercalation within the protein itself, which changes the restrictive environment through which prestin charge moves.

ONCOGENE-LIKE ADDICTION TO ANEUPLOIDY IN HUMAN CANCERS

Girish V, Lakhani AA, Thompson SL, Scaduto CM, Sausville EL, Hagenson R, Lukow DA, Sheltzer JM

Approximately 90% of human tumors exhibit aneuploidy, an alteration in the copy number status of whole chromosomes or chromosomal arms. Aneuploidy affects a greater percentage of the cancer genome than any other somatic genetic alteration, with a typical tumor showing a median of 3 gains and 5 losses of chromosomal arms. However, despite a century of research since the preliminary observation of chromosomal mis-segregation in cancer, we lack an understanding of the mechanistic basis for aneuploidy selection in tumorigenesis.

Here, we describe ReDACT (Restoring Disomy in Aneuploid cells using CRISPR Targeting), a set of chromosome engineering tools that allow us to eliminate specific aneuploidies from cancer genomes.

Using ReDACT, we created a panel of isogenic cells that have or lack common aneuploidies, and we demonstrate that trisomy of chromosome 1q is required for malignant growth in cancers harboring this alteration. Mechanistically, gaining chromosome 1q increases the expression of MDM4 and suppresses p53 signaling, and we show that TP53 mutations are mutually-exclusive with 1q aneuploidy in human cancers.

Thus, tumor cells can be dependent on specific aneuploidies, raising the possibility that these “aneuploidy addictions” could be targeted as a therapeutic strategy.

AN ELEVATED RATE OF WHOLE-GENOME DUPLICATION IN CANCERS FROM BLACK PATIENTS

Brown L, Hagenson R, Sheltzer J

Black patients have higher rates of cancer mortality than any other group. The influence of chromosomal copy number alterations on outcomes remains uncertain. Whole genome- duplication (WGD), an event associated with aggressive disease, has not been investigated.

Genomic and patient data of primary tumors were acquired from MSK-MET, TCGA, and PCAWG. Cancer types with 60 Black patients were included. Logistic regression identified genomic correlates of WGD and race. Available clinical data was analyzed. Significance testing included Chi-squared for association, Wald test for logistic regression, and logrank for survival.

MSK-MET (n=13071), TCGA (n=8060), and PCAWG (n=1963) were analyzed. In pan-cancer analysis, Black/African-ancestry patients exhibited higher rates of WGD compared to white/European-ancestry patients (MSK-MET: BLACK 29.3% vs. WHITE 26.2%, p=0.04; TCGA: BLACK: 39.4% vs. WHITE 35.5%, p=0.02; PCAWG: AFR 39.3% vs EUR 29.1%, p=0.02). In MSK-MET and TCGA, relative to white patients, Black patients demonstrated 1.3-fold, 1.4-fold, and 2.5-fold higher rates of WGD in breast, non-small cell lung, and endometrial cancers respectively ($p<0.01$, all). WGD was associated with similar aberrations in both populations, including TP53 mutations and CCNE1 gains. On pan-cancer analysis, Black race and WGD were associated with worse survival (p=0.024, $p<0.01$, respectively), younger ages of diagnosis ($p<0.01$, $p<0.01$, respectively), first metastasis ($p<0.01$, p=0.002, respectively), and death ($p<0.01$, p=0.04, respectively), along with increased regional ($p<0.01$, both) and distant spread, including intra-abdominal metastases ($p<0.01$, p=0.001, respectively). The increased incidence of WGD may contribute to disparate cancer outcomes. WGD may serve as a prognostic biomarker for Black patients.

TRANSCRIPTOMIC COMPARISON OF CONGENITAL DIAPHRAGMATIC HERNIA LUNG AND NORMAL LUNG DURING LUNG DEVELOPMENT

Rivero R, Mizoguchi S, Edelstein S, Wang N, Raredom MS, Stitelman DHS

Therapy to correct deranged pathways in lung development could alter the pathogenesis of CDH. In our laboratory, through particle-based fetal micro-RNA delivery, we have reversed lung hypoplasia in the CDH rat model. A better understanding of normal and pathologic lung development pathways could improve efficacy of molecular therapy for lung hypoplasia. The purpose of this study was to study differential gene expression and signaling between normal and CDH rat lung throughout lung development to identify cell populations for therapeutic targeting.

Normal and CDH lungs were harvested at E17, 19 and 20 and dissociated into single cell suspension. Seurat was used for single cell analysis. Cell types were identified by canonical genes and differential expression of genes were then analyzed. Findings were confirmed by immunohistochemistry.

The mesenchymal population in early timepoints is significantly lower, particularly the mesenchymal progenitors. An unusual population of Sox9- mesenchymal progenitors are enriched in the CDH lung. This cluster expresses pro-inflammatory and pro-fibrotic genes. Staining for Sox9 confirmed decreased expression in mesenchymal cells surrounding developing airways in CDH.

Mesenchymal cells are critical in the development of the lung epithelium and derangements in their differentiation could be a factor leading to lung hypoplasia. We found a subset of mesenchymal cells that are deficient in Sox9 in CDH. These Sox9- mesenchymal cells in CDH express genes upregulated in fibrosis. We hypothesize this will influence epithelial- mesenchymal signaling leading to arrested epithelial differentiation and a pro-fibrotic inflammatory environment. These cells may be a good target for molecular therapeutics in CDH.

MUTATIONAL FEATURES AND TUMOR MICROENVIRONMENT ALTERATIONS IN HIGH-GRADE APPENDICEAL CANCERS TREATED WITH ITERATIVE HYPERTHERMIC INTRAPERITONEAL CHEMOTHERAPY (HIPEC)

Su DG, Dhiman A, Bansal VV, Zha YY, Shergill A, Polite B, Alpert L, Eng OS, Turaga KK

High grade appendiceal adenocarcinomas (HGAA) with peritoneal metastases (PMs) are associated with poor survival. Hyperthermic intraperitoneal chemotherapy (HIPEC) is a novel treatment approach for unresectable HGAA-PM. However, its influence on immunogenomic profiles has not yet been fully explored.

We obtained 79 samples of metastatic peritoneal tumor deposits from patients diagnosed with HGAA and performed whole-exome sequencing, RNA sequencing, and immunoprofiling before and after HIPEC. Tumor biopsies were subjected to immunogenomic profiling to detect mutational signatures and immune populations associated with oncologic outcomes.

Fifteen patients with HGAA-PMs were included in the study. The median progression-free survival (PFS) was 6.7 months (2.7 to 25.3), and the median OS was 11.4 months (4.7 to 42). Mucin-associated genes (MUC16, MUC17, MUC3A) and titin (TTN) had the highest mutation frequencies. Mutational signatures such as single-base substitution (SBS)29 and double- base substitution (DBS) 11 were present in 50% of single-base and double-base mutations. Higher programmed cell death protein-ligand 1 (PD-L1) co-expression on CD8+ T cells demonstrated a higher PFS both intratumorally ($p = 0.019$) and at the margin ($p = 0.025$).

HIPEC-associated immune populations and mutational signatures were identified in HGAA- PM, offering valuable insights for prognostication in the context of HIPEC treatment.

COCHLEAR DEVELOPMENT IS DEPENDENT ON GJB2-MEDIATEDD GAP JUNCTIONAL COMMUNICATION

Yu YD, Yang Y, Liu LM, Zhai TY, Lu XI, Zhao HB

GJB2 (Cx26) mutations can induce a high incidence of hereditary deafness, responsible for 70-80% of nonsyndromic hearing loss in the clinic. Previous mouse models showed that Cx26 deficiency can produce cochlear developmental disorders, hair cell and spiral ganglion neuron degenerations, endocochlear potential (EP) reduction, and active cochlear mechanics reduction. These data suggest that Cx26 is required and plays a critical role in the cochlear development. In this study, we used the advanced RNA Sequencing (RNA-Seq) technique and investigated GJB2-mediated transcriptional changes during the cochlear postnatal development.

Cx26 conditional knockout (cKO) mice were used and created by LoxP-Cre technique. Cx26 FloxP/FloxP mice were crossed with Pax2-Cre mice. The mouse cochlea at postnatal day 1 (P1), P3, P5, and P10 were collected. Bulk Poly(A) RNA Sequencing was performed.

In comparison with WT mice, Cx26 cKO mice at P3 had the most significant changes. It has been found that the major changes in the pathways of the primary Biological Process (BP) were related to positive regulation of cell projection and cell migration. In Cell Component (CC) analysis, it has been found that the actin cytoskeleton and synapse formation and specialization had the most primary changes. In primary Molecular Function (MF) analysis, the tubulin and microtubule binding had significant changes. In addition, in comparison with WT mice, the downregulations of some genes in the Cx26 cKO mice were identified by significant q-value and logFC changes. These notable genes included Zfhx4, Hey1, and so on. Previous studies demonstrated that deficiency of these genes could also cause hearing loss.

Cx26 deficiency can cause significant changes of gene expression in the transcriptional level during the cochlear development. Cx26 deficiency can also cause other genes downregulations, which can cause hearing loss as well. These data provide valuable information for developing efficient gene therapy for GJB2 mutation induced hearing loss.

CX26 (GJB2) DEFICIENCY CAUSES HYPERACUSIS-LIKE BEHAVIOR IN MICE

Zhai TY, Liu LM, Yu YD, Yang Y, Chen GD, Peng Z, Zhao HB

Connexin 26 (Cx26) recessive heterozygous mutation carriers occur up to ~10-20% of the general population. Our previous study found that Cx26 heterozygous deletion or mutations can induce hyperacusis (hearing oversensitivity) rather than hearing loss (Liu et al., Sci Adv. 9, eadf4144, 2023, PMID: 36753545). However, it is unclear how behavior changes. In this study, the behavioral changes by Cx26 heterozygous mutation were examined.

Cx26 heterozygous deletion mice were used. Acoustic startle response (ASR) was recorded to assess animal behavioral changes. Hearing function tests were also examined by ABR and DPOAE recordings.

Consistent with our previous electrophysiological recording of hearing function, we found that ASR in Cx26 heterozygous mice demonstrated an enhanced response. The ASR and enhancement were increased as the acoustic stimulation increased. At the high stimulus intensities, the ASR in Cx26 heterozygous mice was triple-time larger than that in wildtype (WT) mice. The ASR in Cx26 heterozygous mice also showed an increase as age increased. The ASRs had no significant difference between Cx26 heterozygous mice and WT mice at 2 months old. However, the ASR in Cx26 heterozygous deletion mice was significantly increased in comparison with that in WT mice at 3 months old and afterward. Moreover, oppositely, the ASR in WT mice demonstrated a slightly decreasing as age increased. Finally, there was no significant difference in the peak time of ASR between Cx26 heterozygous mice and WT mice.

These data demonstrated that Cx26 heterozygous mutations can produce hyperacusis changes in behavior, suggesting that persons carried with Cx26 heterozygous mutations could have clinical manifestations, leading to tinnitus, noise sensitivity, learning disabilities, and other psychological abnormalities.

EARLY TRANSCRIPTIONAL GENOMIC CHANGES OF ALZHEIMER'S DISEASE IN THE AUDITORY SYSTEM

Yang Y, Liu LM, Zhai TY, Yu YD, Peng Z, Lu XL, Liang C, Chen GD, Zhao HB

Alzheimer's disease (AD) is a progressive neurodegenerative disorder and is also the most prevalent cause of dementia. Early detection and intervention are crucial for AD treatment and prevention. It has been estimated that delay of dementia even by one year can reduce 10% of dementia population. Recent epidemiological studies reveal that hearing loss is a major high-risk factor for AD and AD-related dementia (ADRD) development and progression. Our previous studies (Liu et al., 2020, PMID: 31870800; Mei et al., 2021, PMID: 34588972) also demonstrated that AD could produce early hearing functional changes (or biomarkers) prior to the occurrence of typical AD phenotypes, suggesting that hearing functional tests could serve as early biomarkers for AD/ADRD diagnosis and assessment. In this study, we continually examine AD-induced genomic changes, particularly, early genomic changes in the auditory system.

In APP/PS1 AD mice were used. The auditory cortex (AC), inferior colliculus (IC), cochlear nucleus (CN), and cochleae at 2, 3, 6, and 9 months old were collected. Bulk Poly(A) RNA Sequencing was performed. The hearing functional tests and behavioral tests were also performed.

As shown early functional changes by hearing functional tests in our previous studies, the auditory system has early significant AD-related transcriptional and genomic changes. At 2 months old, significant changes could already be found in the cochlea. Interestingly, as age increased, transcriptional and genomic changes in the cochlea and CN were quickly reduced, whereas AD-induced changes in the IC and AC in the auditory centers were significantly increased. At 9 months, at which the typical AD phenotypes just occur in the APP/PS1 AD mouse model, little significant changes were found in the CN and cochlea. However, significant changes were still found in the IC and AC. The significant difference was also found between female and male AD mice. Female mice showed more apparent changes in comparison with male AD mice at the early stage. RNA-Seq analysis also revealed that these changes mainly located at pathways involving neurodegeneration, postsynaptic density, and neurotransmitters besides amyloid- I (AI) binding. These changes were also consistent with our electrophysiological recordings and behavioral tests.

AD has early transcriptional and genomic changes in the auditory system. The apparent earliest changes appear in the cochlea. Female mice have more significant changes than male mice at the early stage. These data provide valuable information for AD intervention and prevention at the early stage.

THE DEFICIENCY OF ATP PURINERGIC P2X RECEPTORS PROMOTES ALZHEIMER'S DISEASE DEVELOPMENT AND PROGRESSION

Liu LM, Zhai TY, Peng Z, Lu XL, Zhao HB

Alzheimer's disease (AD) is a neurodegenerative disease with a progressive loss of memory and cognitive decline. Hearing is an important neural-sensory input for cognition. Previous studies demonstrated that hearing loss could accelerate AD and dementia generation. Our previous study demonstrated that ATP-purinergic P2x2 receptor mutations can exacerbate age-related hearing loss (Yan et al., 2013). In this study, we tested whether deficiency of P2X receptors can exacerbate/accelerate AD development and progression.

An AD mouse model (APP/PS1; Jackson Lab: Stock No: 004462) and P2X2 KO mice (Stock No: 004603, Jackson Laboratory) were used. APP/PS1 mice were crossed with P2x2 KO mice to generate APP/P2x2 KO double transgenic mice. Hearing function was assessed by ABR, DPOAE, and other hearing tests. Acoustic startle response (ASR) and gap-detection tests were also recorded to assess behavior changes.

Preliminary data showed that P2x2 deficiency could exacerbate hearing loss in AD mice, although P2x2 KO mice themselves had no apparent hearing loss. APP/PS1 and P2x2 KO double transgenic mice had more significant increase in ABR threshold in comparison with that in "pure" APP/PS1AD mice.

Our preliminary data suggest that deficiency of ATP-purinergic signaling function could accelerate AD development and progression. This study may also provide a clue to prevent or delay AD development and progression.

CX30 (GJB6) IS REQUIRED FOR NEURAL DEVELOPMENT AND DISTRIBUTION IN THE INNER EAR

Liu LM, Lu XL, Yang Y, Yu YD, Zhai TN, Peng Z, Liang C, Zhao HB

Cx26 and Cx30 are predominant isoforms in the cochlea. Both Cx26 mutations and Cx30 mutations can cause hearing loss. However, there are no Cx26 and Cx30 expressions in the hair cells and spiral ganglion neurons in the inner ear. Our previous studies reveal that Cx26 deficiency can cause cochlear developmental disorders. In this study, we found that Cx30 deficiency can cause spiral neuron development and distribution disorders.

Cx30 KO mice and littermate wild-type (WT) mice were used. Hearing function was tested by ABR, DPOAE, and cochlear microphonics (CM) recordings. The spiral neuron development and the ribbon synapses distribution were examined by immunofluorescent staining with confocal microscopy. Animal behavior was also examined by acoustic startle response (ASR). Gene transcriptional changes were analyzed by RNA-Seq technique.

Cx30 KO mice showed hearing loss in comparison with WT mice. In comparison with WT mice, innervations of auditory nerves with inner hair cells (IHCs) in Cx30 KO mice were significantly reduced. Ribbon synapses in Cx30 KO mice were also reduced and demonstrated a “deer-hoof-print” like distribution under IHCs. The behavioral test measured by acoustic startle response (ASR) showed that Cx30 KO mice had the similar ASR as WT mice. However, the peak-time of ASR in Cx30 KO mice had significant delay. In addition, as age increased, the responses of acoustic startle in Cx30 mice was significantly decreased in comparison with WT mice. Consistent with morphological and behavioral changes, RNA-Seq analysis revealed that Cx30 KO caused significant changes in axon and synapse formation and specialization pathways, even spiral ganglion neurons have no Cx30 expression.

These data indicate that gap junction gene Cx30 can modify cochlear neural development and distribution, even though there is no Cx30 expression in the spiral ganglion neurons. These results also reveal that connexin GJs play a critical role not only in the cochlear development but also in the neural development in the inner ear.

ATTENUATION OF NOISE INDUCED HEARING LOSS BY POTASSIUM CHANNEL BLOCKERS

Zhao HB, Liu LM, Lu XL

Noise can induce inner ear ribbon synapse degeneration leading to hidden hearing loss (HHL) and other hearing dysfunctions. Our previous study revealed that excess extracellular K+ elevation, which is a physiological consequence following noise exposure since hair cell and auditory nerve extra-activity, plays a critical role in the ribbon synapse degeneration (Zhao et al., 2021, PMID: 33398038). We also evidenced that in vitro application of K channel blockers can attenuate K+ induced ribbon synapse degeneration. In this study, we continually tested whether in vivo administration of K channel blockers can attenuate noise-induced hearing loss and cochlear synaptopathy.

Adult CBA/CaJ mice were exposed to 95-98 dB SPL white noise for 2 hr, one time. K channel blockers were administrated by intraperitoneal injection (i.p.) before or after noise exposure. Hearing function was assessed by ABR, DPOAE, and other hearing function tests. After one month of noise exposure, the cochlea was collected, and hair cell degeneration and ribbon synapse degeneration were examined by immunofluorescent staining. The ribbon synapses under inner hair cells (IHCs) and outer hair cells (OHCs) were quantified by confocal microscopy.

First, as observed in vitro study, administration of K channel blockers in vivo before noise exposure could significantly attenuate noise-induced hearing loss and ribbon synapse degeneration. Second, administration of K channel blockers after noise exposure also significantly reduced noise-induced hearing loss and cochlear synaptopathy. Finally, because ATP purinergic P2x receptors play a critical role in the recycling K+ to enter the cells in the cochlear supporting cells (Zhu and Zhao, 2010, PMID: 20806014), we further tested if the administration of agonist of P2x receptors could mitigate noise-induced hearing loss and cochlear synaptopathy.

The data demonstrated that administration of K channel blockers in vivo can attenuate noise-induced hearing loss and cochlear synaptopathy. The data further support our previously proposed concept that noise-induced K+ excitotoxicity is a major contributor for the noise-induced cochlear synaptopathy. This study also reveals that K channel blockers are potential agents for prevention and treatment of noise-induced cochlear synaptopathy and hearing loss.

YALE SURGERY RESEARCH DAY 2024

CLINICAL SCIENCE ABSTRACTS

ARTIFICIAL INTELLIGENCE-BASED MORPHO-VOLUMETRIC ANALYSIS OF PRE- AND POST-EVAR INFRARENAL ABDOMINAL AORTIC ANEURYSMS CHARACTERIZED ON COMPUTED TOMOGRAPHY ANGIOGRAPHY

Weiss D, Hager T, Aboian M, Lin M, Renninghoff D, Holler W, Fischer U, Deuschl C, Aneja S, Aboian E

Volumetric assessment of abdominal aortic aneurysms (AAA) is laborious but offers a more precise pre- and post-endovascular aortic repair (EVAR) evaluation compared to maximum aortic diameter (DMAX). This study aimed to train and validate an artificial intelligence (AI)- based network that automatically determines the sac volume of pre- and post-EVAR AAAs.

De-identified CTAs of patients, who underwent EVAR at our institution, were investigated. 80% of these images were used to train a nnU-Net model, with 20% assigned to the internal validation dataset. Ground truth volumetric segmentations were manually performed from lowest renal artery to aortic bifurcation. AI-generated sac volumes and DMAX were correlated with the determined ground truth values. External validation was performed.

The model was trained on 176 pre- and post-EVAR CTAs comprising 35,915 slices; the mean slice thickness was 0.774 millimeters. For the internal validation, the mean Dice similarity coefficient was 0.972±0.013, and mean Hausdorff distance per slice was 2.053±2.379mm. For the external validation, the mean Dice similarity coefficient was 0.959±0.042, and the mean Hausdorff distance per slice was 3.226±9.166mm, respectively. The generated volumes and DMAX showed a very strong correlation with the determined ground truth values on both internal (r=0.998, p<0.01; r=0.993, P<0.001) and external validation datasets (r=0.952, p<0.01; r=0.917, p<0.01).

Our trained network enables automated reliable volumetric analysis of both pre- and post- EVAR infrarenal AAAs. The performance of the algorithm is reproducible and institution- agnostic. Our model could be incorporated into clinical practice to aid more precise, efficient, and standardized morpho-volumetric evaluation of pre- and post-EVAR AAAs.

SPORTS PARTICIPATION & CRANIOSYNOSTOSIS: THE CRITICAL ROLE OF A SURGEON IN PATIENT COUNSELING

Parikh N, Hu K, Allam O, Ihnat J, Rancu AL, Boroumand S, Persing JA, Alperovich M

Despite the fact that previous studies regarding sports participation and craniosynostosis surgery have suggested consistent patient safety with limited post-operative complications, parental anxiety remains high. Therefore, the goal of this study was to evaluate the role of healthcare providers in guiding patients, and their families, through this intricate decision- making process.

A REDCap survey was created to assess sports involvement and parental decision-making for patients ages 6 and older. Questions primarily used 5-point Likert scales. Sport categorizations were made in accordance with the American Academy of Pediatrics. Chi- squared, linear regression, and Pearson correlation tests were used to analyze associations between the questions.

Forty-three parent responses were received. Mean ages at time of surgery and time of sports entry were 7.93 ± 4.73 months and 4.76 ± 2.14 years, respectively. 82% of patients participated in a contact sport. For parents who spoke with their primary surgeon ($p<0.01$) or another provider ($p = 0.002$), their children's surgeries had a greater influence on their decision regarding sports participation. Parents who spoke with their primary surgeon were more likely to desire additional information ($p = 0.003$) and their children started participating in sports at a younger age ($p = 0.034$). Mean comfort level with contact sports was lower than that with limited-contact ($p = 0.0001$) or non-contact ($p<0.01$) sports.

This study stresses the need for surgeons to routinely counsel patients' families post- operatively in order to promote an appropriate understanding of age at sports entry and contact-level participation.

A CRITICAL ASSESSMENT OF RACIAL AND GENDER DIVERSITY WITHIN THE PLASTIC SURGERY PIPELINE

Rivera JC, Hauc SC, Parikh N, Salib A, Zhao KL, Rodriguez J, Hu K, Ihnat J, Butler PD, Alperovich M.

The field of plastic and reconstructive surgery (PRS) remains largely homogenous despite recent focus on diversity initiatives. The purpose of this study was to examine the association between the race and/or gender of academic PRS leadership and the makeup of faculty and resident cohorts within US PRS training programs.

A cross-sectional study was performed to evaluate the race and gender of PRS department chairs/division chiefs (DCs), program directors (PDs), academic faculty, and current residents. Each surgeon's race and gender were determined from their publicly available profiles (institution, Doximity®, LinkedIn®, and social media) by two blinded, independent reviewers.

The proportion of underrepresented in medicine (URiM) faculty was higher when the DC was Black (26.7%, $p = 0.0102$) or Hispanic (42.6%, $p<0.01$) compared to when the DC was White (4.5%) or Asian (8.5%, $p = 0.2328$). Residents were more likely to come from URiM backgrounds in departments where the DC was Black (25.0%, $p = 0.016$) or Hispanic (38.4%, $p<0.01$) versus White (7.5%) or Asian (9.3%, $p = 0.5102$). A female PD was significantly associated with a higher proportion of female faculty ($p = 0.0007$).

This study demonstrates a significant association between the race and gender of PRS program leadership and the composition of faculty and residents, underscoring the critical influence of diverse leadership in academic plastic surgery.

QUANTITATIVE ASSESSMENT OF SOFT TISSUE CHANGES FOLLOWING FEMINIZATION GENIOPLASTY

Parikh N, Hu K, Allam O, Ihnat J, Rancu AL, Collar J, Persing JA, Alperovich M.

As an element of facial feminization surgery (FFS), sliding genioplasty is considered the most effective approach for aligning chin morphology with more feminine ideals. While two- dimensional imaging analysis has previously been used to quantify soft-tissue changes after genioplasty, this study presents a novel three-dimensional (3D) morphometric assessment.

Patients who underwent feminization genioplasty at a large academic medical center were enrolled. To be included, patients needed to have a complete panel of 3D imaging pre- and post-operatively. 3D photogrammetric evaluation was performed to assess nasofacial angle, nasomental angle, facial angle, facial thirds, chin projection, chin height, chin width, and chin angles. For all measurements, standard anthropometric points were placed by two observers in a blinded fashion. Soft-tissue changes were correlated with hard-tissue changes measured through computerized tomography imaging analysis.

Fourteen patients met the inclusion criteria. The mean time between the date of surgery and post-operative 3D imaging was 10.70 ± 8.93 months. Pre- to post-operatively, the mean facial angle increased by 2.07° ($p = 0.003$), chin height decreased by 1.16 mm ($p = 0.033$), right chin angle increased by 1.20° ($p = 0.031$), left chin angle increased by 1.40° ($p = 0.017$), and chin width decreased by 1.59 mm ($p = 0.034$). Soft- and hard-tissue chin projection changes were positively correlated ($r = 0.524$, $p<0.01$).

The quantification and correlation of 3D soft- and hard-tissue changes following feminization genioplasty allow for a comprehensive evaluation of post-operative outcomes and the potential need for secondary, revision surgeries.

TRENDS IN REVISION FACIAL FEMINIZATION SURGERY

Ihnat J, Parikh N, Hu K, Hauc S, Allam O, Alperovich M

Gender affirming surgery (GAS) encompasses procedures such as facial feminization (FFS), breast augmentation or mastectomy, and genital reconstruction. FFS can be staged or done all at once, depending on patient factors and surgeon preference. Patients may also choose to undergo secondary FFS should the results of the index operation not be satisfactory. The rate of unplanned secondary FFS and its contributing factors have not been explored in the literature. This study aims to elucidate trends in FFS revisions to further improve care for transgender patients.

All surgeries from a single institution from 2012 to 2023 that were associated with any one or more of 95 CPT codes related to gender affirming surgery were filtered for patients who had a diagnosis of transsexualism (F64). A total of 134 patients undergoing 280 surgeries were included in retrospective analysis.

107 patients underwent FFS, 37 of these patients underwent FFS surgery more than once, and 21 (19.6%) underwent unplanned secondary FFS. 43% of patients who underwent FFS before other GAS underwent FFS revisions, while 24% and 14% respectively of patients who underwent breast or bottom surgery first underwent FFS revisions ($p=0.0399$). Age at initial FFS surgery and time between social transition or hormone initiation and initial FFS surgery were not associated with rate of revision FFS.

These results can guide surgeons in optimizing outcomes and patient satisfaction, as well as illustrate the need for further research to explore the drivers of revision FFS.

SYSTEMATIC UNDERREPRESENTATION OF HISPANIC CRANIOFACIAL PATIENTS IN THE NATIONAL SURGICAL DATABASES

Hu K, Ihnat J, Parikh N, Kammien A, Rivera JC, Butler P, Alperovich M

This study investigates the impact of missing race/ethnicity data in craniofacial patients in the NSQIP Pediatrics database.

Cleft palate (CP), cleft lip (CL), craniosynostosis (CS), and microtia/anotia (M/A) patients were identified in NSQIP Pediatrics 2016-2020. Patients were labeled “race missing” (RM) and “ethnicity missing” (EM) if those fields were “Unknown”.

9718 CP, 8609 CL, 6827 CS, and 940 M/A patients were identified. From 2016-2020, RM patients increased from 14.5% to 27.9% in CP, 14.2% to 24.0% in CL, 14.4% to 25.1% in CS, and 22.4% to 35.6% in M/A. EM patients increased from 7.1% to 15.9% in CL, 7.6% to 21.0% in CP, 8.2% to 16.8% in CS, and 3.5% to 11.0% in M/A ($p \leq 0.01$).

RM patients were more likely Hispanic in CP (23.3% vs 14.2%), CL (28.9% vs 15.6%), CS (27.1% vs 15.0%), and M/A patients (75.3% vs 48.7%). They had longer hospitalizations in CP (1.7±1.8 vs 1.5±1.9 days), CL (1.3±4.1 vs 1.0±2.2 days), and M/A (1.5±2.1 vs 1.1±1.3 days). They were more likely to receive reoperation in M/A Disparities in race and ethnicity data quality may lead to underestimation of disparities experienced by Hispanic patients.

On multivariate regression, EM patients had longer hospitalizations than non-Hispanic patients with CP (0.24 days), CL (0.26 days), M/A (0.81 days), and CS (0.66 days, p<0.05). RM patients had longer hospitalizations by 0.3 days (p=0.01) in M/A and lower complication rates (OR=0.60, p=0.01) in CS.

Disparities in race and ethnicity data quality may lead to underestimation of disparities experienced by Hispanic patients.

QUANTIFICATION OF CHANGES IN CHIN MORPHOMETRIC PARAMETERS FOLLOWING FEMINIZATION GENIOPLASTY

Hu K, Parikh N, Ihnat J, Williams M, Almeida M, Alper D, Allam O, Alperovich M

No studies have quantified the extent of bony changes in the chin after genioplasty in the context of facial feminization surgery. This study presents a rapid and efficient method for chin segmentation using CT imaging to quantify changes to the chin after feminization genioplasty.

CT scans of 21 patients before/after feminization genioplasty were segmented in Mimics to isolate the chin. The Frankfort horizontal plane (FHP) was established as a reference plane. Two planes intersecting the mental foramina bilaterally, one coplanar and one perpendicular to the FHP, segment the chin. Surface area, volume, and vertical and horizontal chin projection were measured. Patient outcomes were evaluated using the FACE- Q and World Health Organization Quality of Life (WHOQOL) surveys.

Surface area, volume, and vertical chin projection decreased significantly after surgery ($p<0.05$). The magnitude of changes in surface area and vertical chin projection were significantly associated with their presurgical values ($p<0.01$). Patients with greater presurgical vertical projections experienced greater decreases in vertical projection after surgery, with some patients having increases in postsurgical vertical projection. Patient FACE-Q scores improved significantly on all scales, including chin, jawline, and neck satisfaction.

This chin segmentation methodology is rapid, requiring less than 5 minutes per imaging set, and is robust, with ICC ≥ 0.75 for all measurements. Finally, while the measured changes cohere with those expected in feminization genioplasty, these changes are made to achieve holistic facial harmony specific to the patient and therefore may not be uniform across all patients.

THE USE OF CHATGPT IN ASSESSING THE QUALITY OF OPERATIVE NOTES

Ihnat J, Huang T, Allam O, Hu K, Parikh N, Alperovich M

Operative notes are important for patient safety and continuity of care, as well as being important legal documents. However, learning to effectively write a comprehensive operative note can be difficult for residents in busy clinical environments where feedback is limited. In this study we utilized ChatGPT-4 to assess the quality of de-identified operative notes from a range of plastic surgery procedures.

Two reviewers ensured that each not fulfilled each of 20 criteria based on the Royal College of Surgeons' Criteria for Operative Notes. Notes were then modified to each be missing certain elements. ChatGPT and a third reviewer were each asked to grade each modified note based on the 20 criteria and these results were compared.

ChatGPT was able to quickly provide feedback that included a score for each criteria, as well as reasoning. ChatGPT took an average of 1 minute to assess each note, while the human reviewer took about 4.5 minutes. However, ChatGPT performed with an accuracy of 88% (F1=0.92), while the human reviewer achieved an accuracy of 94% overall.

While ChatGPT is a promising new tool, it failed to reach a level of accuracy that would be clinically useful for learning. However, its ability to provide immediate feedback with explanations highlights future potential, as training of the model could certainly improve the accuracy of results. As artificial intelligence becomes integrated into many areas of medicine including EMR systems, it remains important to acknowledge both the strengths and shortcomings of new AI tools.

SEX-BASED PATTERNS OF FOLLOW-UP SURVEILLANCE IN PATIENTS WITH ASCENDING THORACIC AORTIC DISEASE

Assi R.

Studies have shown delayed presentation of women with thoracic aortic aneurysm compared to men, likely contributing to a more severe course of aneurysm sequelae. Little is known about the pattern of surveillance among male and female aortic aneurysm patients, and its contribution to the disease management and course. We assorted to a large dataset of ascending aortic aneurysm patients to ascertain whether a sex-based disparity exists in the patterns of follow-up surveillance.

All echocardiography imaging done between 2017 and 2022 at a single healthcare delivery network were extracted for patients with sinus of Valsalva or ascending aorta measuring equal to or greater than 4 cm using structured database for storage of echocardiography findings. Life-long referrals and imaging including echocardiography and CT scans were acquired to assess sex-based patterns of referral and prospective follow-up imaging for the cohort.

A total of N=32,147 patients were found to have sinus of Valsalva or ascending aorta equal to or greater than 4 cm (root dilation only, N= 6,478, ascending dilation only, N=17,055, root and ascending dilation, N = 8,614). 80.9% (N=26,002, average age 73.2 years) were male and 19.1% (N=6,145, average age 76 years) were female.

Overall, 73.8% (N=23,711, 74.3% males, N= 19,319/26,002, 72.4% females, N= 4,452/6,145) of patients had an appropriate follow up imaging or cardiovascular medicine (CVM) or cardiothoracic surgery (CTS) referral in place.

Of the 81.7% (N=26,263, 81.3% males, N= 21,137/26,002, 81.3% females, N=4,995/6,145) patients who received 90,952 prospective echocardiography or CT imaging for surveillance, 46.7% (N=12,263/26,263, 46.8% males, N=9,897/21,137, 47.4% females, N=2,366/4,995) received imaging within 6-18 months of index study.

Overall, 63.3% (N=20,363, 63.9% males, N=16,619/26,002, 60.9% females, N=3,744/6,145) patients had a CVM (63%, N=20,254, 63.6% males, N= 16,538/26,002, 60.5% females, N= 3,716/6,145) or CTS (3.1%, N=1,008, 3% males, N= 789/26,002, 3.6% females, N= 219/6,145) referral in place. 26.6% (N=5,389/20,254, 26.2% males, N=4,341/16,538, 28.2% females, N=1,048/3,716) new CVM referrals were placed after index study with average time between index study and new CVM referral being 14 months. 70.2% (N=3,784/5,389, 70.4% males, N=3,054/4,341, 69.7% females, N=730/1048) of new CVM referrals were placed within 18 months of index study. 3.4% (N=682/20,254, 3.2% males, N=529/16,538, 4.1% females, N=153/ 3,716) new CTS referrals were placed after index study with average time between index study and new CTS referral being 21.4 months. 55.7% (N=380/682, 54.4% males, N=288/529, 60% females, N=92/153) new CTS referrals were placed within 18 months of index study.

While rates of follow-up imaging was comparable between men and women, women had lesser rates of CVM referral and greater rates of CTS referral compared to men overall.

PREGNANCY-ASSOCIATED THORACIC AORTIC ANEURYSM GROWTH PATTERNS AND COMPLICATIONS

Nasir A, Waldron C, Vallabhajosyula P, Assi R

Conflicting evidence exists regarding the impact of pregnancy on aortic aneurysm behavior. Here, we aim to assess the pattern of thoracic aortic size changes across pregnancy, to characterize incidence and timing of pregnancy-associated arterial complications and to analyze trends of management of high-risk pregnancies due to the presence of thoracic aortic aneurysm.

Electronic health record charts of thoracic aortic aneurysm patients with pregnancy and/or delivery at a single healthcare delivery network were reviewed. Information was collected regarding demographics, aortic size from before, during and after pregnancy period where available, arterial complications, and clinical management of pregnancy.

Twenty-seven patients with a total of 98 pregnancies (median per patient=3, IQR 2,4) were identified. At the time of the 1st index pregnancy, 7/27 mothers had no known diagnosis of thoracic aortic aneurysm despite 2 of the 7 patients known to have connective tissue disease. Rapid aortic size increase was observed in women with heritable thoracic aortic disease (HTAD) (N=14/22*). No type A aortic dissection was noted in relation to pregnancy. Pregnancy-associated arterial complications (N=3, SCAD of LAD, IMH of descending aorta, rupture of the celiac artery) as well as maternal mortality (N=1) was observed in the postpartum period, solely in women with HTAD. Of the 20 patients that carried the diagnosis of thoracic aortic aneurysm prior to or during a total of 32 pregnancies, 25% (N=5/20) had received preconception counseling, 45% (N=9/20) received advice for strict blood pressure control, 80% (N=16/20) had aortic size monitoring during pregnancy via echocardiography and MRA imaging, and only 10% (N=2/20) had a CT surgeon on standby during delivery.

Pregnancy appears to impact growth rate of aortic aneurysm, particularly in heritable thoracic aortic disease. No acute aortic events were observed during pregnancy, however risk of pregnancy-related arterial complications is higher during postpartum period. Aortic surveillance during pregnancy is variable even among patients with known thoracic aortic dilation.

COMPARATIVE ANALYSIS OF REDUCTION MAMMOPLASTY AND ONCOPLASTIC BREAST RECONSTRUCTION: EVALUATING CLINICAL, AESTHETIC, AND PATIENT-REPORTED OUTCOME

Rodriguez J, Hu K, Oh J, Butler P.

Oncoplastic breast reconstruction (OBR) effectively combines tumor removal, breast reshaping, and size reduction for successful breast conservation surgery in macromastia.1-3 This comparative analysis evaluates clinical, aesthetic, and quality of life (QoL) outcomes between bilateral breast reduction (BBR) and OBR.

This single-surgeon retrospective review identified patients who underwent either BBR or OBR from 4/2022-12/2023. BREAST-Q surveys were administered to assess QoL outcomes. Postoperative breast aesthetics were assessed on a scale of 1-5 in 6 domains. Patient characteristics and complications were also analyzed.

66 patients were identified. 44 (66.7%) underwent BBR and 22 (33.3%) underwent OBR. Patients undergoing BBR had lower ASA class (P = 0.012) and greater resection weight (820.6 %C2%B1 379.3 vs 581.7 %C2%B1 341.4 g; p<0.01). Complication rates were not significantly different between the two cohorts. Both cohorts experienced improvement in sexual well-being scores and breast satisfaction (p<0.05), but only the BBR cohort reported improvements in psychosocial and physical well-being scales (p<0.01). In all scales, OBR patients had higher preoperative BREAST-Q scores (p<0.01) and the two had similar postoperative scores, though BBR patients experienced a greater increase in postoperative scores (p<0.01). Among aesthetic domains, patients in the OBR cohort experienced lower scar (3.1 %C2%B1 1.3 vs 3.5 %C2%B1 1.2; P = 0.039) and overall ratings (3.6 %C2%B1 1 vs 3.9 %C2%B1 0.8; P = 0.025).

These results suggest OBR demonstrates a safety profile comparable to BBR. Individuals undergoing BBR exhibited a more pronounced improvement in well-being scales.

UNDERSTANDING VARIATION IN BRA CUP SIZING AMONG LEADING US MANUFACTURERS – A GUIDE FOR PATIENTS AND SURGEONS

Moscarelli J, Judge A, Rodriguez J, Alper D, Carney M, Zhao L, Evans B, Mookerjee V, Butler P.

Bra size is a commonly-used metric when patients and plastic surgeons discuss breast augmentation or reduction procedures. Variations in bra sizing between different manufacturers can affect patient-surgeon communication, expectations, and postoperative satisfaction. This study quantifies bra cup volume across a range of alphanumeric sizes and manufacturers in order to describe the variance and improve preoperative communication and shared decision-making.

Bras sized 36A-DD from seven popular manufacturers were fit to a flat-chested mannequin and filled using custom breast sizers. The sizers were filled to fit each bra, and then weighed and mathematically converted to volume. Kruskal-Wallis tests with post-hoc Dunn's test were performed to assess differences in cup volume.

Cup volume varied significantly between manufacturers at all sizes, with larger cup sizes showing greater variance. The standard deviation in mean cup volume (cc), across all manufacturers, was A: 30.9, B: 40.1, C: 62.2, D: 69.7, and DD: 122.8. Wacoal was significantly larger than both Hanes and Calvin Klein at sizes 36C ($p<0.05$ & $p<0.01$) and 36D ($p<0.05$), and was significantly larger than Calvin Klein at 36DD (P<0.005). Soma was significantly larger than Victoria's Secret at size 36A ($p<0.05$) and Victoria's Secret was significantly larger than Calvin Klein at 36B ($p<0.05$).

This study outlines bra size discrepancies among manufacturers, serving as a reference for surgeons and patients. Converting alphanumeric sizing to volume across different manufacturers enhances communication accuracy and increases patient satisfaction.

UNNECESSARY SCANS LEAD TO UNNECESSARY RE-SCANS: EVALUATING PECARN ADHERENCE AT A TERTIARY CARE HOSPITAL AND AFFILIATED CENTERS

Rivero R, Curran I, Hellman Z, Carroll M, Solomon D, Christison-Lagay ER

The Pediatric Emergency Care Applied Research Network (PECARN) guidelines provide a clinical assessment based algorithm to select patients with mild head trauma at highest risk for clinically important brain injury (ciTBI) in whom CT would facilitate management. Failure to follow PECARN criteria exposes children to unnecessary radiation and contributes to increasing hospital costs, lengths of stay, and parental anxiety. We sought to evaluate compliance with PECARN criteria at initial imaging and downstream effects of non- compliance.

Retrospective review of children ≤16 years old with head injury (GCS ≥14) between 2016-2021. Children with neurological deficits, penetrating head trauma, anticoagulation, or non- accidental trauma were excluded. Demographics, CT/MRI results, PECARN risk category, and need for neurosurgical intervention were collected.

There were 73 low-risk, 319 intermediate-risk, and 73 high-risk children by PECARN criteria. Of the low-risk patients, 57 (77%) underwent CT scan among whom 14 (25%) had intracranial injury. Almost all intermediate-risk group underwent CT scan, in whom 108 (35%) had a radiographic finding, one patient required neurosurgical intervention. Imaging was repeated in 100% of low-risk and intermediate-risk patients with CT demonstrating intracranial injury, without clinically significant progression or change in management. No patients who were managed without cross-sectional imaging experienced an adverse event.

Despite PECARN guidelines, cross-sectional imaging remains overused. Identification of small foci of clinically non-actionable intracranial bleeding in patients who do not meet initial PECARN criteria frequently prompts further cross-sectional imaging without benefit. This suggests that routine interval imaging may not be necessary in the neurologically stable child with low-risk injury.

DOES CENTRALIZING THE CARE OF BILIARY ATRESIA TO HIGH-VOLUME CENTERS IMPROVE OUTCOMES? A SYSTEMATIC REVIEW AND META-ANALYSIS

Curran IL, Mane S, Cowles RA

Hospitals with higher case volumes generally report better outcomes for patients with biliary atresia, so some countries have centralized the care of biliary atresia to a few highly experienced hospitals. This has generally improved outcomes, but results have varied. This study aimed to evaluate the impact of centralization across several countries, and to discuss if this should be reproduced in the United States.

A systematic review and meta-analysis of outcomes before and after centralization in four countries were conducted following PRISMA guidelines. Primary outcomes included survival, native liver survival, clearance of jaundice, and liver transplant.

Twelve studies were included (n = 2,407). After centralization, fewer patients died without intervention (3% to 1%, X2 = 9.5, p = 0.002). Outcomes after portoenterostomy improved: post-operative deaths decreased from 14% to 7% (X2 = 33.9, p = 5.8x10-9), need for secondary liver transplant decreased from 56% to 51% (X2 = 4.8, p = 0.028), clearance of jaundice increased from 39% to 45% (X2 = 5.8, p = 0.016), and native liver survival increased from 45% to 56% (X2 = 28.0, p = 1.2x10-7). Overall survival improved from 80% to 92% (X2 = 69.3, p = 2.2x10-16).

Centralizing the treatment of biliary atresia to higher-volume hospitals (≥3 cases/year) improved nearly all outcomes, including native liver survival and overall survival. These findings highlight the benefit of centralizing patients with biliary atresia to hospitals with more experience, which should be considered in the United States.

NATIONWIDE TRENDS AND OUTCOMES IN THE USAGE OF ADJUNCTS FOR SPINAL CORD PROTECTION IN PATIENTS UNDERGOING OPEN SURGERY FOR THE DESCENDING THORACIC AND THORACO-ABDOMINAL AORTA: ANALYSIS OF THE SOCIETY OF THORACIC SURGEONS ADULT CARDIAC SURGERY DATABASE

Amabile A, Del Vecchio A, Basciano A, Antonios J, Bonnell LN, Kaneko T, Habib R, Di Luozzo G

Spinal cord injury is a devastating complication of open repair of descending thoracic and thoracoabdominal aortic aneurysms (DT/TAAA). We used the Society of Thoracic Surgeons Adult Cardiac Surgery Database (STS-ACSD) to describe nationwide trends and assess outcomes in the usage of adjuncts for spinal cord protection (SCP).

Open repair of DT/TAAA cases were identified from the STS-ACSD between July 2017 and December 2022. The paralysis analysis excluded cases that expired in the operating room. The mortality analysis excluded records with missing 30-day status. Exposure variables included neuroprotective adjuncts (i.e. pre/post–aortic procedure spinal drain (SD), moderate/deep hypothermia, intercostal arteries reimplantation) and neuromonitoring measures (i.e., electroencephalography, somatosensory, and motor evoked potentials). Primary outcomes included lower extremity paralysis 24 hours, composite lower extremity paralysis and/or paresis, and operative mortality within 30 days of surgery. Association of exposure variables and outcomes were assessed via multivariable logistic regression.

A total of 2,535 unique patients with DT/TAAA underwent open repair (N=2,489 paralysis analysis; N=2,441 mortality analysis) from 225 STS-ACSD participating hospitals, with 76% performing 10 procedures. Trends in the use of adjuncts for SCP were stable through time and demonstrated low adoption rate of all neuromonitoring/neuroprotective adjuncts but SD (adopted in 64.0–74.0% patients). In the paralysis analysis, 147/2,489 patients (5.9%) developed lower extremity paralysis 24 hours and 221/2,489 patients (8.9%) developed paralysis and/or paresis. The overall operative mortality rate was 12.6% in the mortality cohort (307/2,441). The rate of operative mortality was doubled in patients who developed lower extremity paralysis >24 hours compared to those who did not (25.2 vs. 11.8%). In multivariable regression, age, diabetes, emergent and salvage status, Crawford extent II and III, and cerebral perfusion time were all significant predictors of lower extremity paralysis and/or paresis 24 hours (p=0.05). Interestingly, the usage of spinal drain was also a significant predictor (odds ratio [OR]=2.35, p=0.03). Conversely, intercostal arteries reimplantation (OR=0.52, p=0.02) and moderate/deep hypothermia (OR=0.48, p=0.01) were significant protective factors.

Acceptable neurologic outcomes can be achieved despite low volume at centers. Adjuncts for SCP appear stable over time, with spinal drain being the most adopted. Operative mortality rates are doubled in patients developing spinal cord injury. Intercostal arteries reimplantation and moderate/deep hypothermia can mitigate development of neurologic complications.

UNDERSTANDING UTILITY AND MINIMIZING MISPERCEPTIONS: SOLUTIONS TO EVALUATING SURGICAL TEACHERS

Flom E, Coppersmith N, Lui F, Cheung M, Brown, L, Rosenkranz K, Reddingon H, Caffee J, Britt R, Clark J, Bahna H, Guido J, Hope W, Relles D, Meier A, Duffy A

Faculty evaluations promote teaching improvement and professional development; however programs struggle to obtain meaningful evaluations. This multi-institutional study elucidates resident barriers while formulating solutions to better provide useful feedback to surgical teachers.

In this mixed-method, multi-institutional study, Program Directors from each institution were contacted for recruitment and distribution of the survey to their residents. Basic descriptive statistical analyses were completed, and a textual analysis was performed for qualitative components.

Solutions to each barrier were identified:

1. Process: Evaluations should be completed after each rotation during protected time, take less than 15 minutes to evaluate 2-3 attendings and given to attendings biannually to maintain confidentiality while incorporating change.
2. Utility: Specify how evaluations will be reviewed and used for personal teaching improvement (employing specific teaching goals curated by PGY level) while also clarifying how evaluations are used within the division for promotion or professional development.
3. Standing: Residents encouraged methods that promoted effective evaluations or better explained evaluation components, either through experience or milestone-based
4. Perceived Consequences: Programs could utilize a third party to further de-identify evaluations to ensure confidentiality while simultaneously adding more frequent informal, bidirectional feedback sessions could encourage constructive feedback and a culture of non-punitive feedback.

The current system does not promote teaching and professional improvement. Future efforts should include better allocating time and maintaining confidentiality while increasing transparency on the evaluation process with non-punitive review of evaluations to overcome the identified barriers and improve success in surgical education.

LIPID PROFILES IN PATIENTS WITH DESCENDING AORTIC ANEURYSMS

Gokey N, Kalyanasundaram A, Weininger G, Zafar M, Elefteriades JA

We previously reported that, paradoxically, patients with ascending thoracic aortic aneurysms (ATAA) are largely spared from atherosclerosis. They have lower coronary and total body calcium scores, lower intimal medial thickness (IMT), and almost complete protection from myocardial infarction. Additionally, ATAA patients have low LDL levels. We have not explored these relationships in descending aortic aneurysm (DescAA) patients. In this report, we focus on lipid profiles in those patients in this report.

We identified 298 patients with DescAA (≥ 4 cm) imaged between 2013 and 2020. Information was collected on lipid profiles (LDLs, HDLs, Triglycerides, and Total Cholesterol) and C-reactive protein (CRP). We compared lipid profiles with a non-aneurysm population (National Health and Nutrition Examination Survey) propensity matched for age, gender, hypertension, BMI, smoking status, statin use, and diabetes. We calculated the odds of aneurysm at different lipid values. Patients with concurrent ATAA and/or Marfan's syndrome were excluded. The absolute standardized mean difference between all covariates for the two groups was ≤12%, indicating adequate matching.

A restricted cubic spline model revealed an inverse relationship between LDL, HDL, and Total Cholesterol levels and odds of DescAA. Lower LDL (75 mg/dL - OR 1.56; 95% CI 1.03–2.35), HDL (40 mg/dL - OR 2.86; 95% CI 1.78-4.59), and total cholesterol levels (100 mg/dL - OR 6.81; 95% CI 3.35-13.82) were associated with higher odds of DescAA compared with NHANES controls. A sigmoidal relationship between Triglyceride levels and odds of DescAA was observed (100 mg/dL - OR 1.29; 95% CI 0.86-1.95, 200 mg/dL - 2.25; 95% C 1.45-3.49 and 300 mg/dL - 1.82; 95% CI 1.08-3.05). A positive relationship was demonstrated between CRP and Cholesterol:HDL ratio, finding increased odds of DescAA with higher CRP (75 mg/L - OR 56.63; 95% CI 21.03-152.54) and Cholesterol:HDL ratio (6 - OR 2.00; 95% CI 1.15-3.45).

LDL and total cholesterol are known to contribute to the development of atherosclerosis, however our results show that elevated serum LDL and total cholesterol decrease the odds of DescAAs. This is a powerful but counterintuitive finding. This novel data on lipid profile levels provides a new piece of the puzzle in understanding the relationship between DescAA and atherosclerosis. Mechanisms of this relationship remain to be investigated.

NOVEL AORTIC ROOT MEASUREMENT TECHNIQUE MORE EFFECTIVELY IDENTIFIES PATIENTS AT RISK FOR TYPE A DISSECTION

Kalyanasundaram A, Zafar M, Ellauzi H, Ziganshin BA, Elefteriades JA

Per Laplace's law, aortic wall stress is directly proportional to luminal diameter. However, determining the aortic root "diameter" is challenging due to its cloverleaf shape. Commonly used measurements (sinus-to-commissure) underestimate wall tension and dissection risk. We investigate the utility of a new, biomechanically optimized measuring technique1 in potentially preventing aortic dissections.

The electronic health records of a large hospital were reviewed to identify patients with a type A aortic dissection (2003-2020) who had at least one pre-dissection chest CT scan. From these scans, the "Laplace root diameter" was measured with our new technique:

1. Viewing plane is rotated in the axial, sagittal, and coronal axes to make it exactly perpendicular to the long axis of the aorta at the level of the aortic root.
2. Lines are then drawn connecting the midpoint of each sinus to the directly opposite commissure.
3. A measurement is taken from the intersection point of these 3 lines ("center") to the midpoint of the furthest sinus ("Laplace radius" --Fig.1).
4. This is doubled to get the Laplace diameter. Among 212 ascending aortic dissections, 33 patients had pre-dissection CT scans. 14 scans were of sufficient quality to take this measurement.

The mean root diameter using standard techniques (sinus-to-commissure) was 42.8mm, while the mean Laplace root diameter was 49.7mm (16.1% increase).

Under the old surgical guideline for ascending aortic aneurysms of 55mm (applicable at the time of the patients' pre-dissection scans), none of the patients would have qualified for surgery if standard measurements were used. However, 3 patients would have qualified for surgery based on a Laplace root diameter ;55mm, meaning 3/14 dissections (21.4%) could have been prevented by an operation.

Under the new surgical guideline of 50mm, 2 patients would have qualified for surgery using standard measurements on the aortic root, and likewise for the ascending aorta only. 4 would have qualified if the largest diameter in either the root or ascending portions were considered. However, 9 patients would have qualified if Laplace root measurements were taken, representing an increase of 125% (5 more dissections prevented; Fig. 1).

Our recently published root measurement technique is here validated clinically, utilizing pre-dissection CT scans of a retrospective patient cohort. More patients qualify for surgery using Laplace measurements. Thus, their dissections could have been prevented. We encourage consideration of this novel technique (based on bioengineering analysis) to enhance surgical decision making.

ASCENDING INTRAMURAL HEMATOMA (IMH) -- DOES IT REALLY OCCLUDE ARCH BRANCH VESSELS?

Elefteriades J, Kalyanasundaram A, Zafar M.

The 2022 AATS Aortic Guidelines indicate that for ascending aortic intramural hematoma (IMH) branch vessel involvement is an appropriate indication for surgical intervention. Not recalling branch vessel involvement by this entity, we investigated its true prevalence.

We reviewed scans of 3055 patients in our aortic database to identify patients with ascending IMH. IMH was defined as concentric intramural hemorrhage without dissection flap or ulceration. We excluded patients with penetrating aortic ulcers (PAU) in addition to the ascending IMH. Of 628 patients with acute aortic syndromes, 22 patients with ascending IMH were identified. 19 patients with available scans meeting these criteria were identified. Their CT/MRI scans were reviewed in detail by a multi-member team with experience in interpreting such images. On contrast and non-contrast CT scans, IMH was identified as a hyper dense circular zone forming a rim around the main aortic lumen, and without a dissection flap appearing across the aortic lumen. The scans were reviewed to determine the frequency and degree of arch branch vessel occlusion.

Among the 19 patients, there were 10 females and 9 males aged 50-84 (mean age 70.3, median 71.5). The maximum ascending aortic diameter at presentation ranged from 42.7 to 59.6mm, with a mean of 50.6mm. All patients were treated with anti-impulse therapy (beta blocker and after load reduction) in an ICU setting. The IMH was limited to the ascending aorta in 5 cases and extended to the descending aorta in 14. 13 patients required surgery during the initial hospitalization, and the remainder were treated solely medically. Of those who were operated, 12 (92.3%) survived hospitalization and 1 (7.7%) died within 1 month post-operatively. Patient follow-up was 100% complete (0.1 to 22.3 years, mean 7.0). 11 patients died during follow-up. It was confirmed that 0 patients died directly of rupture. Of the IMHs in the discharged patients, 3 resolved spontaneously within 1.5-4 months and 0 progressed to typical aortic dissection. 0 of the total 19 patients manifested involvement of the great vessels, including innominate, left carotid, left subclavian. For all observed cases, blood flow to the great vessels was unimpaired.

Branch vessel involvement from ascending IMH seems a rare phenomenon. If experience from other institutions is found to be similar, the surgical stipulation in the Guidelines may not be necessary.

AORTIC WALL LAMELLAR STRUCTURE IN PHYLOGENY AND IN HUMANS

Kargin N, Ziganshin B, Zafar M, Grewal N, Elefteriades J

Despite a voluminous literature on the aorta in health and disease, relatively little has been written about the lamellar architecture constituting the aortic wall. In this study, we provide a histological overview of the lamellar organization of the developing aorta in individuals with a tricuspid aortic valve (TAV). We further have undertaken literature review to elucidate (1) the number of aortic wall lamellae in various animals, as well (2) in (adult) humans, the number of aortic lamellar layers, and the decrement in lamellar layers in proceeding distally along the course of the aorta.

Non-dilated (n=60) ascending aortic wall samples were collected (embryonic–70 years of age), categorized in eight age groups. On PubMed we queried the following search terms: “aortic lamellar layers”, “lamellar layers in ascending aorta”, “lamellar layers in descending aorta”, “extracellular matrix”, “elastin”, “vascular smooth muscle cells”. This yielded 287 articles pertinent to our quest, which were reviewed in detail. Only five of these articles contained estimations of lamellar counts.

Our study demonstrated that in the premature aorta, the medial layer consists of neatly organized elastic lamellae without pathological features such as elastic fiber thinning, fragmentation, or degeneration, whereas in the adult aorta progressive elastic fiber pathology is seen resulting in decreased aortic wall strength. A significant difference in the number of lamellae is further seen between the various age categories (figure 1). The neonate group contains the lowest number of lamellae, which increases significantly till the age of 6 years ($p = 0.01$). In adolescence a slight decrease in the number of lamellae is observed ($p = 0.049$), and a further decrease is seen in the adult group ($p=0.018$) (figure 1). Our literature review revealed: (A) Animals The number of lamellar units in mammals is closely proportional to the aortic radius, which itself is proportional to the animal body size: The smaller the mammal, the fewer the lamellar layers. (B) Humans The first published studies in humans estimated a thickness of 53 to 78 lamellar layers in the ascending thoracic segment of the aorta. Additional studies reported thoracic aortic lamellar counts ranging from 45 to 56. For the abdominal aorta, recent studies have disclosed about 28 layers. Thus, the lamellar count decreases as one descends the human aorta.

Dedicated studies on lamellar number in phylogeny is scant. Dedicated studies on number and progression of aortic lamellar layers with aging are also scant. Nonetheless, our study on the lamellar architecture in human aortic tissue and literature review supports the following conclusions: (1) In phylogeny, number of aortic layers increases proportionately with animal body size. (2) In human children, the number of lamellae increases progressively until age 6. (3) Adult human aortas carry approximately 50 to 75 lamellar layers. (4) In humans, lamellar layers decrease slowly but progressively from adulthood to old age, which in combination with progressive lamellar pathology likely contributes to the enhanced adverse event rate in the elderly.

DISPELLING FEARS: BLOOD TRANSFUSION EFFECT ON SURVIVAL IN ASCENDING AORTIC SURGERY

Ellauzi H, Melendez M, Fordyce K, Zafar M, Kalyanasundaram A, Velasquez C, Kumari V, Babcock M, Ziganshin B, Elefteriades J

Amidst prevailing concerns that perioperative blood transfusions elevate morbidity and mortality in cardiac surgery, leading to a tendency to permit lower hematocrit levels, our objective was to investigate the influence of blood transfusion on survival outcomes among patients undergoing ascending aortic surgery.

We analyzed 1,190 patients who underwent proximal aortic surgery, with or without arch involvement, from 2004 to 2020 by a single surgeon, identifying 482 (40.5%) who received perioperative transfusions. Through propensity matching and Cox regression analysis, we assessed transfusions' impact on survival, incorporating Kaplan-Meier and Cox proportional hazards analyses to identify significant survival predictors in both original and matched cohorts.

Initial Kaplan-Meier analysis showed a significant survival difference between Transfused and Non-transfused patients ($p=0.0003$). All baseline characteristics were well matched, with a standardized mean difference $p<0.01$. After matching for baseline characteristics, with 360 patients in each group, this difference disappeared ($p=0.47$). Survival rates at 1, 5, and 10 years showed no significant differences. Univariate and multivariate analyses confirmed no significant variance in 30-day mortality (p-values: 0.8, 0.15). Cox analysis indicated transfusion status did not significantly affect survival ($p=0.17$). Significant survival factors included age, gender, chronic type B dissection, smoking, family history, emergent surgery, and stage I Elephant Trunk procedure. High volume transfusion (5 units) and subgroup analysis for patients with low pre-operative hematocrit revealed no significant impact on survival ($p=0.22$ and $p=0.24$, respectively).

Our findings indicate that the fear of negative effects from blood transfusion should not deter surgeons from maintaining appropriate hematocrit levels to ensure optimal patient outcomes in proximal aortic surgery.

SEX-BASED DIFFERENCES IN THE DISTRIBUTION OF ASCENDING AORTIC DIAMETERS AT THE TIME OF TYPE A DISSECTION

Waldron C, Zafar MA, Perez Z, Elefteriades JA

Acute type A aortic dissection (TAAD) is a catastrophic disorder associated with a high mortality rate. Current guidelines recommend a threshold diameter of 5.0-5.5 cm for surgery, irrespective of sex. Although men are more affected than women, the distribution of aortic diameters at the time of TAAD stratified by sex remains unknown.

Maximal ascending aortic size at the time of naturally occurring acute flap-type TAAD was measured in 258 patients with still-available radiographic images of sufficient quality to permit size measurement presenting between 1990-2023. Demographic and comorbidity data were extracted from electronic medical records. Aortic size was re-measured from CT or MRI images in a standardized method. We compared the ascending aortic diameter at time of dissection between male and female patients. Aortic diameters were indexed to height, and histograms were constructed to display the raw and indexed aortic size at time of dissection.

Among 258 patients with measurable TAAD (median age 63 years [IQR 53, 73]; 33% (N=86) female), the average maximal ascending aortic diameter was 5.05 cm [4.6, 5.6]. Men were taller (178 cm vs 163 cm, p=0.001), had a higher BMI (28 kg/m2 vs. 26 kg/m2, p=0.005), and had lower rates of COPD than women (9.9% (N=15/172) vs. 20% (N=15/86), 0.04). Other comorbidities were comparable. Women had a smaller ascending aortic diameter (4.95 vs. 5.10 cm, p=0.014) and presented at an older age than men (69 vs. 60, p<0.001). Among women, a larger proportion of aortic diameters were below 5.5 cm (77% (N=66/86) vs. 66% (N=114/172), p=0.084) and 5.0 cm (51% (N=44/86) vs. 37% (N=63/172), p=0.025) compared to men. After normalizing the ascending aortic diameter to the patient's height, the difference in ascending aortic diameter between women and men diminished (3.03 cm/m vs. 2.87 cm/m, p=0.079, respectively).

Although overall aortic diameter at the time of TAAD is consistent with updated guideline recommendations for prophylactic surgery, more than half of female patients dissected below 5.0 cm. An earlier intervention criterion below 5.0 cm may prove to be appropriate for women. Indexing aortic diameter to patient height reduces the size disparity and risk for women, endorsing the use of aortic diameter indexing when determining patient risk for TAAD. Female patients were almost a decade older at presentation; the pathophysiologic reasons for this age difference remain to be clarified.

LIPID PROFILES UNDERLIE PROTECTION FROM ATHEROSCLEROSIS SEEN IN PATIENTS WITH ASCENDING THORACIC AORTIC ANEURYSMS

Weininger G, Kalyanasundaram A, Gokey N, Waldron C, Zafar MA, Elefteriades JA

Multiple indicators such as low coronary artery calcium score, low carotid intimal-medial thickness, and low myocardial infarction rate suggest that ascending thoracic aortic aneurysms (ATAAs) are protective against systemic atherosclerosis. Our aim was to investigate whether ATAA patient lipid levels help explain this anti-atherogenic phenomenon.

We conducted two large case-control studies. Firstly, we compared lipoprotein levels between 532 matched pairs of isolated ATAA patients and controls who were propensity- score matched on age, sex, smoking, statin prescription, diabetes, hypertension, and BMI. In a second case-control study, we compared lipoprotein levels between propensity-score matched ATAA and abdominal aortic aneurysm (AAA) patients.

A restricted cubic spline model revealed that lower LDL levels were associated with higher odds of ATAA compared to NHANES controls (OR: 1.7; 95% CI 1.3 – 2.4) and higher LDL levels were associated with lower odds of ATAA (OR: 0.5; 95% CI 0.4-0.6). A similar inverse relationship was seen between total cholesterol and odds of ATAA. In the second comparison, higher HDL levels were associated with higher odds of ATAA compared to AAA (OR: 2.0; 95% CI 1.1 - 3.4). Triglyceride levels and cholesterol-to-HDL ratios were also inversely associated with odds of ATAA compared to AAA.

The existence of ATAAs is associated with lower LDL and total cholesterol compared to controls and higher HDL compared to AAA patients. Lipoprotein levels may help explain the protection of ATAA patients from atherosclerosis. Further exploration of this relationship may provide insights into the pathophysiology of both ATAA and atherosclerosis.

EVIDENCE ACCUMULATES: PATIENTS WITH ASCENDING ANEURYSMS ARE STRONGLY PROTECTED FROM ATHEROSCLEROTIC DISEASE

Waldron C, Zafar MA, Ziganshin BA, Weininger G, Grewal N, Elefteriades JA.

Ascending thoracic aortic aneurysms (ATAAs) may be fatal upon rupture or dissection and remain a leading cause of death in the developed world. Understanding the pathophysiology of the development of ATAAs may help reduce the morbidity and mortality of this disease. Here, we will discuss our current understanding of the protective relationship between ATAAs and the development of atherosclerosis, including decreased carotid intima–media thickness, low-density lipoprotein levels, coronary and aortic calcification, and incidence of myocardial infarction. We also propose several possible mechanisms driving this relationship, including matrix metalloproteinase proteins and transforming growth factor-β.

Extensive literature review was conducted to investigate the association of ATAAs with atherosclerosis along the spectrum of disease presentation from the earliest detection via carotid intima-media thickness to low-density lipoprotein levels, total body calcium scores, and ultimately myocardial infarctions. Addition literature review was conducted to investigate the understand proposed mechanisms of this protective relationship between ATAAs and atherosclerosis. Each reference was reviewed by at least two authors.

Having operated on thousands of ATAAs, our team noticed that ATAA patients have soft, supple femoral arteries and ascending aortas free from atherosclerosis, calcification, and thrombus. Subsequent clinical studies by our team demonstrated that ATAA patients had lower carotid intima-media thickness and total body calcium scores compared to controls, inversely correlated low-density lipoprotein levels, and near-total protection from myocardial infarction. Recent histologic evidence also suggests a dearth of atherosclerosis in ATAA patients. Several potential molecular mechanisms behind the observed pro-aneurysmal and anti-atherosclerotic effects of ascending thoracic aneurysms were proposed in the literature. These include 1) impaired phenotypical switching of vascular smooth muscle cells (VSMCs) from a contractile to a synthetic phenotype which contributes to intimal thickening, foam cell creation, and fibrous cap formation, 2) dysregulation of matrix metalloproteinases (MMPs), and 3) elevated transforming growth factor-β levels (TGF-β).

As we see, a thorough body of evidence suggests that the underlying mechanisms of ATAAs protect against atherosclerosis, with potential mechanisms including impaired VSMC phenotypic switching and changes in the expression and levels of MMPs and TGF-β. These studies showing anti-atherosclerotic protection span carotid, coronary, and aortic imaging, as well as aortic histology and lipid homeostasis. These sources contribute a vast amount of supportive data manifesting and confirming the anti-atherosclerotic effects of ATAAs. We speculate the dedifferentiated VSMCs and MMP and TGF-β pathways may be involved, but the true anti-atherogenic mechanisms in the ATAA setting remain to be clarified. Elucidation of these mechanisms may well add to our fundamental understanding of atherosclerosis, as well as lead to potential novel therapies for both ascending aortic aneurysm disease and even atherosclerosis itself. If we could therapeutically stimulate whatever pathways produce dramatic anti-atherogenic protection in ATAA patients, it is conceivable that this could beneficially impact the scourge of atherosclerotic disease on the human population.

EVALUATION OF RADIOGRAPHIC PREDICTORS OF ADVERSE OUTCOMES IN MEDICALLY MANAGED ACUTE TYPE B AORTIC DISSECTION PATIENTS

Khattak MA, Zafar MA, Kalyanasundaram A, Ellauzi H, Perez ZG, Ziganshin B, Elefteriades JA

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 within patients with medically managed, initially uncomplicated acute type B aortic dissections (devoid of rupture, ischemia, expansion).

81 uncomplicated acute type B dissection patients presenting to our institution for medical management between 1994 and 2021 with a contrast enhanced CT scan on file were analyzed. Radiographic features at presentation analyzed included: maximal descending aortic and true and false lumen diameters, maximal ascending aortic diameter, dissection origin location (greater vs. lesser curvature), degree of false lumen thrombosis, and branch vessel perfusion and true vs false lumen supply. 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.

The mean age at presentation was 60 years. 48 (59.3%) were males and 33 (40.7%) were females. The 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 and 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%.

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 within patients with medically managed, initially uncomplicated acute type B aortic dissections (devoid of rupture, ischemia, expansion).

EXPLORING CONVOLUTIONAL NEURAL NETWORKS FOR FACIAL-IMAGE-BASED DIAGNOSIS OF MARFAN SYNDROME

Saksenberg D, Mukherjee S, Zafar MA, Ziganshin B, Elefteriades JA

Marfan Syndrome (MFS), a genetic disorder impacting connective tissue, manifests in a wide array of phenotypes which can affect numerous bodily systems, especially the thoracic aorta. The syndrome often presents distinct facial features that potentially allow for diagnostic clinical recognition.

This study explores the utilization of Convolutional Neural Networks (CNN) for MFS identification through facial images, offering a novel, non-invasive, automated, and computerized diagnostic approach. The research examines the accuracy of Neural Networks in the diagnosis of Marfan Disease from ordinary on-line facial images. The model was trained on 80% of 672 facial images (490 Marfan and 182 control). The other 20% of images were used as the test set.

Overall accuracy was 98.5% (0% false positive, 2% false negative). F1 score was 97% for Marfan facies and 99% for non-Marfan facies. Area under the ROC curve was 100%.

An Artificial Intelligence (AI) program was able to distinguish Marfan from non-Marfan facial images (from ordinary on-line photographs) with an extremely high degree of accuracy. Clinical usefulness of this program is anticipated.

ASSOCIATION BETWEEN BASELINE HEMOGLOBIN A1C AND 30-DAY OUTCOMES AFTER SLEEVE GASTRECTOMY AND ROUX-EN-Y GASTRIC BYPASS

Hamid S, Graetz E, Schneider E, Gibbs K.

Metabolic and bariatric surgery (MBS) is a well-established treatment option in the management of obesity and its complications. At times, surgeons may delay MBS if the preoperative hemoglobin A1c (HbA1c) is elevated above a specified cutoff value. It remains unclear if there is a HbA1c value above which MBS is prohibitive or should be delayed.

We identified patients who underwent primary sleeve gastrectomy (SG) or Roux-en-Y gastric bypass (RYGB) from 2017 to 2021 in the Metabolic and Bariatric Surgery Accreditation and Quality Improvement Program (MBSAQIP) database who had preoperative HbA1c data recorded. Using patients with HbA1c; 5.7% as a reference group, we used logistic regression models to test the association between five HbA1c groups (5.7-6.5%, 6.5-8%, 8-9%, 9-10%, and 10%) and various 30-day postoperative outcomes available in the MBSAQIP. We covaried for age, sex, race, BMI, procedure type, functional status, ASA class, operation length, insulin-dependence, steroid use, and smoking status.

A total of 802,205 patients underwent primary SG or RYGB from 2017 to 2021. Preoperative HbA1c data was missing for 56.79% of these patients. Our final sample size, therefore, included 346,613 patients. The mean age of the sample was 44.2 years (SD=12). 62.8% of patients were White, 20.2% were Black, and 15.8% were Hispanic. The proportion of patients that were insulin-dependent significantly increased with increasing HbA1c values up until the 10% group which had a lower proportion of insulin-dependent patients compared to the 6.5-8%, 8-9%, and 9-10% groups (p=0.001). All HbA1c groups except the >8-9% group were associated with more superficial incisional surgical site infections (SSIs). All comparative elevated HbA1c groups were associated with more unplanned ICU admissions. There were no significant associations between any of the HbA1c groups and anastomotic/staple line leaks, organ space or deep incisional SSIs, sepsis, GI tract bleeding, and 30-day mortality. Unexpectedly, the 10% group had the fewest adverse postoperative events while the 9-10% group had the most.

Among SG and RYGB patients, odds of anastomotic leaks, deep incisional SSI, sepsis, and mortality were not increased in patients with elevated HbA1c values. A trend toward a positive dose response relationship between HbA1c levels and the incidence of superficial incisional SSI and unplanned ICU admissions was observed; however, it is possible that patient HbA1c levels may have influenced preoperative decision making, which might bias the findings of this study.

OUTCOMES OF SADI AND OAGB COMPARED TO RYGB FROM THE METABOLIC AND BARIATRIC SURGERY QUALITY IMPROVEMENT PROGRAM: THE NORTH AMERICAN EXPERIENCE

Chao GF, Canner J, Hamid S, Ying LD, Ghiassi S, Schwartz J, Gibbs KE

Rapid adoption of sleeve gastrectomy (SG) in the last decade aptly reflects desires of patients and surgeons for alternatives to RYGB and DS. While SG provides excellent outcomes, options addressing specific patient needs are warranted. Recently approved by ASMBS, SADI and OAGB have garnered increasing interest due to their single anastomosis technique.

Using the Metabolic and Bariatric Surgery Quality Improvement Program database, we examined laparoscopic and robotic cases from 2018-2021 to understand percentage of primary cases that are SADI and OAGB. We used coarsened exact matching for patients who underwent SADI or OAGB to patients who underwent RYGB. We examined outcomes of matched patients using logistic regression.

Of 667,979 patients that underwent bariatric-metabolic surgery, 1,326 (0.2%) underwent SADI, and 2,541 (0.4%) underwent OAGB. SADI was not identified in the database until 2020. In 2020, there were 487 SADIs compared to 839 in 2021. From 2018-2021, OAGBs went from 149 to 940. Compared with RYGB, SADI was associated with higher rates of anastomotic or staple line leak [OR:2.21 (95%CI:1.08-4.53)] and sepsis [OR:3.62 (95%CI:1.62- 8.12)]. Compared with RYGB, OAGB was associated with lower rates of gastrointestinal bleeding [OR:0.29 (95%CI: 0.12-0.71)] and bowel obstruction [OR:0.10 (95%CI: 0.02-0.39)]. Of note, there were no differences compared to RYGB for mortality.

More SADIs and OAGBs are being performed. In this early phase, OAGB was associated with lower complication rates compared to RYGB. However, there was a higher complication rates associated with SADI. Further studies are needed to better understand key drivers for outcomes.

VARIABLES IN PATIENTS UNDERGOING PARATHYROIDECTOMY FOR UREMIC HYPERPARATHYROIDISM: WHAT MAKES A DIFFERENCE?

Machado N, Haider S, Allen W, Maduka R, Ogilvie J, Gibson C

Uremic hyperparathyroidism (UH) is a serious medical condition that often develops in patients with ESRD and disproportionately affects minority ethnic groups. Though KDIGO and AAES guidelines provide a framework for patient referral, definitive guidelines remain elusive. We sought to evaluate our institutional experience of surgical referrals for UH to identify disparities that can be addressed at a systems level.

UH patients who underwent a subtotal parathyroidectomy at our institution from 2013-2022 were evaluated. Patients were stratified based on pre-operative parathyroid hormone levels (PTH = 1500 or PTH =1500 pg/mL). Demographic and insurance variables were compared between the groups. Univariate analysis was performed to assess the effect of PTH on surgical outcomes.

A total of 85 cases with recorded pre-operative parathyroid hormone levels were identified. There was a difference in age between PTH = 1500 patients (M = 54.02, SD = 14.08) and PTH =1500 (M = 47.62, SD = 15.64), (p = 0.05). There was a difference in BMI between PTH =1500 patients (M = 32.64, SD = 9.96) and PTH 1500 (M = 28.42, SD = 8.04), (p = 0.03). Patients with PTH 1500 were more likely to be Black.

Our study demonstrates disparities in time to surgical referral for UH at an established tertiary care center with a designated pipeline of transplant nephrologists and integrated bone mineral center. Black patients had higher disease severity and younger age at a time of surgery. Timely referral for all patients with uremic hyperparathyroidism needs improvement.

"PEACE OF MIND" AFTER MASTECTOMY: A SCOPING REVIEW

Hamid S, Bakkila B, Schultz K, Grimshaw A, Gunderson G, Godfrey E, Lee C, Berger E, Rosenberg S, Greenup R.

Many women eligible for breast conservation therapy (BCT) elect unilateral mastectomy (UM) with or without contralateral prophylactic mastectomy (CPM) and cite a desire for “peace of mind.” We aimed to characterize how peace of mind is defined and measured and how it relates to surgical choice.

We searched nine databases for relevant articles through October 8, 2023 and extracted data from articles meeting inclusion criteria.

Twenty studies met inclusion criteria. Most were prospective cohort studies (65%; 13/20). In the majority (72%; 13/18), Non-Hispanic White/Caucasian women comprised 80% or more of the study’s sample. Almost half used the phrase “peace of mind” in their publication (45%; 9/20) and few directly defined the construct (15%; 3/20). Instead, words representing an absence of peace of mind were common, specifically “anxiety” (85%; 17/20), “fear” (75%; 15/20), and “concern” (75%; 15/20). Most studies (90%; 18/20) measured peace of mind indirectly using questionnaires validated for anxiety, fear, worry, distress, or concern, which were administered at multiple postoperative timepoints (55%; 11/20). Most studies (95%; 18/19) reported at least one statistically significant result showing no difference in peace of mind between BCT, UM, and/or CPM at their latest time of assessment.

Peace of mind is largely framed around concepts that suggest its absence, namely anxiety, fear, and concern. Existing literature suggests that peace of mind does not differ among average-risk women undergoing BCT, UM, or CPM. Shared surgical decisions should emphasize at least comparable emotional and/or psychosocial wellbeing between CPM versus breast conservation.

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EFFECTS OF THE HEALTH INSURANCE MARKETPLACE ON GASTROINTESTINAL CANCER SURGERY OUTCOMES

Butensky S, Kerekes D, Bakkila B, Kurbatov V, Kunstman J, Billingsley K, Khan S

The Health Insurance Marketplace was initiated on October 1, 2013, as part of the Affordable Care Act (ACA) implementation. Research on ACA coverage expansion and cancer care has focused mainly on dependent coverage expansion (DCE) and Medicaid expansion. Our aim was to evaluate whether the ACA marketplace affected surgical outcomes in patients with gastrointestinal (GI) cancer and whether its impact was moderated by race.

Patients diagnosed with 12 GI cancers from 2011-2017 in the National Cancer Database were categorized into three groups: before the ACA marketplace (2011-2012, period 1), immediately after inception (2014-2015, period 2), and two years afterwards (2016-2017, period 3). Our main outcomes were focused on the oncologic standard of care, as defined by negative resection margin, adequate lymphadenectomy, and receipt of indicated adjuvant chemotherapy and/or radiotherapy.

Across the three time periods, 147,891 patient records were available to evaluate margin status and adjuvant therapy, while 121,734 patient records were available for adequate lymphadenectomy analyses. Compared to before the ACA marketplace inception, uninsured patients decreased from 2.8% in 2011-12 to 1.6% in 2016-17 ($p = 0.001$). There were fewer patients diagnosed with Stage 4 cancer after the ACA marketplace versus before (7.3% vs. 10.2%, $p = 0.001$).

On multivariate analysis, Black and Asian patients were less likely to have negative margins in period 1 as compared to period 2 (OR 0.79, [95% CI 0.69-0.91]), whereas White patients were more likely to have negative margins in period 3 as compared to period 2 (OR 1.18, [95% CI 1.11-1.126]). With regards to adequate lymphadenectomy, Asian patients were more likely to have an inadequate lymphadenectomy in period 1 as compared to period 2 (OR 1.35, [95% CI 1.14-1.60]). Hispanic patients also saw decreased inadequate lymphadenectomies, but only in period 3 (OR 0.88, [95% CI 0.78-0.99]). Both White and Black patients saw reductions in inadequacy of lymphadenectomy over time, likely related to improved quality of care.

Surgery for pancreas (OR 0.80, [95% CI, 0.67-0.97]) and peritoneal (OR 0.50, [95% CI, 0.34-0.71]) cancers were less likely to have negative margins in period 1 as compared to period 2, while anal cancer (OR 0.78, [95% CI, 0.62-0.97]) had decreased inadequate lymphadenectomy in period 3. Patients with esophagus (OR 0.63, [95% CI, 0.45-0.90]), bile duct (OR 0.77, [95% CI 0.62-0.96]), and pancreatic (OR 0.81, [95% CI, 0.67-0.97]) cancers were less likely to receive adjuvant therapy in period 1 as compared to period 2.

The ACA marketplace had an impact on cancer outcomes in GI cancer patients treated by surgery, some of which varied based on race/ethnicity. Further studies are warranted to understand why the marketplace had these effects.

IMMUNOTHERAPY INITIATION AT THE END OF LIFE IS INCREASING IN PATIENTS WITH METASTATIC CANCER IN THE US

Kerekes DM, Frey AE, Prsic EH, Tran TT, Clune JE, Sznol M, Kluger HM, Forman HP, Becher RD, Olino KL, Khan SA

While immunotherapy is being used in an expanding range of clinical scenarios, the incidence of immunotherapy initiation at the end of life (EOL) is unknown. The study aim was to describe patient characteristics, practice patterns, and risk factors concerning EOL- initiated (EOL-I) immunotherapy over time.

Patients with metastatic melanoma, non-small cell lung cancer (NSCLC), or kidney cell carcinoma (KCC) diagnosed after US Food and Drug Administration approval of immune checkpoint inhibitors for the treatment of each disease through December 2019 were identified in the National Cancer Database. Initiation of immunotherapy within one month of death was considered to be EOL-I treatment. National trends in EOL-I immunotherapy were described.

The study included 20,415 patients with melanoma, 197,331 patients with NSCLC, and 24,625 patients with KCC, of which 29.3% received immunotherapy. The percentage of patients who received EOL-I immunotherapy increased over time for all cancers. More than 1 in 14 immunotherapy treatments in 2019 were initiated within 1 month of death. Risk- adjusted patients with 3 or more organs involved in metastatic disease were 3.8-fold more likely (95% CI, 3.1-4.7; P<0.001) to die within 1 month of immunotherapy initiation than those with lymph node involvement only. Treatment at a high-volume center was associated with a 30% (OR 0.70; 0.65-0.76; P<0.001) decrease in odds of death within a month of initiating immunotherapy.

The initiation of immunotherapy at the EOL is increasing over time. Tracking EOL-I immunotherapy can offer insights into national prescribing patterns and serve as a harbinger for shifts in the clinical approach to patients with advanced cancer.

FIFTEEN-YEAR ANALYSIS OF GENDER TRENDS IN CARDIOTHORACIC SURGERY JOURNAL EDITORIAL BOARDS

Acuna Higaki AR, Papageorge M, Waldron C, Huggins L, Brinker M, Erez E, Lee ME

Gender disparities within leadership roles of academic surgery were analyzed by examining the gender trends on editorial boards of major cardiothoracic surgery journals.

Data was extracted from editorial board pages in “The Annals of Thoracic Surgery (ATS)” and “The Journal of Thoracic and Cardiovascular Surgery (JTCVS)” from January 2008 to August 2023. Editors’ names and positions (categorized as “General Member” or “Leadership”) were collected. Genderize.IO was used to classify names as male or female. Association of American Medical Colleges Physician Specialty Data Reports were used for proportion of active women in cardiothoracic surgery. Statistical analysis included Cochran- Armitage test, student’s t-test, and Chi-square or Fisher’s exact test.

Annual data included 2,296 names from JTCVS and 1,345 from ATS. Proportion of women in editorial boards increased dramatically from 2.5% (3 of 118) in 2008 to 17.8% (71 of 399) in 2023 (P=.001) compared to 3.8% (181 of 4,820) in 2007 to 8.3% (369 of 4,448) in 2021 (P=.001) in the surgery workforce. “Leadership” positions had a greater proportion of women than “General Member” (18.9%, 235 of 1,242 and 10%, 240 of 2,399). The average length of participation for men was 53.8 months, and for women was 44.5 months (P=.01). Women were internally promoted at 1.9 higher odds than men (95% CI, 1.08- 3.28; P=.05).

In the last 15 years, women’s appointment to high-impact cardiothoracic surgery journal editorial boards has increased, exceeding the overall field representation, indicating progress in diversity and insight for reducing academic gender disparities.

THE EFFECT OF BINDING MEDIAL CRURA FOOTPLATES ON THE DOMES: A CADAVERIC STUDY

Wride AM, Bourdillon AT, Lee JY, Lee YH

Medial crural footplates can be bound when footplate lateralization produces undesirable contouring of the columella base or impedes nasal respiration. We sought to determine if footplate binding widens the positioning of the medial crura and middle crura (domes) and if severing the interdomal and intercrural ligaments exacerbates these effects.

Photographs of 26 cadavers were taken at baseline after open rhinoplasty approach, after footplate binding, and after dividing the interdomal and intercrural ligaments. For each stage, the pixel distances between crura were measured using Photoshop at three points: base, midpoint, and domes. Distances were standardized by dividing the pixel width by alar width. T-testing was used to determine whether these widths varied significantly after binding and dissection.

After footplate binding, the width of the base of the medial crura decreased by an average of 0.75%. Interdomal and intercrural ligament dissection increased this distance by 16.44% ($p=0.01$). At the midpoint, the distance decreased by 1.79% after binding, but dividing the ligaments produced a 22.99% net increase ($p= 0.01$). The interdomal distance increased by 2.36% after footplate binding and reached 15.72% after dividing ($p = 0.01$).

Medial crural footplate binding decreased medial crura width at the base and midpoint and increased the width of the domes. Dividing the interdomal and intercrural ligaments increased the width at all three points. These findings demonstrate that sutures at the base of the nose can have cosmetic repercussions along the columella up to the domes, potentially affecting the nasal tip.

EVALUATING THE SAFETY OF EMPIRIC TAMSULOSIN TO PREVENT POSTOPERATIVE URINARY RETENTION IN A COLORECTAL SURGERY RECOVERY PATHWAY

Schultz KS, Butensky SD, Hickey TR, Murthy SS, Ahuja V, Perkal MF, Kunstman JW, Leeds IL

Postoperative urinary retention (POUR) is a common complication. The purpose of this study was to evaluate the safety of empiric tamsulosin in male Veterans undergoing colorectal surgery (CRS).

This was a retrospective study of male patients at a single VA Medical Center undergoing CRS. Patients were prescribed tamsulosin for three days prior to surgery (2021-2023) and compared to historical controls (2017-2022). Primary outcome was adverse events associated with tamsulosin use. Secondary outcomes included POUR, length of stay (LOS), 30-day complications, and readmissions. Groups were compared using Fisher's exact and student's t-test.

We identified 100 patients (40 pathway patients and 60 historical controls). 12 (30%) pathway patients were on BPH medications prior to surgery. Of pathway patients, 15 (37.5%) had right colectomies, 20 (50%) left colectomies, 4 (10%) proctectomies, and 1 (2.5%) ileostomy closure. There were no cases of orthostatic hypotension or tamsulosin discontinuation in the pathway patients. There was no difference between pathway patients and historical controls in LOS (6.6 vs. 7.2 days, p=0.550), readmission (5.0% vs 5.0%, p=0.580), or complications (20.0% vs. 18.3%, p=0.835). There were also no differences in POUR (5.0% vs. 11.7%, p=0.309) or urinary tract infections (5.0%% vs. 1.7%, p=0.562).

Empiric tamsulosin use is safely tolerated in male patients undergoing CRS. Given the fast- onset effects of tamsulosin and the known risk of POUR in this patient population, these data merit future studies powered to assess whether empiric tamsulosin will convey a clinically significant benefit to male Veterans.

HIGH-THROUGHPUT, SYSTEM-WIDE SOCIAL DETERMINANTS OF HEALTH SCREENING AND COMPLEX SURGERY OUTCOMES

Schultz KS, Moore MS, Mongiu AK, Pantel HJ, Reddy VB, Schneider EB, Leeds IL

Health systems are implementing bedside social determinants of health (SDOH) screening. The purpose of this study was to assess the association of SDOH domains with 30-day complications after hepatopancreatobiliary (HPB) and colorectal (CRS) surgery.

This was a retrospective study of HPB and CRS patients at a single institution from January 2022 to June 2023. SDOH data was linked with NSQIP institutional data. The primary outcome was any 30-day NSQIP-defined complication, and secondary outcomes were 30-day readmission and length of stay (LOS). Categorical variables were compared by chi-square tests and median LOS by rank-sum test.

671 patients (226 HPB, 445 CRS) met inclusion criteria. For SDOH domains, 1.0% (n=7) had medium- or high-risk housing situations, 0.7% (n=5) had unmet transportation needs, 2.5% (n=17) had food insecurity, and 2.7% (n=18) had medium or high financial strain. 4.3% (n=29) had any SDOH domain, with 30.8% (n=207) having “unknown” recorded on at least one domain. For patients with no SDOH risk, 30-day complications were 15.3% (n=98) compared to 31.0% (n=6) for patients with at least one risk factor (p=0.01). 30-day readmissions were non-significant. Median LOS was longer for patients with any SDOH risk factor compared to those with none (6 days vs. 4 days, p=0.01).

A strong correlation exists between SDOH domains and short-term outcomes after complex surgery. This study also suggests there is under detection of SDOH risk when using high throughput, low-fidelity screening given the expected proportion of these SDOH domains from prior literature using more comprehensive screening instruments.

A THOUSAND CUTS: CLINICAL AND SOCIOECONOMIC MODELING OF ANAL DYSPLASIA SCREENING

Schultz KS, Islam N, Xu Z, Pantel HJ, Mongiu AK, Reddy V, Leeds IL

Findings from randomized clinical trials suggest that screening and treating anal dysplasia in HIV-positive patients prevents anal cancer. However, the optimal approach of who to screen remains uncertain. Annual screening with reflex high resolution anoscopy (HRA) for all at-risk patients risks overburdening patients and backlogging anal dysplasia care pathways. The purpose of this study was to identify the optimal approach to anal dysplasia screening that would maximize quality-adjusted life expectancy and minimize healthcare costs.

We designed a Markov model that included a hypothetical cohort of 2000 patients, representing the average patient living with HIV in the United States, with varying degrees of anal dysplasia. We assigned patients in a 1:1: fashion to anal dysplasia screening with annual anal pap and reflexive HRA versus no screening. Regardless of screening strategy, patients were assigned a 2% annual risk of developing low-grade squamous intraepithelial lesions (LSIL) and a 2% annual risk of progressing to high grade squamous intraepithelial lesions (HSIL), if LSIL present in the prior year. Patients with HSIL who were not receiving annual screening were estimated to have a 4% annualized chance of developing anal cancer while patients who were receiving annual screening and reflex treatment were assigned a

When accounting for costs and benefits, the no-screening strategy dominated the screening for anal dysplasia strategy as it generated more quality adjusted life years (50.1 QALYs versus 49.9 QALYs) and reduced total costs of care by $24,872 per patient. When examining high-risk individuals, where most patients in the model had biospy-proven HSIL at baseline, the screening group generated more quality adjusted life years (49.0 QALYs versus 48.4 QALYs) but resulted in more than double the cost per patient compared to the no screening group ($58,147 versus $25,683; ICER = $54,107 per QALY).

Screening for anal dysplasia offers an important clinical benefit to high-risk individuals, but targeted populations for screening defined by current guidelines likely overpromote its use with increased patient harm and societal costs. More restrictive screening strategies would produce a more favorable population-wide benefit.

PREOPERATIVE PSYCHOSOCIAL RISK BURDEN AMONG PATIENTS UNDERGOING MAJOR THORACIC AND ABDOMINAL SURGERY

Park EY, Schultz KS, Mastrorilli J, Leeds IL

Risk factors such as age, diabetes, and smoking portend worse outcomes in patients undergoing surgery. Less is known about the effects of psychosocial risk factors (PSRFs). Our aim was to characterize the PSRF burden in patients undergoing major surgery by demographic groups.

A prospective psychosocial risk assessment of adult patients undergoing major elective thoracic or abdominal surgery at a single institution was conducted from July to December 2023. We used a comprehensive questionnaire, comprised of validated survey instruments for PSRFs. High psychosocial risk was defined as ≥ 2 PSRFs. Chi-squared tests and t-tests were used to analyze continuous and categorical variables, respectively.

Of 102 patients, 56 (54.9%) had anxiety, 21 (20.6%) had depression, 14 (13.7%) had addiction, 39 (38.2%) had high-risk alcohol use, 58 (56.9%) had a smoking history, 29 (28.4%) had low resilience, and 5 (4.9%) had limited resourcefulness. 61.8% of patients had high psychosocial risk. High-risk alcohol use was more prevalent in white (40.0% vs 14.3%, p=0.001) and male (41.3% vs 35.7%, p=0.01) patients. Male (p=0.01) and low socioeconomic status (SES) (p= 0.05) patients were more likely to have a history of smoking. Low resilience was most prevalent in individuals with high SES (p= 0.001).

Most patients undergoing major surgery at a tertiary academic center have multiple PSRFs that do not necessarily coincide with traditional indicators of psychosocial risk. Future studies should investigate whether comprehensive PSRF assessments better explain surgical disparities compared to traditional psychosocial markers.

INTRAOPERATIVE HYPERLACTATEMIA DURING FACIAL GENDER AFFIRMATION SURGERY

Sarathy A, Bhethanabotla RM, Mohan S, Park A, Knott PD, Seth R

While lactatemia during head and neck surgery is well-documented, the impact of such elevation on outcomes following facial gender affirmation surgery (GAS) remains unclear, causing potentially concern for anesthesiologists and surgeons. There is limited literature on trends and management of intraoperative lactate elevation during GAS.

Single institution retrospective cohort study including patients from a large academic medical center who underwent GAS between 2015 and 2023 with at least two intraoperative lactate levels. Patient demographics, procedure details, and intraoperative lactate levels were collected and plotted against surgery duration.

Of 130 patients examined, seventeen patients met inclusion criteria, all undergoing comprehensive male-to-female gender affirmation surgery. Peak lactate levels ranged 1.2-10.9 mmol/L (normal <2 mmol) and normalized either by the end of surgery or on the first postoperative day. Surgery duration was 710 minutes on average, with an average estimated blood loss of 427 mL. All patients received preoperative hormone replacement therapy with estradiol.

In this study, we summarize trends in lactate level during GAS and highlight the reassuring normalization within one day of surgery. We cautiously conclude that intraoperative lactatemia during GAS procedures may be managed expectantly in the absence of other signs of end organ dysfunction.

ASSOCIATION BETWEEN CHEMOTHERAPY INDUCED PERIPHERAL NEUROPATHY AND LOW ANTERIOR RESECTION SYNDROME

Linhares SM, MD, Schultz K, MD, Coppersmith N, MD, Pantel H, MD, FACS, Reddy V MD, PhD, Leeds Ira MD, MBA, Mongiu AK MD, PhD

Two common side effects of rectal cancer treatment include chemotherapy-induced peripheral neuropathy (CIPN) and low anterior resection syndrome (LARS). We sought to evaluate if there was an association between sensory CIPN and LARS in patients during the treatment of rectal cancer.

This was a retrospective study of patients who underwent an LAR and chemotherapy between 2017-2023. Patients were identified using the ICD10 code C20 (malignant neoplasm of the rectum) and contacted by telephone to consent and complete the questionnaire. We used the validated LARS Score to measure LARS and the European Organization for Research and Treatment of Cancer Quality of Life Questionnaire Chemotherapy-Induced Peripheral Neuropathy-20 to measure neuropathy. Major LARS was defined as a score of ≥30/42.

There were 45 out of 65 contacted patients who completed the questionnaire (69% response rate). There were 19 (42%) female patients with a mean age of 59 years (SD ± 11, range 35-82). There were 41 (91%) of patients with LARS. There was a mean LARS score of 33 (SD ± 7) and median score of 35 (IQR = 10, range 11-41). The mean sensory CIPN score was 33 (SD ± 24, range 0 – 89). The correlation between LARS score and sensory CIPN was r= 0.27 (p = 0.073).

LARS and sensory CIPN can have significant negative effects on a patient's quality of life. In this study, we found that there was a positive correlation seen between the two effects trending towards significance. Further investigation of the mechanisms underlying LARS and sensory CIPN could identify potential interventions that mitigate both effects on rectal cancer care recovery.

THIS ABSTRACT HAS BEEN WITHDRAWN

EARLY OBSERVATIONS WITH AN ERAS PATHWAY FOR THYROID AND PARATHYROID SURGERY: MOVING THE GOALPOSTS FORWARD

Machado N, Mortlock R, Maduka R, Cunha A, Dyer E, Long A, Canner J, Tanella A, Gibson C, Hyman J, Ogilvie J

Enhanced recovery after surgery pathways have become the standard of care in various surgical specialties. In this study, we discuss our initial experience with a staged enhanced recovery after surgery pathway in endocrine surgery and assess the impact of this pathway on select perioperative outcomes.

We collected information regarding all thyroid/parathyroid surgeries performed by endocrine surgeons at our institution before and after the implementation of the multi- intervention enhanced recovery after surgery pathway. We compared outcomes for all cases 1 year before (n = 479) and 1 year after (n = 166) implementation of the pathway.

Enhanced recovery after surgery was associated with a significant decrease in total length of stay (9.2 vs 7.5 hours, P = .0001). Whereas there was no significant decrease in all-cause unanticipated postoperative admissions, there was a decrease in patient-initiated admissions in the Enhanced recovery after surgery group. There was also a significant decrease in mean postoperative morphine milligram equivalents (14.4 vs 16.2 vs 24.8, P =.0015), average daily morphine milligram equivalents (25.6 vs 45.6 vs 53, P = .0001), and average daily pain scores (1.89 vs 2.38 vs 2.74, P = .0045) in the Enhanced recovery after surgery group (particularly with increasing Enhanced recovery after surgery compliance). There were no significant differences in the requirement for postoperative antiemetics or in the post-anesthesia care unit length of stay.

This study demonstrates a significant benefit from Enhanced recovery after surgery pathways for thyroidectomies and parathyroidectomies, even with initial data and a staggered roll-out plan.

SEX DIFFERENCES IN THE MANAGEMENT, INTERVENTION, AND OUTCOMES OF PATIENTS WITH SEVERE PRIMARY MITRAL REGURGITATION

Waldron C, Hundito A, Krane M, Geirsson A, Mori M

Sex-based outcome disparities in mitral valve disease exist, however the factors associated with these differences are unknown. Identifying these differences is essential in devising strategies to mitigate them. We evaluated sex-based differences among severe primary mitral regurgitation (MR) patients across treatment phases.

We conducted a retrospective cohort study of patients with new diagnoses of severe primary MR between 2016-2020. We compared multidisciplinary evaluation incidence, defined as cardiology and cardiac surgery services, and 2-year survival between male and female patients. We analyzed a subgroup meeting Class 1 indications for intervention in primary MR which includes: severe symptomatic MR or severe asymptomatic MR with EF 60% or LVESD 40 mm. Logistic regression models identified predictors associated with the likelihood of multidisciplinary evaluation.

Among 330 patients meeting Class 1 indications, female patients were older (79 vs 76, p=0.01) and had higher STS risk scores for MV repair than male patients (2.5% vs. 1.4%, p=0.003). Female patients were less likely to undergo multidisciplinary evaluation (57% vs. 84%, p=0.001) and intervention (47% vs. 69%, p=0.001) than male patients. Median days-to-intervention for female and male patients were 77 and 43, respectively. Female patients had higher 2-year mortality than male patients (31% vs. 21%, p=0.035). On multivariable model, female sex and older age were associated with lower odds of undergoing multidisciplinary evaluation (OR: 0.26, p=0.001; OR: 0.95, p=;0.001, respectively).

Female patients with severe primary MR with Class 1 indication for intervention were less likely to undergo multidisciplinary evaluation and intervention and had longer interval to intervention than male patients. Survival was comparable after accounting for age and comorbidity differences.

A NATIONWIDE ANALYSIS ON MAJOR UPPER EXTREMITY AMPUTATIONS AND REPLANTATIONS

Viola A. Stögner, MD1, Sacha C. Hauc, BS, BA*, Helia Hosseini, MS, Mica C.G. Williams, BA, Sam Boroumand, BS, Lioba Huelsboemer, MD, Martin Kauke-Navarro, MD, Bohdan Pomahac, MD, David Colen, MD*

The loss of an upper extremity is a severely disabling condition made medically challenging by the limited window for replantation. This study aims to investigate the burden of traumatic major upper extremity amputations in the US and uncover possibilities for improvements in treatment.

The Healthcare Cost and Utilization Project's National Inpatient Sample (NIS) was screened for ICD9/10 diagnosis/procedure codes for traumatic and non-traumatic major upper extremity amputations and replantations within the years 2008 – 2017. The resulting pool of cases was analyzed for multiple variables, including level of injury, patient demographics, hospital type and location, length of stay, costs, comorbidities, and complications.

A total of 15,155 major upper extremity amputations were recorded, of which 15.20% (n = 2,305) were traumatic amputations – almost half of them related to the upper arm (49.6%, p = 0.0002). The great majority of replantations, however, was conducted at the lower arm level (87.4%, p = 0.0001), with an overall replantation rate of 22.3%. Non-traumatic amputations were overall associated with significantly higher burden of comorbidities relative to traumatic amputations except for chronic alcohol use (p=0.0001). Both, amputations and replantations, were predominantly treated in large urban teaching hospitals, and were significantly more likely to occur in white males. The Southern region of the U.S was handling the highest proportion of amputations in the US but had the lowest likelihood of replantation.

This study provides an invaluable overview of the national trends in major traumatic upper extremity amputations and replantations, revealing potential health care shortcomings.

PRECLINICAL PERFORMANCE OF THE COMBINED APPLICATION OF TWO ROBOTIC SYSTEMS IN MICROSURGERY – A TWO-CENTER STUDY.

Viola A. Stögner, MD, Kai Wessel, MD, Catherine Yu, Bohdan Pomahac, MD, Tobias Hirsch, MD, Maximilian Kueckelhaus, Haripriya S. Ayyala, MD1

Microsurgery pursues perfection. The increasing relevance of (super-)microsurgical robotics could therefore represent the natural next step towards improved performance in microsurgery. Capable of downscaling movements and eliminating tremor, robotic systems bear the potential to offset manual surgical limitations. Several robotic systems, tailored to the specific needs of microsurgery are recently being introduced. Training with these devices is essential to verify their potential clinical utility. This study assesses the training and learning curve of microsurgeons with different level of experience and complete novices using a robotic surgical system in combination with an exoscope.

In a preclinical two-center approach 18 participants (6 experienced microsurgeons, 6 microsurgeons in training and 6 complete novices) performed a total of 180 anastomoses (90 manual and 90 robot-assisted anastomoses). The robotic setup included the Symani Surgical System (Medical Microinstruments, Inc.) in combination with the exoscope RoboticScope (BHS Technologies GmbH). Time for anastomosis completion as well as surgeon's satisfaction with anastomosis and setup were assessed. Video- and photo- recordings were analyzed for anastomoses' quality using the Structured Assessment of Microsurgery Skills (SAMS) and the Anastomosis Lapse Index (ALI), while the Rapid Entire Body Assessment (REBA) was used for ergonomic evaluation.

All 3 participant groups improved their microsurgical performance during training, with significant improvements in the unexperienced robotic and manual group and experienced robotic group. The use of robotic systems was associated with improved microsurgical skills among less experienced participants, while SAMS categories 'steadiness' and 'tissue handling' scored higher in all robotic groups, regardless of microsurgical experience. In total more errors were observed in the conventional group (n=410) compared to the robotic group (n=375). The number of errors decreased among all robotic groups, with a significant decline of errors in the novices group. Postural analysis displayed significantly impaired neck posture among experienced microsurgeons using the robotic systems only, while significantly improved upper extremity postures were recorded in all participant groups. The overall participant satisfaction with anastomosis and the combined robotic systems increased significantly over time.

The concept of robotic microsurgery holds great potential to improve precision and ergonomics in microsurgery. In addition, combined surgical and visual robotic systems could leverage remote microsurgery in the future. Acceptance and specialized training are crucial for successful clinical integration of microsurgical robots – both are addressed in this two- center approach, which shows that a steep learning curve can be expected upon the introduction of those systems.

DEVELOPMENT AND COMPARATIVE EVALUATION OF COMPUTER-BASED ASSESSMENT TOOLS FOR MANUAL AND ROBOTIC MICROSURGERY

Viola A. Stögner, MD, Kai J. Wessel, MD, Catherine T. Yu, BS, Sam Boroumand, BS, Mary Xie, Hannah Ji, Alex Shi3, Alex Wong, PhD, Bohdan Pomahac, MD, Tobias Hirsch, MD, Maximilian Kueckelhaus, MD, Haripriya S. Ayyala, MD

Robot-assisted microsurgery is gaining increasing clinical importance as we push the boundaries of super microsurgery. With the ability to compensate for physiological limitations in microsurgical dexterity and potential to enable remote microsurgery in the future, robotics hold great promise to revolutionize the standards of microsurgery. However, successful clinical integration and optimization will strongly depend on specific user training and evaluation. This study aimed to develop and verify automated, practical tools that enable qualitative assessment of both manual and robotic microsurgical performance.

Two deep convolutional neural network-based computer algorithms were developed to facilitate computer-assisted:

1. Tracking of microsurgical instruments
2. Evaluation of anastomosis quality

The first algorithm employed a combination of supervised and semi-supervised learning to train models to track both needle driver and forceps in recorded microsurgical videos. A trajectory was plotted based on the tracked area of interest and neighboring tracked points subsequently averaged to a smooth trajectory. Tremor-movements of both instruments at each instant in time were measured as the absolute deviation from the smooth trajectory. The second algorithm was trained to detect anastomosis stitches and tears as well as metrics of the stitches, while filtering out common nuisance variabilities, such as glares and noise, in images of the everted anastomoses. Both algorithms were used to verify 180 microvascular anastomoses (90 manual and 90 robot-assisted anastomoses) performed by participants with different levels of microsurgical experience in a two-center approach. For robot-assisted anastomoses the Symani surgical system (Medical Microinstruments Inc.) was used in combination with the RoboticScope (BHS Technologies).

Both computer algorithms were successfully developed and verified, enabling both manual and robotic microsurgical self-assessment. Both models worked efficiently without the need for any tracking sensors or markers. Application of the microsurgical instrument tracking algorithm in our study population revealed a markedly higher overall degree of tremor in manually performed compared to robot-assisted anastomoses. The algorithm for anastomosis quality assessment allowed for reliable evaluation of:

1. Estimates of the anastomosis line (accounting for any disruptions)
2. Distance between stitches (accounting for unequal distancing of sutures)
3. Angles of each stitch (accounting for oblique stitches causing distortion)
4. Visible tears in vessel wall

Microsurgical assessment is essential for microsurgical skill development, however, necessitates intensive time and personnel resources to be done effectively. Robotic microsurgery involves technology-related learning curves for surgeons of all experience levels, and thus requires time-efficient, practical, and accurate evaluation methods specific to robotic surgical paradigms. We established two completely automated algorithms for reliable skill self-assessment applicable to both conventional and robotic microsurgery. These algorithms not only make microsurgical assessment much more accessible but can substantially accelerate the process of robotic training and evaluation, ultimately promoting their integration in clinical microsurgery.

THIS ABSTRACT HAS BEEN WITHDRAWN

UNRECOGNIZED BURDEN OF TRAUMATIC INJURIES RELATED TO SOCIAL RISK FACTORS: A PATIENT LEVEL SOCIAL DETERMINANTS OF HEALTH STUDY

Mathew P, Sznol J, Ullrich S, Schuster K

Social determinants of health (SDOH) are recognized modifiers of patient outcomes in large epidemiologic studies using community level rather than patient level data to assign social risk factors (SRFs). Using patient level data, we analyzed the correlation between the SRF, traumatic injuries and outcomes.

Patient demographics, social work interview data and trauma admission data were combined for the years 2019-2020 at YNHH. The SRFs identified included housing insecurity, financial security, food vulnerability, employment, insurance, language interpreter requirement, psychiatric history, alcohol use, and education level. Correlations between the SRFs, injuries and outcomes were obtained via non-parametric ANOVA analysis and chi- square. Multivariable negative binomial and logistic regressions with backward selection were used to analyze outcomes.

904 patients had complete social work evaluations. After controlling for age, injury severity score (ISS), mechanism of injury (MOI), and SRFs, the SRF were not predictive of mortality, discharge location, in hospital falls, delirium, or pneumonia. Length of stay was associated ISS (p=0.001), graduate education (p=.039), alcohol use disorder (p=.0084), disability (p=.0122), and inversely with falls from height (p=018) or standing (p=.012) compared to motor crashes. Odds of readmission increased with financial insecurity (OR 5.60 CI[1.34- 23.38]). Insurance provider was strongly associated with MOI, including 78.25% presenting after fall from standing were on Medicare and 76.09% of assaults were on Medicaid.

Utilizing patient level SDOH data in trauma patients, SRFs did not affect outcomes in traumatic injuries, however, there were strong relationships between SRFs, readmissions and MOI. MOI may identify a patient population that would benefit from thorough screening for SRFs.

AIR QUALITY IS NOT CORRELATED WITH INCREASED RATES OF ADMISSIONS FOR EXTRACORPOREAL MEMBRANE OXYGENATION

Hellmann ZJ, Curran IL, Solomon DG

Human caused climate change has led to more and more powerful wildfires. Research has demonstrated links between poor air quality due to wildfire smoke and asthma. We utilized publicly available air quality metrics to determine whether decrements in air quality were associated with an increase in rates of extracorporeal membrane oxygenation (ECMO) cannulations for patients in status asthmaticus.

The Pediatric Health Information System database was queried for patients 1-18 years-old who underwent ECMO cannulation for a diagnosis of status asthmaticus between 2017 and 2022 at both high volume ECMO centers as well as centers in regions associated with recent wild fire plumes. Air quality data for those municipalities was then queried from the environmental protection agency (EPA).

320 patients admitted between 2017 and 2022 with a diagnosis of status asthmaticus and a surgical code for ECMO cannulation.; 65 were admitted to one of 15 pediatric hospitals within the defined metropolitan centers. Most patients were admitted between October 1st and March 31st (68%). There was no significant difference in average air quality index during the week prior to any admission for a patient who was subsequently canulated and days on which no patient was admitted for ECMO ($p = 0.35$, Figure 1). During respiratory viral season, air quality index during the week prior to an admission for ECMO for status asthmaticus were significantly lower than prior to days with no admission ($p = 0.008$). Outside of respiratory viral season, there was no difference in air quality during the week prior to an ECMO admission and days with no admission ($p = 0.49$).

There was no significant correlation between air quality index in a given week and admissions for status asthmaticus necessitating ECMO. This is likely due to the majority of patients being admitted in winter months when respiratory infections are high and airborne particulates are low, as well as the many complex factors interposed between an asthma exacerbation and the potential need for ECMO. Nevertheless, continued surveillance determining the relationship between climate change and pediatric health is paramount.

A DATA-DRIVEN APPROACH TO INGUINAL HERNIA REPAIRS IN INFANTS AND CHILDREN

Hellmann ZJ, Shaughnessy MP, Hornick MA, Cowles RA, Solomon DG

Laparoscopic inguinal hernia repair has become increasingly popular in children. Laparoscopic technique inherently assesses the contralateral processus vaginalis, reducing the risk of metachronous contralateral hernias. We hypothesized that primary laparoscopic repair would be associated with lower rates of subsequent hernia repair in the youngest patients, in whom metachronous contralateral hernias are most common.

The Pediatric Health Information System (PHIS) database was queried for patients 0 to 18 years-old, who underwent inguinal hernia repair between 2016-2022. The primary outcome was the need for subsequent hernia repair. CPT and ICD-10 procedure codes were used to determine laparoscopic versus transinguinal repair. Patients were excluded if the only recorded code was for recurrent hernia or if both laparoscopic and transinguinal codes were present for the same procedure.

109,879 patients were included in the study, with 20,636 patients (18.78%), undergoing laparoscopic inguinal hernia repair initially, and 2,546 patients (2.32%) requiring a second hernia repair. Patients 6 months old and younger undergoing unilateral laparoscopic repair were less likely to require subsequent surgery ($p= 0.001$, Figure 1). In all age groups, transinguinal bilateral repair less often required subsequent repairs ($p= 0.001$).

Laparoscopic unilateral inguinal hernia repair decreases the need for subsequent surgical repair in infants 6 months and younger. No difference was detected in older patients. Transinguinal repair of bilateral hernias decreases the need for second hernia operation in all age groups, suggesting that transinguinal repair is more durable.

WIDENING INTER-CANTHAL DISTANCE WITH ORBITAL BOX OSTEOTOMIES: A COSMETIC APPLICATION

Rodriguez J, Khetpal S, Reategui A, Lopez J, Diluna M, Steinbacher D.

Orbital repositioning procedures have been utilized in order to correct orbital hypertelorism and other orbital anomalies, such as vertical orbital dystopia and cranio-orbital lesions. Cosmetic applications of such techniques, however, have rarely been explored given its invasive nature. This study systematically reviews orbital osteotomies in craniofacial surgery and showcases the cosmetic use of orbital box osteotomies (OBO) to widen intercanthal distance in a 31-year-old male.

A systematic literature review was performed in order to survey articles that discussed applications of OBO within craniofacial surgery. A patient receiving the operation for cosmetic purposes was included as a case report. Video footage was collected. 3D-planning was utilized using computed tomogram and virtual surgical planning (VSP). Custom plates were utilized in order to achieve the desired intercanthal distance.

An initial literature review found 38 articles. Following exclusion criteria, eleven articles were analyzed. OBO were utilized in indications, including craniosynostosis, craniofacial clefts, cranio-orbital lesions, vertical orbital hyperplasia, cranium bifidum occultum, craniofrontonasal dysplasia, facial feminization surgery, and neurofibromatosis. No articles discussed cosmetic application of OBOs. Our patient successfully underwent OBO with favorable aesthetic results.

This video vignette demonstrates the use of OBO to manipulate the patient's intercanthal distance while achieving favorable aesthetic results. Future studies should explore the utility of orbital repositioning procedures for aesthetic purposes, and how adjunct procedures may be used to refine the overall facial appearance.

SINGLE INSTITUTION ANALYSIS OF GENETIC SCREENING FOR PATIENTS WITH THORACIC AORTIC ANEURYSM DISEASE- IMPLICATIONS FOR CLINICAL EFFICACY OF CURRENT ACC/ AHA GENETIC SCREENING GUIDELINES

Acuna Higaki AR, Erez E, Cupo M, Phu A, Verma S, Assi R, Vallabhajosyula P

We analyzed the clinical efficacy of the American College of Cardiology (ACC) and American Heart Association (AHA) genetic screening guidelines for thoracic aortic aneurysm (TAA) patients.

Retrospective genetic screening analysis in TAA patients from February 2020 to September 2023 at a single center with IRB approval. Genetic outcomes were evaluated by ACC/AHA guideline criteria: age under 60, connective tissue disease symptoms, or family history of arterial aneurysms/unexplained sudden death. The groups were compared to patients not meeting any criteria. Some patients met multiple criteria. Test results were classified as positive, variants of uncertain significance (VUS), or negative. Chi-squared test assessed differences, significance at p=0.05.

Of 629 patients tested, 247 (39.3%) had family history, 232 (36.9%) were under 60 years of age, 148 (23.5%) exhibited connective tissue disease features, and 202 (32.1%) did not meet any criteria. Genetic testing yielded 29 (4.6%) positive results, 174 (27.7%) VUS, and 426 (67.7%) negatives. No significant difference was observed in the frequency of positive genetic mutations, negative genetic mutations or VUS between the criteria-matched groups and the group without criteria (p=0.81). Notably, 8 out of 29 (27.6%) patients with positive results and 53 out of 174 (30.4%) patients with VUS did not meet any of the criteria.

The positive gene mutation rate in TAA patients was lower than previously reported frequency. The ACC/AHA guidelines may require finetuning to improve risk stratification. The high VUS prevalence across all patient cohorts highlights the need for a deeper understanding of VUS clinical significance.

SIX-YEAR OUTCOMES, RISK OF DEATH, AND RISK OF LUNG CANCER-RELATED MORTALITY AMONG PATIENTS FOUND TO HAVE SEMI-SOLID LUNG NODULES ON CHEST CT

Prince S, Kane E, Woodard G, Blasberg J, Dhanasopon A, Mase V, Boffa D, Detterbeck F, Dacic S, Bader A.

Ground glass and semi-solid lung adenocarcinoma (SSN) are increasingly incidentally identified on outpatient chest CT scans and represent varying etiologies. An improved understanding of lung cancer development and necessity of invasive procedures is needed.

A comprehensive manual retrospective chart review was performed of patients with an SSN identified on a chest CT in the year 2017. CT scans from prior to and within 6 years following SSN identification were reviewed to evaluate nodule persistence and growth.

From a total of 17,276 outpatient chest CT scans done in 2017, 7% reported SSN findings in 953 individual patients. Of these, 25% had metastatic cancer, 22% had infectious or inflammatory lesions, and 20% had findings with unclear etiology. The remaining 322 (34%) patients had nodules that persisted on imaging and appeared to be on the adenocarcinoma spectrum. For nodules that were repeatedly scanned after 2017, 51% enlarged, 23% remained stable, and 26% decreased in size or resolved. By 2023, 18% had died; however, only 4 deaths (1%) were SSN-related. Only 43 (13%) patients underwent surgical resection of their SSN, and 6 died. Among these, 2 deaths were lung cancer-related following disease recurrence, and 4 were unrelated to the SSN.

While SSN are a common finding on chest CT, only a small number of these patients require surgical intervention. Death from SSN is rare but does occur, and in this study, patients with a SSN were more likely to die of an unrelated cause.

SOLID GROWTH PATTERNS AND ASSOCIATED 6-YEAR OUTCOMES FOR PATIENTS FOUND TO HAVE SEMI-SOLID LUNG NODULES ON CHEST CT

Kane E, Prince S, Woodard G, Blasberg J, Dhanasopon A, Mase V, Boffa D, Detterbeck F, Dacic S, Bader A.

Semi-solid lung nodules (SSN) are found with increasing frequency on outpatient chest CT scans. Growth of a solid, invasive component frequently triggers intervention, but growth patterns and their associations with long-term outcomes are poorly understood.

A comprehensive manual retrospective chart review was performed of patients with an SSN identified on a chest CT in the year 2017. CT scans from the 6 years following 2017 were reviewed to evaluate nodule persistence and growth.

From the 17,276 outpatient chest CT scans done in 2017, this chart review isolated 322 patients with SSN suspected to be on the adenocarcinoma spectrum. Of these, 36% had a solid component to their primary nodule. For 279 patients, their SSN was followed with repeat CT scans. Among these, 30% had a persistent solid component, 13% developed a solid component, 53% had stable ground glass, and 4% resolved. Patients with a persistent solid component had the highest 6-year mortality (23%) followed by those who developed a solid component (20%), those with stable ground glass (14%), and those whose SSN resolved (7%). The solid size increased for 63% of patients with sufficient measurement data at an average rate of 2.6 mm per year. Many patients with enlarging solid components (24%) underwent surgical resection of their SSN, and 1 died from a lung-cancer related cause following disease recurrence.

An improved understanding of SSN growth trends and how they relate to long-term outcomes may provide physicians and patients with an additional individualized factor for determining the necessity of intervention.