YALE SURGERY
RESEARCH DAY 2020
Your Research, Our Future

With the world still wrapped in the throes of the global COVID-19 pandemic, the value of medical science and discovery is ever apparent. The limitations of the circumstances caused us to cancel the Department of Surgery's 3rd Annual Research Day, originally scheduled for April 1, 2020. Although the in-person program could not take place, the ethos of the event, to come together as a scientific community to share and inspire new knowledge, is very much alive and well, however.

It was in this spirit, that the Department held a virtual event at Grand Rounds, April 24, 2020. Each of the five first-place poster competition winners gave a ten-minute presentation of their research, as summarized in their award-winning abstracts, across the domains of Basic Science, Clinical Research, and Outcomes Research.

More than 80 abstracts were submitted to the showcase; included here-in. The research presented in this digital collection represents the thinking, planning, and hard work of students, trainees, researchers, and principal investigators across the Department. Moreover, it represents the boundless potential of the next generation of surgeon-scientists, and the promising — important — future of surgical research.

Sincerely,

Nita Ahuja MD MBA FACS
Chair, Department of Surgery

Special Thanks

RESEARCH DAY STEERING COMMITTEE
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Yale Surgery Research Day
2020 Poster Competition

Abstract Submissions

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Basic Science ............................................................... Abstracts #44-75
Outcomes Research ....................................................... Abstracts #76-83
**Department of Surgery**  
**Faculty Research Laboratories & Groups**

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Hasan et. al. “Bioadhesive nanoparticles as a delivery vehicle in pancreatic cancer epithelial cells and pancreatic fibroblasts.”

**Ahuja, V.**  
Maducka et. al. “Racial Disparities in Surgical Outcomes for Benign Thyroid Disease.”  
Oliviera et. al. “The Unintended Consequences of Non-operative Management for Acute Appendicitis.”

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Allam et. al. “A Craniomorphometric Comparison Analysis Distinguishing Unilateral Lambdoid Craniosynostosis from Deformational Plagiocephaly.”  
Chandler et. al. “Comprehensive Craniomorphometric Analysis of 167 Patients with Metopic Craniosynostosis”  
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**Avraham**  
Ly et. al. “The effects of post-mastectomy radiotherapy on immediate autologous breast reconstruction.”

**Chaar**  
Kim et. al. “Improving long term outpatient vascular follow-up among patients undergoing lower extremity revascularization in Patients with lower extremity revascularization.”  
Kim et. al. “Risk factors for progression of claudication to chronic limb-threatening ischemia following revascularization.”

**Christison-Lagay**  
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**Clune**  
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Dardik
Fereydooni et. al. “Altered Hemodynamics During Arteriovenous Fistula Maturation Leads to Reduced Fistula Patency in Female Mice.”
Lee et. al. “Transcriptomics Reveal Cardioprotective Features of Arteriovenous Fistula-induced Cardiac Hypertrophy.”
Matsubara et. al. “Inhibition of PD-L1 reduces regulatory T-cells and M2 macrophages and inhibits vascular wall thickening during AVF maturation.”
Taniguchi et. al. “A Novel Mouse Arteriovenous Fistula Model Recapitulates Central Venous Stenosis.”

Elefteriades
Abdelbacky et. al. “Safety of Perioperative Cerebrospinal Fluid Drain as a Protective Strategy During Descending and Thoracoabdominal Open Aortic Repair”
Ellauzi et. al. “Fate of Preserved Aortic Root Following Acute Type-A Aortic Dissection Repair.”
Papanikolaou et. al. “Routine Whole Exome Sequencing for Thoracic Aortic Aneurysm and Dissection”
Rohde et. al. “‘Retrosternal Sponge’ Re-Entry Technique Avoids Pre-Sternotomy Cardiopulmonary Bypass in Complex Redo Cardiac Surgery”

Geirsson
Vinholo et. al. “Combined Valve Operations in the Aortic and Mitral Positions With or Without Added Tricuspid Valve Repair.”

Gruber
Wadwha et. al. “Whole exome sequencing of atrioventricular septal defect demonstrates key contributions from Plexin-Semaphorin, Hedgehog and cilia signaling in cardiac development.”
Yang et. al. “SLU7 regulates cardiac developmental programs and contributes to the pathogenesis of hypoplastic left heart syndrome.”

Guzman
Cai et. al. “Cyclic nucleotide phosphodiesterase 10A regulates medial artery calcification”

Hsia
Dash et. al. “Matrix Density Dependent Modulation of Secretory Function of iPSC-VSMCs.”

Judson
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Singh et. al. “Treatment of HPV Positive Oropharyngeal Cancer: Predictors and Outcomes”
Torabi et. al. “The Epidemiology, Surgical Management, and Impact of Margins in Skull and Mandibular Osseous Site Tumors.”

Khan
Kurbatov et. al. “Impact of Medicaid Expansion Under the Affordable Care Act on Stage at Diagnosis of Breast Cancer.”

Korah
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Mehra

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Krykbaeva et. al. “CD40 agonist in combination with checkpoint inhibition boosts anti-tumor immunity to melanoma.”

Wang et. al. “Survival and adverse effects of sequential IL-2 and immune checkpoint blockade in patients with cutaneous metastatic melanoma.”

**Pantel**

Baratta et. al. “Are women colorectal surgeons overrepresented in treatment of pelvic floor disorders?”

**Park**

Le Blanc et. al. “Impact of Medicaid Expansion Under the Affordable Care Act on Stage at Diagnosis of Breast Cancer”

**Persing**

Chuang et. al. “Long-Term Neurocognitive Outcomes in Sagittal Synostosis: The Impact of Reoperation.”

Lu et. al. “Airway volume is restricted by subcranial skeletal structural development in Apert syndrome.”

Persing et. al. “Tracing the Course of the Cervical Branch of the Facial Nerve.”

Singh et. al. “Neurologic functional connectivity in unilateral coronal craniosynostosis: a side-based comparison.”

**Santos-Sacchi**

Surguchev et. al. “Progress in SLC26A6 (A6) structural studies by Cryo-EM.”

Tan et. al. “Microtubule-Associated Protein 1S (MAP1S) is Required for Normal OHC Electromotility and Hearing.”

**Sasaki**


Kasle et. al. “In vivo temporal characteristics of NF-κB inhibition in bile-induced early oncogenic molecular events in murine hypopharyngeal mucosa.”

Vageli et. al. “Long-term exposure of laryngopharyngeal mucosa to acidic bile is carcinogenic.”

**Schuster**

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Harris et. al. “Assessment of Institutional Practices to Guide Implementation of a Colorectal Clean Closure Tray.”

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Ullrich et. al. “Utilization of an Ultrasound Template for Evaluation of Pediatric Appendicitis at Bridgeport Hospital.”

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Stitelman
Maassel et. al. “Bio-distribution of Microparticles in Mice following Intra-placental Injection.”
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Thomson
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Tsia et. al. “Trigger Finger: Staging and Treatment Outcomes.”

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Bracaglia et. al. “New strategy to maximize nanomedicine delivery during ex vivo perfusion.”
Edwards et. al. “Evaluating the impact of anatomic variability in kidney cortical wedge biopsies on human organ research results.”
Haakinson et. al. “Developing Infrastructure for High Impact Transplant Declined Human Organ Research in the US and Opportunities as a Platform for Surgical Education.”
Harris et. al. “Rouleaux Formation in Human Livers During Normothermic Machine Perfusion.”

Vallabhajosyula
Abdelbaky et. al. “How Do Patients with Thoracic Aortic Aneurysm Die?”
Yousef et. al. “Prevalence of Aortic Arch Anomalies and Congenital Variants in the General Population and Associated Thoracic Aortic Aneurysm Disease.”

Yoo
Hernandez et. al. “Assessment of Resident Cost Consciousness for Common Operating Room Expenses.”
White et. al. “Examining the Last 24 Hours: An Opportunity to Reduce Excessive Opioid Prescriptions at Post-Operative Discharge.”
Winning Abstracts

Alexei Surguchev, Associate Research Scientist, Santos Sacchi Laboratory
Progress in SLC26A6 (A6) structural studies by Cryo-EM (Abstract #63)

Mohamed Abdelbaky MD, Postdoctoral Fellow, Elefteriades Laboratory
Safety of Perioperative Cerebrospinal Fluid Drain as a Protective Strategy During Descending and Thoracoabdominal Open Aortic Repair (Abstract #22)

Walter Hsiang, MD/MBA Candidate, Schuster Laboratory
Predictors of Access to General Surgical Care at Urgent Care Centers in the United States (Abstract #14)

Matthew Harris, MD, General Surgery Resident, Schuster Laboratory
Assessment of Institutional Practices to Guide Implementation of a Colorectal Clean Closure Tray of Institutional Practices to Guide Implementation of a Colorectal Clean Closure Tray (Abstract #83)

Lindsay Eysenbach, Student, Solomon Laboratory
Protocolized Management of Abscess Drains Safely Reduces Resource Utilization in Complicated Pediatric Appendicitis (Abstract #78)

Honorable Mentions

Jolanta Gorecka, General Surgery Resident, Dardik Laboratory
Delivery of Induced Pluripotent Stem Cell Derived Smooth Muscle Cells in a Collagen Scaffold Enhances Cell Survival and Accelerates Wound Healing (Abstract #50)

Nicholas Peters, General Surgery Resident, Kunstman Laboratory
Development of an Organoid–based Model System for Intraductal Papillary Mucinous Neoplasia of the Pancreas (Abstract #71)

Norm Nicolson, General Surgery Resident, Carling Laboratory
Transcription Factor Profiling Identifies Spatially Heterogenous Mediators of Follicular Thyroid Cancer Invasion (Abstract #52)

Chris Edwards, Postgraduate Associate, Tietjen Laboratory
Evaluating the impact of anatomic variability in kidney cortical wedge biopsies on human organ research results (Abstract #48)

Holly Blackburn, General Surgery Resident, Flavella Laboratory
Elucidating the cells and pathways driving fibrosis in the intestine (Abstract #74)
Abstract #1: Evaluation of firearm related hospitalization recidivism in Connecticut: An opportunity for gun violence prevention

Authors: Kathleen M O’Neill, MD, MHS, James Dodington, MD, Pina Violano, PhD, MSPH, RN-BC, CCRN

Introduction: Firearm injury and interpersonal violence is a major epidemic within the United States resulting in over 33,000 deaths every year. One underserved population that is an important target for prevention efforts is those who have had a firearm injury in the past. This population is known to have an increased risk for repeat firearm-related injury and overall mortality, but the regional extent of this risk for patients in Connecticut is unknown.

Methods: Using 2014-2019 medical record data from the Yale New Haven Hospital (YNHH) system in Connecticut in combination with 2014-2019 data from the Connecticut Medical Examiners Office, we conducted a cohort study of patients with a firearm-related hospitalization in 2014 to determine their risk of a repeat firearm-related hospitalization in the next 5 years and mortality from homicide. In addition, we used a control population of non-violence-related trauma patients to complete a logistic regression analysis with adjustment for relevant covariates.

Results: We identified 101 patients with a firearm-related hospitalization in the YNHH system from 2014 that survived to discharge. Of these patients, 7.9% were found to have a repeat firearm-related injury within the next 5 years. There was an overall homicide mortality rate of 2% among the cohort over the next five years. Compared to non-violence-related trauma patients from 2014, those with a firearm-related hospitalization in 2014 had six times the odds of homicide mortality. There were no firearm-related hospitalizations in the control group of non-violence-related trauma patients from 2014 in the subsequent 5 years after discharge.

Conclusions: Of the patients presenting with an initial firearm-related hospitalization in the YNHH system, 1 in 12 will experience another gunshot wound within the next 5 years. These patients also have a 2% overall mortality rate with a six-fold increased risk in homicide mortality compared to non-violence-related trauma patients.
Abstract #2: The Effect of Intraoperative Temperature on Microvascular Thrombosis

Authors: Smetona John T, Gabrick Kyle, Dinnis Jacob, Chouhari Fouad, Alperovich Michael, Thomson James Grant

Introduction:
The trauma literature provides evidence of a correlation between hypothermia and mortality. Anesthesia guidelines require intraoperative temperature monitoring and prevention of hypothermia (T < 36 C). There has been less concern with mild intraoperative hyperthermia for plastic surgery patients. However, previous data from our institution suggest that intraoperative hyperthermia is associated with increased rates of microvascular thrombosis in free tissue transfer. We present a series of free tissue transfers to further assess for correlation between intraoperative hyperthermia and microvascular thrombosis.

Methods:
A retrospective chart review was conducted of all free flap breast reconstructions performed at Yale New Haven Hospital from 2013 to 2018. Thrombosis was assessed across octiles of maximum intraoperative temperature. Aggregate thrombosis rates were assessed at a previously defined ideal temperature range (36.0-36.4 C). Multivariate regression analysis was also performed to control for confounders in the assessment of intraoperative thrombosis requiring revision, post-operative venous thrombosis, and post-operative arterial thrombosis as a function of temperature.

Results:
416 consecutive patients with 686 free flaps were identified. Patient age, cancer status and comorbidities were recorded. Octile analysis showed that extremely low temperatures were associated with high thrombosis rates, but then thrombosis fell to 0% followed by a rise in thromboses with increasing intraoperative Tmax. Patients with intraoperative temperature greater than 37.5 C (99.5 F) had a 14% rate of intraoperative microvascular thrombosis, while patients with an intraoperative Tmax of 36.0-36.4 C had a 0% rate of thrombosis on bivariate analysis. Multivariate regression analysis showed that the rate of intraoperative revisions increased by 1.54 x for each increase of Tmax by one degree F. Post-operative venous thrombosis increased by 3.07x for each degree F increase in Tmax; and post-operative arterial thrombosis showed a change of .824x which was not statistically significant (p .682). Of note, smoking was found to be a very strong predictor of post-operative venous thrombosis (odds ratio 9.27, p .037).

Conclusions:
These data suggest that mild intraoperative hypothermia is protective of microvascular patency. This effect is seen most strongly on post-operative venous thrombosis, while post-operative arterial thrombosis is unaffected. Smoking is an extreme risk factor for post-operative venous thrombosis. A randomized prospective trial should be carried out to definitively establish the need for new paradigm for intraoperative temperature management for free flap patients.
**Abstract #3:** Fate of Preserved Aortic Root Following Acute Type-A Aortic Dissection Repair

**Authors:** Hesham Ellauzi MD, Mohammad A. Zafar MBBS, Jinlin Wu MD, Bilal Saeed MD, Dimitra Papanikolaou MD, Usman Tariq MD, Mohamed Abdelbaky MD, Paris Kalogerakos MD PhD, Joelle Buntin MSN RN RN-BC, Bulat A. Ziganshin MD PhD, Sandip Mukherjee MD, Prashanth Vallabhapushula MD, John A. Elefteriades MD PhD(hon)

**Objective:** The purpose of this study was to ascertain the long-term fate of the preserved aortic root after emergent repair of acute type A aortic dissection.

**Methods:** 144 patients (60% males, mean age at presentation 60.51 ± 13.95 years) underwent supracoronary ascending aortic replacement for acute type A aortic dissection. Long-term survival, as well as growth, reoperation and adverse events of the aortic root (rupture, pseudoaneurysm, and persistent dissection) were retrospectively assessed.

**Results:** The aortic valve was resuspended in 64 patients (46.7%) and replaced in 20 patients (14.6%). Aortic replacement extended to the aortic arch in 104 patients (76%) (Hemi-arch in 93 patients 68% and total arch in 11 patients 8%). 30-day mortality was 9%, and overall survival at 1, 5, and 10 years was 87.8%, 76.4%, and 64.6%, respectively. Survival free from aortic root adverse events at 1, 5, and 10 years was 95.9%, 93.5%, and 93.5% respectively. Survival free from proximal aortic reoperation at 1, 5, and 10 years was 96.6%, 94.5%, and 92.2%, respectively. Reoperation on the proximal aorta was performed in 14 patients (9.7%) within a median of 2.5 years following the initial procedure. Indications for reoperation were severe aortic insufficiency (AI) (8 patients), persistent dissection of the aortic root (3 patients), and aortic root pseudoaneurysm (4 patients). Amongst survivals (n=131), aortic root dilation (≥45mm) or valve regurgitation (≥2+) was observed in 28 (21%) and 20 (15%) patients, respectively. Aortic root dilation rate was 0.2mm/year (interquartile range 0-0.8).

**Conclusions:** Root sparing ascending aortic replacement for acute type-A aortic dissection shows satisfactory postoperative and long-term outcomes with relatively low rates of re-intervention or adverse events. No free rupture of the retained aortic root occurred. We believe free rupture is very unusual because of dense scarring and adhesions around the retained aortic root.

**Table:**

![Kaplan-Meier analysis of overall survival](image-url)
Abstract #4: The Epidemiology, Surgical Management, and Impact of Margins in Skull and Mandibular Osseous Site Tumors

Authors: Sina J. Torabi BA, Alexandra Bourdillon BS, Parsa P. Salehi MD, Samipya Kafle BS, Saral Mehra MD, MBA, Rahmatullah Rahmati MD, Benjamin L. Judson MD

Objectives: To characterize the frequency, epidemiology, and treatment outcomes of tumors arising from the head and neck (HN) osseous sites (mandible and skull/facial bones), as well as characterize the effect of margins on overall survival (OS).

Methods: A retrospective 2004-2016 analysis of the National Cancer Database was performed. Descriptive analyses were performed on 6 histological subtypes, and a multivariate Cox regression was performed to analyze the effect of surgery on OS. The effect of margins on OS was similarly analyzed in histological subgroups. Binary logistic regression was utilized to find factors associated with positive margins.

Results: We identified 2,449 tumors arising from osseous sites (chordomas 32.5%, cartilage tumors 28.7%, osteosarcomas 26.6%, and Ewing sarcoma [ES] 9.8%). The majority of tumors arose within the skull/facial bones (83.2%), though 42.5% of osteosarcomas were mandibular. Surgery was utilized in 84.5% of cases. OS was significantly worse in osteosarcoma (5-year OS: 53.4% [SE: 2.5%]) compared to cartilage tumors (5-year OS: 84.6% [SE: 1.8%]) with ES, fibrous tumors, and chordomas exhibiting moderate OS (log-rank p<0.001).

Treatment regimens that included surgery were associated with improved OS on multivariate analysis (HR 0.495 [95% CI: 0.366-0.670]; p<0.001). Positive margins were found in 40.8% of cases, and found to be associated with decreased OS in osteosarcomas (HR 1.304 [0.697-2.438]; p=0.003) and chordomas (HR 2.073 [1.071-4.015]; p=0.031), but not in cartilage tumors (HR 1.304 [0.697-2.438]; p=0.406) (Table).

Conclusion: Treatment that included surgery was associated with a positive survival benefit within our cohort of HN osseous site tumors, though rates of positive margins were >40%. At this time, achievement of negative margins is most prognostic in the setting of osteosarcomas, which experience the poorest survival rates.

Table

Multivariate Analyses of the Association of Positive Margins with Overall Survival

<table>
<thead>
<tr>
<th>Subgroup Analysis</th>
<th>Number of Patients</th>
<th>5-Year Survival</th>
<th>Log-Rank Univariate P value</th>
<th>Multivariate Cox Regression Hazard Ratio (95% CI)</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>All Patients with Known Margins</td>
<td>1084</td>
<td>73.7% ± 2.0%</td>
<td>71.8% ± 2.5%</td>
<td>0.178</td>
<td>1.442 (1.121-1.854)</td>
</tr>
<tr>
<td>Primary Site</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Skull, Face, and Associated Joints</td>
<td>835</td>
<td>79.2% ± 2.2%</td>
<td>74.5% ± 2.6%</td>
<td>0.032</td>
<td>1.489 (1.114-1.990)</td>
</tr>
<tr>
<td>Mandible</td>
<td>249</td>
<td>61.9% ± 3.8%</td>
<td>48.4% ± 8.3%</td>
<td>0.071</td>
<td>1.562 (0.890-2.742)</td>
</tr>
<tr>
<td>Histology</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Chordomas</td>
<td>293</td>
<td>87.7% ± 3.6%</td>
<td>80.8% ± 3.8%</td>
<td>0.072</td>
<td>2.073 (1.071-4.015)</td>
</tr>
<tr>
<td>Cartilage Tumors</td>
<td>303</td>
<td>86.7% ± 3.0%</td>
<td>85.3% ± 3.3%</td>
<td>0.832</td>
<td>1.304 (0.697-2.438)</td>
</tr>
<tr>
<td>Osteosarcomas</td>
<td>385</td>
<td>60.4% ± 3.3%</td>
<td>35.5% ± 5.4%</td>
<td>&lt;0.001</td>
<td>1.712 (1.199-2.444)</td>
</tr>
</tbody>
</table>

NOTE: All regressions control for age, sex, race, CDCC score, AJCC clinical T and N stage, and grade.

a Also controls for histology

b Also controls for primary site
Abstract #5: Treatment Selection for the Initial Management of Node-Negative Merkel Cell Carcinoma and its Implications

Authors: Daniel Jacobs BA, Kelly Olino MD, Henry S. Park MD MPH, James Clune MD, Barbara Burtness MD, Harriet Kluger MD, Benjamin L. Judson MD

Background: Practice guidelines for Merkel cell carcinoma (MCC) have been published by the National Comprehensive Cancer Network (NCCN) since 2004. However, treatment selection for patients with MCC continues to be widely variable. We investigated trends in the initial treatment selection for patients with clinically node negative, non-metastatic (cN0M0) MCC, and its effect on mortality.

Methods: The National Cancer Database (NCDB) was queried between 2004 and 2016. Trends in compliance with NCCN guideline recommendations since 2004 and a retrospective application of current NCCN guidelines, defined as sentinel lymph node biopsy and wide local excision of the primary tumor, on mortality were assessed. Subgroup analysis sites included head and neck, trunk, and extremities.

Results: 8,899 subjects with cN0M0 MCC were included in the analysis. The percentage of patients evaluated at academic programs (APs) increased by 1.14% per year (95% CI: 0.89, 1.39) while evaluation at comprehensive community programs (CCCPs) declined by 1.03% per year (CI: 0.67, 1.38). NCCN guideline-compliant care has plateaued since 2009 but has been more likely to be delivered when patients have been evaluated at academic programs (APs) compared to other institutions (OR 1.88; CI: 1.69, 2.09). Patients who received care within current guidelines, care outside of guidelines, or no treatment had median survival times of 97.5 months (95% CI: 91.2, 103.8), 39.6 months (95% CI: 36.7, 42.5), and 13.1 months (95% CI: 7.3, 18.9), respectively. On multivariable analysis, receipt of care within compared to outside of current guidelines was associated with a survival advantage (HR 0.65; 95% CI: 0.60, 0.71), as was evaluation at APs (p-value 0.007). Similar trends in factors associated with receipt of guideline-compliant care and survival were seen in subgroup analysis by tumor primary site.

Conclusions: Patients who have received at least part of their care at APs have been more likely to receive guideline-compliant care, a treatment approach which is associated with a survival benefit.

Trends in care: Adherence to NCCN guidelines

Figure legend: Trends in the level of care provided. Dashed lines represent outputs of fitted logistic curves.
Abstract #6: The Natural History of Bicuspid Aortic Valve Associated Ascending Thoracic Aortic Aneurysm

Authors: Mohammad A. Zafar MD, Thais Faggion Vinholo BS MSc, Jinlin Wu MD, Dimitra Papanikolaou MD, Paris Kalogerakos MD PhD, Yupeng Li PhD, Sophie Jang BS, Paris Charilaou MD, Joelle Buntin MSN RN RN-BC, John A. Rizzo PhD, Sandip K. Mukherjee MD, Bulat A. Ziganshin MD PhD, Prashanth Vallabhajosyula MD, John A. Elefteriades MD PhD(hon)

Introduction: Ascending thoracic aortic aneurysm (ATAA) is a well-established finding in patients with bicuspid aortic valve (BAV) disease, the most common congenital cardiac disorder affecting the human heart. Thus, for bicuspid-related aneurysms, elucidating the critical ascending aortic size at which natural complications occur (rupture, dissection, and death) is of paramount importance to guide prophylactic surgery. In this study, we aim to outline the natural history of a large number of BAV associated ATAA (BAV-ATAA) followed over time, to ascertain if their behavior differs from trileaflet aortic valve ATAA (TAV-AATA), and to determine if a different threshold for intervention is required for BAV related ATAA.

Methods: Aortic diameters and long-term complications of 514 BAV patients with ATAA prior to operative repair were reviewed. Growth rates (instrumental variables approach), yearly complication rates, 5-year event-free survival (Kaplan-Meier), and risk of complications as a function of aortic size (logistic regression) were calculated.

Results: The estimated mean growth rate of BAV-ATAA was 0.21 cm/year, increasing with increasing aortic size. An ATAA diameter ≥ 6cm was associated with a 13% yearly rate of rupture, dissection, and death. 5-year complication-free survival progressively decreased with increasing ATAA size. Hazard of complications showed a 13-fold increase at an ATAA size of ≥ 6cm, compared to an aortic size of 4.0-4.4cm (P < .05). The probability of natural complications (rupture, dissection, and death) increased sharply at 3 hinge points: 5.0, 5.5, and 6.0cm. This behavior is quite similar to our previously published data for TAV-ATAA. Surgical mortality in operated BAV-AATA patients was 4/425 (0.9%).

Conclusion: The threshold for surgical repair of BAV-ATAA should not differ from that of TAV-ATAA. Prophylactic size-based surgery in BAV-ATAA patients should be considered at 5.0 cm at expert aortic centers as a means to afford protection from natural complications.
Abstract #7: Long-Term Neurocognitive Outcomes in Sagittal Synostosis: The Impact of Reoperation

Authors: Carolyn Chuang MD, Tafadzwa L Chaunzwa MD, Robin Wu MD, Anusha Singh BS, Anup Patel MD MBA, Jenny F Yang MD, Peter W Hashim MD, Roberto Travieso MD, Jordan S Terner MD, Linda C Mayes MD, Charles C Duncan MD, John A Jane Jr MD, Kant Y Lin MD, David J Bridgett PhD, John A Persing MD

Background: Optimal age at surgery in nonsyndromic sagittal craniosynostosis continues to be debated. Previous reports suggest that earlier age at whole vault cranioplasty more frequently requires reoperation, which may have adverse impacts on children’s neurocognitive outcomes; therefore, delayed surgery may be better. However, it is unknown whether reoperation negatively affects neurocognitive outcome. This study examined the impact of reoperation on neurocognitive outcome in children with nonsyndromic sagittal craniosynostosis using comprehensive neurocognitive testing.

Methods: Forty-seven school-age children (age 5-16 years) with nonsyndromic sagittal craniosynostosis who underwent whole-vault cranioplasty were included in this analysis. Twenty-four participants underwent early surgery (operated at age 6 months or younger) with mean age at surgery 4.8 months, and 23 participants underwent later surgery (operated at age greater than 6 months) with mean age at surgery 14.3 months. Participants were administered a battery of standardized neuropsychological testing (Wechsler Abbreviated Scale of Intelligence, Wechsler Fundamentals, Beery-Buktenica Visual Motor Integration) to measure neurocognitive outcomes.

Results: Thirteen out of the 47 participants underwent a reoperation (27.7%); 11 out of the 13 reoperations were minor revisions while 2 reoperations were cranioplasties. Of the two major revisions, initial surgery was performed at age less than 6 months in one patient, and the other patient was in the greater than 6 months age group. Reoperation rate, overall, was not statistically greater in those patients who had early surgery (at age ≤6 months) when compared to late surgery (at age >6 months). Later age at operation patients, not undergoing revisional surgery, did not perform statistically better than early surgery patients, even when the early surgery patients underwent reoperation, on any outcome measure of neurocognitive function, including IQ, academic achievement, visuomotor integration, executive function, and behavior (p>0.05 for all). Comparing reoperated early surgery patients with non-reoperated late surgery patients, reoperated early surgery patients scored significantly higher on word reading, reading comprehension, spelling, numerical operations, and visuomotor integration (p<0.05), and had fewer indicators of suspected learning disabilities compared to non-reoperated late surgery patients.

Conclusion: Reoperation rate after whole vault cranioplasty was observed to be 27.7%, with few cases of repeat cranioplasty (4.3% of all patients). Operated and reoperated early surgery patients performed better in IQ, academic achievement, and visuomotor integration compared with non-reoperated late surgery patients. This provides evidence that whole-vault cranioplasty before 6 months of age is associated with better neurocognitive outcome compared to after 6 months of age, even when early surgery requires a reoperation.
Abstract #8: Trigger Finger: Staging and Treatment Outcomes  
Authors: David M. Tsai MD, Raysa Cabrejo BA, J. Grant Thomson MD

Introduction – Trigger finger is a common ailment. However, no accepted classification system exists that can be reliably utilized to determine an optimal treatment strategy. Often the decision to try a corticosteroid injection or surgical intervention depends on a patient’s personal preference. We have previously performed a study that looked at the cost effectiveness of multiple injections. This study seeks to expand on that by stratifying the patients into a staged classification scheme to determine when immediate surgical intervention should be offered versus multiple attempts with corticosteroid injections.

Methods – Retrospective charts of all patients with trigger fingers were reviewed over a 5 year period from 2013 to 2018 for a single surgeon. These fingers were retrospectively graded in a classification scheme as follows: Stage 0, stiffness; Stage 1, tenderness/swelling/pain/nodule; Stage 2, clicking or catching; Stage 3, locking but correctable with active movement; Stage 4, locking but correctable with passive movement; Stage 5a, uncorrectable stuck in flexion; Stage 5b, uncorrectable stuck in extension. The success of injections were determined and tracked.

Results – 204 fingers were treated first with injection of steroids. These were stratified in our classification scheme as follows: Stage 1, n =31; Stage 2, n = 98; Stage 3, n = 54; Stage 4, n = 0; Stage 5, n = 10. The respective % success of treatment was 77%, 79%, 72%, 33%, 70%. There was no statistical difference among the groups. Overall success of treatment was 74.5%. Females had 2.5 higher odds of failing treatment (p < 0.02).

Conclusions – Trigger fingers tend to present in its early stages and appear to have higher success rates with injections when they do. Late stages, in which the fingers start to lock and require active or passive correction or when the fingers are permanently stuck in flexion or extension, appear to have less success with injections. Our staging classification may be useful for stratifying the severity of trigger fingers, and ultimately determining whether an steroid injection or surgical intervention should be the initial course of treatment.
Abstract #9: How Do Patients with Thoracic Aortic Aneurysm Die?

Authors: Mohamed Abdelbaky MD, Mohammed A. Zafar MD, Dimitra Papanikolaou MD, Jinlin Wu, Julia Fayanne Chen MD, Paris Charilaou MD, Ayman Saeyeldin MD, Mohamed Ahmed Elashwal, Laxman Singanamala, Joelle Buntin MSN RN RN-BC, Bulat Ziganshin MD PhD, Sandip K. Mukherjee MD, John A. Elefteriades MD PhD(hon), Prashanth Vallabhajosyula MD MS

Introduction: To evaluate causes of death in patients with thoracic aortic aneurysm or dissection (TAAD).

Methods: Our TAAD database comprises 2606 patients, of whom 694 died during follow-up, which was achieved via published institutional survival analysis method. This entails clinical follow-up, online database mortality query, EPIC clinical and mortality query, referring doctor follow-up, online obituary search, and death certificate acquisition. Aortic deaths included “definite” and “possible” categories (Lederle).

Results: The cause of death was ascertained in 345 patients. 168 patients were surgical, and the remainder were medically treated. Deaths included 43(12.4%) patients with ascending thoracic aortic aneurysm (ATAA), 85(24.6%) patients with descending or thoracoabdominal aneurysm (DTA), and 217(62.8%) with both. Four (9.3%) patients with ATAA suffered aortic death, all in the non-surgical group. Surgical intervention successfully eliminated all later aortic deaths in the surgical group. In the DTA group, 43(50.5%) patients suffered aortic death, with the majority in the non-surgical group (n=28, 65.1%). The group with both ATAA and DTA included 72(33.1%) aortic deaths, most of which were non-surgical (n=40, 55.5%). The non-surgical group comprised significantly more aortic deaths (n=72/177, 40.6%) compared to the surgical group (n=47/168, 27.9%) (p=0.01).

Conclusions: TAAD patients die from a variety of non-aortic causes. Surgical therapy substantially curtails death from aortic causes.

Table 1. Detailed Breakdown of Causes of Death

<table>
<thead>
<tr>
<th>Causes</th>
<th>Number (percentage)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Aortic Death</strong></td>
<td></td>
</tr>
<tr>
<td>Ascending aortic</td>
<td>20 (5.7)</td>
</tr>
<tr>
<td>Descending aortic</td>
<td>84 (24.3)</td>
</tr>
<tr>
<td>Abdominal aortic</td>
<td>10 (2.9)</td>
</tr>
<tr>
<td>Aortic unspecified location</td>
<td>5 (1.4)</td>
</tr>
<tr>
<td><strong>Non-aortic death</strong></td>
<td></td>
</tr>
<tr>
<td>Cardiac*</td>
<td>56 (16.2)</td>
</tr>
<tr>
<td>Cancer</td>
<td>38 (11)</td>
</tr>
<tr>
<td>Respiratory failure</td>
<td>25 (7.2)</td>
</tr>
<tr>
<td>Renal failure</td>
<td>15 (4.3)</td>
</tr>
<tr>
<td>Sepsis</td>
<td>14 (4.1)</td>
</tr>
<tr>
<td>Perioperative</td>
<td>13 (3.7)</td>
</tr>
<tr>
<td>Dementia</td>
<td>11 (3.1)</td>
</tr>
<tr>
<td>Multisystem organ failure</td>
<td>8 (2.3)</td>
</tr>
<tr>
<td>Intracranial hemorrhage</td>
<td>7 (2)</td>
</tr>
<tr>
<td>Stroke</td>
<td>11 (3)</td>
</tr>
<tr>
<td>Gastrointestinal bleed</td>
<td>8 (2.3)</td>
</tr>
<tr>
<td>Trauma</td>
<td>3 (0.8)</td>
</tr>
<tr>
<td>Pulmonary embolism</td>
<td>2 (0.5)</td>
</tr>
<tr>
<td>Pneumonia</td>
<td>5 (1.4)</td>
</tr>
<tr>
<td>Liver failure</td>
<td>3 (0.8)</td>
</tr>
<tr>
<td>Peripheral vascular disease</td>
<td>1 (0.2)</td>
</tr>
<tr>
<td>Encephalopathy</td>
<td>1 (0.2)</td>
</tr>
<tr>
<td>Bleeding (unspecified cause)</td>
<td>1 (0.2)</td>
</tr>
<tr>
<td>Massive hemoptysis</td>
<td>1 (0.2)</td>
</tr>
<tr>
<td>Endocrinologic, metabolic</td>
<td>1 (0.2)</td>
</tr>
<tr>
<td>Suicidal</td>
<td>1 (0.2)</td>
</tr>
<tr>
<td>Third degree burn</td>
<td>1 (0.2)</td>
</tr>
<tr>
<td><strong>Total</strong></td>
<td><strong>345</strong></td>
</tr>
</tbody>
</table>

*Death due to heart failure or coronary artery disease with rule out of dissection or rupture
**Abstract #10:** Routine Whole Exome Sequencing for Thoracic Aortic Aneurysm and Dissection

**Authors:** Dimitra Papanikolaou MD, Mohammad A. Zafar MBBS, Bulat A. Ziganshin MD PhD, Adam J. Brownstein MD, Mohamed Abdelbaky MD, Paris Kalogerakos MD PhD, Joelle Buntin MSN RN RN-BC, Hesham Ellauzi MD, Thais Faggion Vinholo BS MSc, Sandip Mukherjee MD, Prashanth Vallabhajosyula MD, Allen E. Bale MD, John A. Elefteriades MD PhD(hon)

**Introduction:** To present our experience routinely performing whole exome sequencing (WES) for patients with thoracic aortic aneurysm or dissection (TAAD).

**Methods:** WES was performed in 453 TAAD patients. Mean age was 58.1 years, and 322 (71.1%) patients were male. The most recent panel analyzed with WES includes 44 genes.

**Results:** Figure 1 shows the patient breakdown. 155 rare genetic variants in TAAD-related genes were identified in 133 (29.4%) patients. Eleven (2.2%) and 10 (2.2%) patients carried definite pathogenic and likely pathogenic variants, respectively. 134 suspicious variants were classified as variants of uncertain significance (VUS), 120 of which were previously unreported (Figure 1). No significant findings were detected in 305 (67.3%) patients. Most patients had ascending aortic aneurysms (n=364, 80.4%). Among these patients, aneurysm growth rate in patients with VUS was 0.2±0.08 cm/year, compared to 0.11±0.02 cm/year in patients with no genetic findings (p=0.27). Overall, the 112 patients with VUS had positive family history of aortic aneurysm or dissection (n=51, 45.5%) more frequently than the 305 patients with no findings (n=105, 34.4%) (p=0.04).

**Conclusions:** Rare VUS represent a clinical challenge, as pathogenicity is not yet proven. Yet, we must remember that all pathogenic mutations present first as VUS, until further clinical reports substantiate pathogenicity. For now, the surgeon must use specific variant characteristics to assess whether identification of a VUS should influence clinical decision making.
Abstract #11: Radiographic Predictors of FACE-Q Outcomes Following Non-Operative Orbital Floor Fracture Management

**Authors:** Gabrick KS, Smetona J, Iyengar R, Dinis J, Chouiari F, Peck C, Persing JA, Alperovich M

**Background:** Orbital floor fractures are common injuries treated by multiple surgical subspecialties. Controversy exists regarding the operative indications. This study sought to correlate radiographic characteristics of orbital floor fractures with validated patient reported outcome measures following non-operative management.

**Materials and Methods:** Patients who underwent non-operative management of an orbital floor fracture at Yale New Haven Hospital from 2013-2018 were queried retrospectively. Patients with GCS < 15 and/or distracting facial soft tissue or bony injuries were excluded from analysis. CT images, demographic information, and FACE-Q patient reported outcomes (Satisfaction with Eyes, Psychological Function, Social Function, and Appearance Related Psychosocial Distress) were reviewed. Statistical analysis was performed with SPSS with statistical significance set at p<0.05.

**Results:** Eighteen patients were included in the study. The mean time between injury and completion of the survey was 3.6 years. Fifty-six percent of patients had a right-sided fracture. The mean fracture area was 73.6mm$^2$ (Range:15-172mm$^2$), and 913 mm$^3$ (Range: 0-3106) was the mean volume displaced into the maxillary sinus. The unaffected inferior rectus muscle shape (height/width) was 0.5 (Range: 0.2-0.98) compared to 0.8 (Range 0.4-1.6) for the affected inferior rectus. After controlling for the time interval between survey and injury, gender, income, and education, rounding of the inferior rectus muscle was a significant predictor of appearance related psychosocial distress (p=0.006). Inferior rectus rounding was stratified into “severe” (75%) and “moderate” (25%) categories. Severe rounding was associated with a larger orbital floor fracture area (110 vs. 64 mm$^2$; p=0.074), volume displaced into the maxillary sinus (1,716 vs. 610 mm$^3$; p=0.024), and worse appearance-related psychosocial distress (70 vs. 25; p=0.013). Sixty-one percent of patients followed up in clinic with a mean duration of 194 days. One patient reported diplopia at time of follow up.

**Conclusion:** Prior studies have correlated presenting radiographic findings to follow-up clinical findings. However, this study is the first to assess long-term outcomes using validated patient-reported questionnaires. Inferior rectus muscle belly rounding significantly correlated with appearance related psychosocial distress. This radiographic finding may be valuable to consider in orbital floor fracture management.
Abstract #12: Ear Scanners: Audiologists’ Impressions and Motivation
Authors: Kayla Cormier

Introduction
Custom components for hearing aids require the completion of impressions of the ear. Even though ear impressions are routinely taken on patients, it is important to remember that there is a risk of injury to the patient (Salterrelli, 2008; Leong, Banhegyi, & Panarese, 2012; Jacob, Morris, & Welling, 2006; Lee & Cho, 2012). Additionally, obtaining an accurate impression is extremely important to ensure that the patient is receiving appropriate amplification from their hearing aids and that the custom components are comfortable (Salterrelli, 2008). Both this consideration and the risk of injury highlight an area in which improvements could be achieved in audiology. Ear scanner technology has recently become available to the field of audiology for obtaining ear impressions. This technology is thought to reduce the risk of injury to the patient and increase the accuracy of impressions. However, it is unknown if ear scanning would help attract patients to a practice or audiologists’ motivation or impressions on embracing this new technology.

Methods
A survey employing 31 questions was utilized to determine the impressions of persons in audiology related fields regarding older methods of ear impression techniques, as well as new ear scanner techniques. The survey was made available to only persons in fields related to audiology using social media groups that were closed to the general public.

Results
352 people of various years of experience in the field of audiology and from various occupational settings responded to the survey. Most participants felt they were both adequately taught how to take an impression and are comfortable taking impressions. Meanwhile, less than half of respondents stated that taking impressions can be dangerous to the patient. 65% of subjects reported never causing harm to a patient while completing a traditional ear impression. However, only 32% of participants agreed with the statement that they would purchase an ear scanner. On the other hand, 61% stated that ear scanners are a valuable tool for the profession of audiology and 64% of subjects believed them to be valuable to a clinical practice.

Conclusions
A major motivator to accepting such technology is the potential harm that could be inflicted on a patient. Yet, most respondents did not perceive this process as dangerous. Additionally, respondents did not feel that ear scanners would reduce the remake rates of custom components. This suggests low motivation for embracing this technology. Many respondents felt that ear scanner technology was valuable to both clinical practice and the field of audiology. It was also agreed that patients would enjoy having scans of their ears, and custom products would arrive sooner, suggesting an enhanced patient experience with the use of ear scanner technology. Yet, participants did not feel ear scanners would attract patients to their practice and the majority would not purchase ear scanners. It appears at this time, while value can be seen in this technology for the field of audiology, persons related to this field are not ready to adopt such technology.
Abstract #13: The effects of post-mastectomy radiotherapy on immediate autologous breast reconstruction
Authors: Catherine L. Ly MD, Sumun Khetpal BA BS, Danielle R. Heller MD, Susan A. Higgins MD, Brigid Killelea MD MPH, Michael Alperovich MD MSc, Tomer Avraham MD

Introduction: While some previous studies have evaluated the effect of post-mastectomy radiation therapy (PMRT) on autologous reconstruction, these studies have been of variable quality and outcomes. Further, variability of PMRT protocols, disease states, and inadequate controls, make outcomes difficult to interpret. Therefore, in this study, we sought to compare irradiated free-flaps with contralateral, non-irradiated free-flaps acting as internal controls, and to analyze risk factors for complications.

Methods: Patients who underwent immediate bilateral autologous reconstruction followed by unilateral PMRT were identified through retrospective review. Chi-squared tests were performed to compare irradiated and non-irradiated free-flaps. Multivariate regression was used to assess the effect of patient and treatment characteristics on complications in the irradiated free-flaps.

Results: A total of 73 women met the inclusion criteria, resulting in 73 irradiated free-flaps and 73 non-irradiated controls. There was no significant difference between complication rates for irradiated and non-irradiated free-flaps (39.7 versus 38.4%, \( p = 0.78 \)), although irradiated free-flaps were more likely to have multiple complications (\( p = 0.02 \)). Interestingly, both groups underwent a similar number of revision surgeries (\( p = 0.29 \)). Looking at the irradiated flaps only, internal mammary node (IMN) (IRR 3.80, CI 1.32-10.97; \( p = 0.01 \)) irradiation was the only factor predictive of complications.

Conclusions: Immediate autologous reconstruction may be safely performed prior to PMRT. However, additional counseling is warranted if IMN irradiation is likely, as it may result in an increased risk of complications.
Abstract #14: Predictors of Access to General Surgical Care at Urgent Care Centers in the United States

Authors: Walter R. Hsiang, Alison Mosier-Mills, Grace Jin, Michael Najem, Laurie Yousman, Akshay Khunte, Siddharth Jain, Howard P. Forman, Daniel Wiznia, Kevin M. Schuster

Background: Over the last decade, visits to urgent care centers (UCCs) have doubled as patients increasingly seek immediate and affordable healthcare. However, access to urgent care, particularly for disadvantaged patients, has remained unexplored. Our study identified predictors of Medicaid acceptance for patients seeking hernia care at UCCs.

Methods: Using a secret shopper methodology, we called UCCs across all 50 states pretending to be Medicaid patients seeking urgent care for a painful hernia. Primary outcome measure was Medicaid acceptance. Center-specific and community-level demographic information was collected for each UCC, including the category of UCC, accreditation, and UCC zip code’s population/income. Multivariate analysis of Medicaid acceptance was performed. Additionally, we evaluated whether proximity to a teaching hospital or state Medicaid reimbursement rate affected Medicaid acceptance.

Results: Of 1,245 UCCs contacted, 982 (79%) accepted Medicaid. Medicaid acceptance was higher at academic UCCs (OR 15.09, 95% CI 2.04-111.59, p<0.0001) compared to independent UCCs. Joint Commission-accredited UCCs were more likely to accept Medicaid (OR 4.81, 95% CI 1.47-15.72, p<0.0001). UCCs located in wealthier zip codes were less likely to accept Medicaid (OR 0.99, 95% CI 0.98-0.99, p=0.013). UCCs located within 5 miles of a teaching hospital were less likely to accept Medicaid than those located further away (OR 0.72, 95% CI 0.53-0.99, p=0.041). More UCCs accepted Medicaid in states with higher Medicaid reimbursement rates (Beta=0.30, RSquare=0.09, p=0.039).

Conclusion: Numerous center-specific and community-level variables affect Medicaid patients’ ability to access hernia care and possibly all medical and surgical care at UCCs across the United States. Additionally, UCCs near teaching hospitals were less likely to accept Medicaid patients, and UCCs in states with lower state Medicaid reimbursement rates were less likely to accept Medicaid. Future investigation is necessary to understand the impact of UCCs on referral rates, safety net systems, and delays to care.

Table: Center-specific and community-level characteristics impacting Medicaid acceptance

<table>
<thead>
<tr>
<th>Classification of center</th>
<th>Univariate odds ratio (95% CI)</th>
<th>P value</th>
<th>Multivariate odds ratio (95% CI)</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Independent (n=634)</td>
<td>Ref</td>
<td>&lt;0.0001</td>
<td>Ref</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Primary Care/UCC (n=198)</td>
<td>1.37 (0.95, 1.99)</td>
<td>0.091</td>
<td>1.25 (0.86, 1.82)</td>
<td>0.25</td>
</tr>
<tr>
<td>Health Network/Hospital System (n=369)</td>
<td>5.64 (3.66, 8.71)</td>
<td>&lt;0.0001</td>
<td>4.82 (3.10, 7.50)</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Academic (n=44)</td>
<td>38.14 (2.34, 622.59)</td>
<td>&lt;0.0001</td>
<td>15.09 (2.04, 111.59)</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Joint Commission accredited</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>No</td>
<td>Ref</td>
<td>&lt;0.0001</td>
<td>Ref</td>
<td>4.81 (1.47, 15.72)</td>
</tr>
<tr>
<td>Yes</td>
<td>9.72 (3.06, 30.91)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Urgent Care Association accredited</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>No</td>
<td>Ref</td>
<td>0.1905</td>
<td>Ref</td>
<td>2.00 (1.12, 3.56)</td>
</tr>
<tr>
<td>Yes</td>
<td>1.44 (0.83, 2.51)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Population per UCC (thousands)</td>
<td>0.99 (0.98, 1.00)</td>
<td>0.1069</td>
<td>1.01 (1.00, 1.02)</td>
<td>0.1104</td>
</tr>
<tr>
<td>Household median income per UCC (thousands)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>0.99 (0.98, 0.99)</td>
<td>&lt;0.0001</td>
<td>0.99 (0.98, 0.99)</td>
<td>0.013</td>
</tr>
</tbody>
</table>
Abstract #15: Survival and adverse effects of sequential IL-2 and immune checkpoint blockade in patients with cutaneous metastatic melanoma

Authors: Melinda Wang BA, Nicholas Klemen MD, Tristen Park MD, Sarah Weiss MD, James Clune MD, Harriet Kluger MD, Mario Sznol MD, Charles Cha MD FACS, Kelly Olin MD FACS

Background: Administration of interleukin-2 (IL-2) has the potential to alter immune homeostasis, such as by promoting the proliferation of regulatory T cells. Whether such alterations modulate the efficacy or toxicity of subsequent treatment with checkpoint inhibitors (CPI) is unknown. We sought to determine if there was any evidence of altered treatment efficacy, toxicity or peripheral lymphocyte counts in patients with sequential IL-2 and CPI treatment.

Methods: We performed a retrospective single institution 1:2 matched-pair study. We identified patients with stage IV cutaneous melanoma who were treated sequentially with IL-2 and CPI (including anti-CTLA-4, anti-PD-1 or anti-PD-L1 antibodies) between 2007 and 2019 (IL-2 group). Our matched control population was only treated with CPI (control group); we matched for M stage of disease, time between initial diagnosis and metastatic disease, and age. We analyzed overall survival (OS) after CPI treatment for 5 years using the log-rank method. We measured the incidence of immune-related adverse events (irAEs) after CPI, and quantified peripheral blood populations of lymphocytes, neutrophils, eosinophils, and monocytes before and after CPI treatment.

Results: We identified 21 patients who were treated with IL-2 and CPI sequentially. They were matched with 42 control patients who did not receive IL-2. Patient characteristics are shown in Table 1. The IL-2 and control groups had similar median overall survival after CPI treatment (41.3 months versus 35.8 months, p = 0.907), with similar five-year survival. However, patients in the IL-2 group had fewer grade 1 & 2 irAEs than control patients (28.6% vs. 64.2%, p = 0.015) but similar grade ≥3 irAEs (0.0% vs. 16.7%, p = 0.085, including pancreatitis (1), hypopituitarism (1), hyperthyroidism (1), abdominal pain (1), transaminitis (2), and colitis (1)). Comparison of peripheral blood populations before and after CPI treatment showed monocytes were elevated in the IL-2 group before CPI treatment, but no other differences were present.

Conclusion: Sequential treatment with IL-2 and CPI did not result in different overall survival or significant alterations in circulating peripheral blood lymphocytes. There were however fewer irAEs in the IL-2 group. Further investigation into the role of IL-2 in immune homeostasis, adverse events, and as an adjunct to CPI therapy is warranted.

Table 1. Clinicopathologic differences between IL-2 and control groups

<table>
<thead>
<tr>
<th>Factor</th>
<th>Control group (n = 42)</th>
<th>IL-2 group (n = 21)</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (mean, SD)</td>
<td>60.55 (14.09)</td>
<td>55.37 (11.73)</td>
<td>0.145</td>
</tr>
<tr>
<td>Gender</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Male</td>
<td>16 (38.1%)</td>
<td>7 (33.3%)</td>
<td>0.786</td>
</tr>
<tr>
<td>Female</td>
<td>26 (61.9%)</td>
<td>14 (66.7%)</td>
<td></td>
</tr>
<tr>
<td>Stage of Disease</td>
<td></td>
<td></td>
<td>1.000</td>
</tr>
<tr>
<td>M1a</td>
<td>8 (19.0%)</td>
<td>4 (19.0%)</td>
<td></td>
</tr>
<tr>
<td>M1b</td>
<td>6 (14.3%)</td>
<td>3 (14.3%)</td>
<td></td>
</tr>
<tr>
<td>M1c</td>
<td>18 (42.9%)</td>
<td>9 (42.9%)</td>
<td></td>
</tr>
<tr>
<td>M1d</td>
<td>10 (23.8%)</td>
<td>5 (23.8%)</td>
<td></td>
</tr>
<tr>
<td>CNS disease before CPI therapy</td>
<td>10 (23.8%)</td>
<td>5 (23.8%)</td>
<td>1.000</td>
</tr>
<tr>
<td>Disease Status</td>
<td></td>
<td></td>
<td>0.246</td>
</tr>
<tr>
<td>DOD</td>
<td>17 (40.5%)</td>
<td>14 (66.7%)</td>
<td></td>
</tr>
<tr>
<td>AWD</td>
<td>12 (28.6%)</td>
<td>3 (14.3%)</td>
<td></td>
</tr>
<tr>
<td>NED</td>
<td>12 (28.6%)</td>
<td>4 (19.0%)</td>
<td></td>
</tr>
<tr>
<td>DOC</td>
<td>1 (2.4)</td>
<td>0 (0.0%)</td>
<td></td>
</tr>
<tr>
<td>Time from Diagnosis to CPI (mean, SD)</td>
<td>77.98 (210.17)</td>
<td>51.24 (42.34)</td>
<td>0.444</td>
</tr>
<tr>
<td>Time from Diagnosis to Advanced Disease</td>
<td>42.48 (44.10)</td>
<td>43.62 (42.98)</td>
<td>0.646</td>
</tr>
<tr>
<td>Checkpoint Inhibitor</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>CTLA-4</td>
<td>8 (19.0%)</td>
<td>5 (23.8%)</td>
<td>0.745</td>
</tr>
<tr>
<td>PD-1/PDL-1</td>
<td>13 (31.0%)</td>
<td>5 (23.8%)</td>
<td>0.768</td>
</tr>
<tr>
<td>Combination</td>
<td>21 (50.0%)</td>
<td>10 (47.6%)</td>
<td>1.000</td>
</tr>
</tbody>
</table>
Abstract #16: Comprehensive Craniomorphometric Analysis of 167 Patients with Metopic Craniosynostosis

Authors: Ludmila Chandler BS, Kitae Eric Park BA, Omar Allam BS, Mohammad Ali Mozaffari MD, Sumun Khetpal BS BA, John Smetona MD, Navid Pourtaheri MD Ph.D, Xiaona Lu MD, John A. Persing MD, Michael Alperovich MD

Background: Metopic craniosynostosis is the second most common form of single suture synostosis, associated with a characteristic trigonocephalic head shape. Due to physiologic closure of the metopic suture in infancy, controversy persists regarding the most accurate method to diagnose and assess severity. The goal of this study was to compare and validate previously described and newly developed measurements of severity for trigonocephaly. Additionally, a new severity scale was proposed to help distinguish between severe and non-severe cases of trigonocephaly and to guide clinical decision making.

Methods: Morphometric analysis using Materialise Mimics was performed on preoperative CT scans of infants with metopic synostosis and control age matched infants. Measurements included endocranial bifrontal angle (EBF), adjusted endocranial bifrontal angle (aEBF), frontal angle, posterior angle of the anterior cranial fossa, metopic index, horizontal orbital cone angle, temporal depression angle, foramen ovale midline distance, and bitemporal/biparietal distance ratio. Volumetric and area analyses of the frontal cranium were conducted to determine the degree of restriction in the metopic cohort. Results were analyzed using an independent sample t-test, Pearson’s correlation coefficient, and receiver operating characteristic (ROC) curve analysis.

Results: Analyses were performed for 167 patients with metopic synostosis, mean age of 7.2±4.9 months, and compared to 44 control subjects, mean age of 7.6±7.6 months. The EBF, aEBF, frontal coronal angle, anterior fossa angle, horizontal cone angle, and bitemporal/biparietal ratio were all significantly smaller in the metopic cohort compared to the control cohort (p<0.05 for all). Contrarily, measurements such as the metopic index, temporal depression angle, and foramen ovale to midline distance were not significantly different from the control cohort. Metopic skulls demonstrated a significantly decreased anterior cranium area (average 2466.12 mm², p<0.001) and significantly increased anterior-posterior (AP) length (average 4.00mm, p=0.003) and cranio-caudal height of the anterior cranium (average 6.41mm, p=0.01) compared to normal skulls. The frontal angle significantly correlated with the increases in vertical height and AP length. The aEBF significantly correlated with only the AP length. Other measurements did not demonstrate significant correlation with the changes in anterior calvarium dimensions. ROC curve analysis identified a frontal angle of 101.3 degrees as the threshold between operated metopic synostosis and normal skulls.

Conclusions: In the largest radiographic series of metopic synostosis patients to date, this study examined the validity and concordance of measurements for severity of metopic craniosynostosis. Angles such as the EBF, aEBF, frontal angle, anterior fossa angle, horizontal cone angle, and bitemporal/biparietal distance ratio were significantly smaller in the metopic cohort compared to control skulls. The frontal angle represents the best measure of metopic severity as it best correlated with compensatory changes in the anterior cranium due to synostosis. A frontal angle of 101.3 degrees can be used to distinguish between severe and non-severe cases of metopic synostosis. Furthermore, the bitemporal/biparietal distance ratio, metopic index, cranial volumes, cranial base structures, and orbital structures should be reconsidered as measures of metopic severity as they are either nonconcordant with the anterior-cranium compensatory changes or not significantly different from the control cohort.
Abstract #17: Prognostic Factors in Determining the Recurrence of Desmoplastic Melanoma

Authors: Raysa Cabrejo MD, Sarah Persing MD, Wael Ibrahim MD, Anjela Galan MD, Stephan Ariyan MD, Kelly Olino, MD, James Clune MD

Introduction: Desmoplastic melanoma is a rare subclass of melanoma with unique clinical implications. Staging in melanoma relies heavily on sentinel lymph node biopsies. However, the predictive value of sentinel node biopsies in desmoplastic melanoma has been difficult to determine due to small studies with short follow-up. Therefore, staging desmoplastic melanoma and predicting those that may benefit from upfront check point inhibitor therapy is difficult. The purpose of this study is to identify patients that are likely to have recurrence utilizing pathological characteristics, mutation analysis and sentinel lymph node biopsies and clinical/demographic characteristics.

Methods: From 1998 to 2018, 147 patients with desmoplastic melanoma underwent treatment at Yale New Haven Health System. Of these, 94 patients had sentinel lymph node biopsies. The patients were divided into pure and mixed desmoplastic melanoma, 66% and 34%, respectively. All dermatopathology reports, sentinel lymph node biopsy results, demographics, and clinical outcomes were recorded for all patients. A binomial logistic regression was performed with the coefficients of depth of the initial pathology, age, and the number of positive nodes from the sentinel lymph node biopsy. All statistics were done utilizing STATA 10.

Results: Desmoplastic melanoma had a recurrence rate of 17% in our cohort. The average age of diagnosis was 69.9 (±14.2) years. The average depth of the desmoplastic melanoma was 4.4 (±4.2) mm. Only 6% of the patients had a positive sentinel lymph node biopsy; 78% of them had complete lymphadenectomies subsequently. For pure desmoplastic melanoma, the binomial logistic regression calculated an odds ratio of recurrence for depth of 1.3 (p=0.04, CI: 1.01-1.61), for age of 1.07 (p=0.04, CI: 1.01-1.15), and for a positive lymph node of 0.43 (p=0.65, CI: 0.01-15.1). For mixed desmoplastic melanoma, the binomial logistic regression calculated an odds ratio of recurrence for a positive lymph node of 43.7 (p=0.02, CI: 1.78-65.93).

Conclusions: In this study, we study pathological characteristics, sentinel lymph node biopsies, and overall clinical outcomes. For desmoplastic melanoma, the division of pure and mixed demonstrated different characteristics important in determining recurrence. For mixed desmoplastic melanoma, a positive sentinel lymph biopsy was a significant factor in determining recurrence, similarly to other cutaneous forms of melanoma. For pure desmoplastic melanoma, age and depth were the most important factors in determining recurrence. However, unlike most cutaneous melanomas, sentinel node biopsy was not predictive of recurrence. Currently we are investigating specific mutations in “pure” desmoplastic melanoma that may better predict recurrence as we are unable to rely on traditional sentinel node biopsies in this subtype.
Abstract #18: Racial Disparities in Surgical Outcomes for Benign Thyroid Disease

Authors: Richard C. Maduka MD, Courtney E. Gibson MD, Alexander S. Chiu MD, Raymond A. Jean MD, Noel Wills-Johnson, Sara Abou-Azar MD, Kristen Oliveira MD, Vanita Ahuja MD

Introduction: Surgery for benign thyroid disease encompasses a significant proportion of endocrine surgery operations. While racial disparities in outcomes of surgery for thyroid cancer has been proven, disparities for benign disease have not been previously characterized. We hypothesize that minority groups have higher incidence of post-operative complications following total and partial thyroidectomy for non-malignant disease.

Methods: All adult patients (>17 years) undergoing thyroid surgery for an indication other than malignancy were identified in the NSQIP Thyroidectomy targeted database between 2016-2017. Surgical indications included Graves’ disease, goiter, adenoma, and “other benign nodule” (Hashimoto’s thyroiditis, hyperplastic nodule, colloid nodule, pseudonodule, trabecular adenoma). Primary outcomes of interest included rate of neck hematoma, recurrent laryngeal nerve (RLN) injury, and clinically significant hypocalcemia within 30 days. Univariate and multivariate logistic regression models were performed to analyze the association between these complications and patient race. Multivariate models controlled for patient age, gender, indication for surgery, history of neck surgery, ASA class, and type of operation (partial thyroidectomy, total thyroidectomy, or thyroidectomy with extended dissection).

Results: A total of 6,817 patients were identified in the NSQIP database, of which 55.0% were non-Hispanic white, 20.1% were black, 4.6% Hispanic, 4.2% Asian, and 16.2% other/unknown. The most common indication for surgery was goiter (65.2%), followed by adenoma (11.2%), other benign nodule (10.2%), Graves’ disease (9.7%), and severe goiter (3.8%). Overall, 2.0% of patients had a postoperative neck hematoma, 5.2% had RLN injury, and 4.9% had significant hypocalcemia. Controlling for demographic and clinical factors, black patients were associated with greater odds of neck hematoma (OR 2.32, 95% CI 1.51-3.55) and RLN injury (OR 1.97, 95% CI 1.53-2.55) compared to white patients. Asian patients also had significantly greater odds of RLN injury (OR 1.88, 95% CI 1.15-3.06) compared to white patients. Hispanic patients had similar outcomes to white patients; however, they trended towards greater odds of postoperative hypocalcemia (OR 1.42, 95% CI 0.89-2.28).

Conclusion: Minority patients are more likely than White patients to have significant postoperative complications following surgery for benign thyroid disease. This disparity in outcomes is similar to findings of malignant thyroid disease, indicating broader racial disparities in the surgical treatment of endocrine disease.

Figure 1: Complication Rate by Race in Surgical Outcomes for Benign Thyroid Disease

- White
- Black
- Hispanic
- Asian

*P < 0.05 compared to White
Abstract #19: Are women colorectal surgeons overrepresented in treatment of pelvic floor disorders?

Authors: Vanessa Baratta, Vadim Kurbatov, Haddon Pantel

Purpose/Background
Graduating medical school classes consist of approximately half women, yet women remain underrepresented in surgical fields. A multitude of contributing factors have been examined, some involving overt gender bias while, some involving a more implicit bias. The purpose of this study was to examine if within the field of colorectal surgery, there is a gender bias towards women surgeons preferentially treating pelvic floor disorders. We hypothesized that women are overrepresented in treatment of pelvic floor diseases compared to other colorectal conditions.

Methods/Interventions
We compared the percent of women colorectal surgeons in the United States to the percent of women performing pelvic floor research. As a control group, we examined the percent of women performing research in benign colorectal diseases, a field we hypothesized would have no potential gender bias. The gender distribution of Colorectal Surgeons in the United States was calculated utilizing name to gender inference analysis software on the current American Society of Colon and Rectal Surgeons (ASCRS) membership directory. The gender distribution of surgeons participating in the treatment of pelvic floor disorders and benign colorectal disease was calculated through a retrospective review of the ASCRS Annual Scientific Meeting Program from 2016 to 2019. Name to gender inference analysis software was used to assign a gender to each cited author’s name in abstracts for pelvic floor podium and poster presentations. This same method was employed for the benign colorectal disease control group, but only for the 2019 annual meeting. Using a Chi squared test, statistical comparisons were made between observed representation of women based on ASCRS Annual Scientific Meeting abstracts, compared to expected representation of women based from ASCRS membership.

Results/Outcomes
A total of 2,568 names were analyzed from the current ASCRS directory with 30% women. Review of abstracts in the pelvic floor section from 2016 to 2019 yielded 247 cited names, 53% women. A chi-square test was significant with women more likely to be involved in pelvic floor care compared to men, X² (1, N = 2815) = 52.5, p < 0.00001. As a control, abstracts for benign colorectal podium and poster presentations from the 2019 annual meeting yielded 254 authors of which 35% were women. A chi-square test did not demonstrate any difference between men and women being involved in benign disease, X² (1, N = 2822) = 1.9, p = 0.2.

Conclusion/Discussion
Women are involved in the treatment of pelvic floor disorders at a higher rate compared to the gender distribution of colorectal surgeons in the United States. Additional work is needed to determine why this disproportionate representation exists, as it may be due to bias within our field towards women participating in certain aspects of care or may be due to patient and medical legal factors.
Abstract #20: Novel Technique for Dorsal Nasal Augmentation Utilizing Crushed Septal Cartilage and Autologous Fat

Authors: Arvind Gowda MD, Eric Park BS, Omar Allam BS, Karl Bruckman MD DMD, Navid Pourtaheri MD PhD, Derek Steinbacher MD DMD FACS

Purpose: Cartilage grafts are widely accepted for dorsal onlay in primary and revisionary rhinoplasty. Controversy exists regarding the best technique for long term graft retention and optimal aesthetic outcome. The aims of this study were to describe a novel technique for dorsal nasal augmentation utilizing crushed septal cartilage mixed with autologous fat, to objectively assess long-term graft retention and evaluate patient reported outcomes.

Methods: A retrospective study of all patients who underwent primary open rhinoplasty and dorsal onlay grafting with the senior authors technique was performed. Three-dimensional photographic images were acquired. Graft retention was calculated by global registration and volumetric subtraction of images acquired at two separate time points, both greater than 12 months postoperatively. Patients completed the rhinoplasty module of the Aesthetic Face-Q to assess satisfaction.

Results: Fourteen patients were included in the study. Mean intermediate follow up photographs were taken at 17.8 months (Range: 11.4 – 40.5) and mean long-term follow up photographs were taken at 28.9 months (Range: 19.1 – 56.8). In this interval approximately 0.27 ± 0.53 cc of graft reabsorption occurred. Patients reported a high degree of satisfaction with the appearance of their face 66.0 ± 40, nasal appearance 70.4 ± 39, nostrils 78.0 ± 39, psychological functioning 72.6 ± 43, and social functioning 70.0 ± 42. There were no major or minor complications related to the dorsal onlay graft. One patient underwent reoperation for vestibular stenosis.

Conclusion: Crushed septal cartilage mixed with autologous fat is a viable option for dorsal augmentation and is associated with a high degree of graft retention and patient satisfaction.
Abstract #21: Trends and Outcomes of TEVAR with Cervical Debranching

Authors: Kirthi S. Bellamkonda MSc, Sameh Yousef MD, Naiem Nassiri MD, Alan Dardik MD PhD, Raul Guzman MD, Arnar Geirsson MD, Cassius I. Ochoa Chaar MD

Introduction: TEVAR has become the preferred surgery for pathology of the descending thoracic aorta. Cervical debranching in the form of carotid-subclavian bypass or transposition (CSBT) and carotid-carotid bypass (CCB) enables the use of TEVAR for treatment of more complex anatomy involving the arch. This study examines the impact of concomitant cervical bypasses on the perioperative outcomes of TEVAR.

Method: The ACS-NSQIP files (2005-2017) were reviewed. Based on CPT codes, all patients undergoing TEVAR were identified and were divided into 3 groups: TEVAR, TEVAR with 1 bypass (CSBT or CCB), and TEVAR with 2 bypasses (CSBT and CCB). Patient characteristics and peri-operative outcomes of the 3 groups were compared. Multivariable analysis was performed to determine factors associated with mortality.

Results: There were 3,291 TEVAR and 10% had concomitant debranching (1 bypass = 9%, 2 bypasses = 1%). The frequency of debranching increased from 3.4% to 10.9% (P =.01) during the study period. There were significant differences between the 3 groups in sex, age, smoking, urgency of surgery, and anesthesia technique. Patients undergoing TEVAR with cervical debranching had significantly higher morbidity, longer operating time, and longer hospital stay compared to TEVAR alone. The mortality of TEVAR with 2 bypasses (22.6%) was significantly higher than TEVAR alone (7.5%), and TEVAR with 1 bypass (6.8%) (P<.01). A subgroup analysis of patients undergoing TEVAR with 1 bypass showed no significant difference in mortality between TEVAR + CSBP (6.5%) vs TEVAR + CCB (8.8%) (P=.61). Multivariable analysis showed that TEVAR with 2 bypasses was associated with significantly increased mortality compared to TEVAR alone (OR = 0.23 [CI 0.09-0.57]) and TEVAR with 1 bypass (OR = 3.5 [1.27-9.71]). Age (OR = 1.74 [1.42-2.13]), dependent functional status (OR = 1.48 [1.00-2.19]), dialysis (OR = 2.61 [1.57-4.33]), and emergent status (OR = 3.65 [2.72-4.89]) were also associated with mortality.

Conclusion: TEVAR with concomitant cervical debranching is being increasingly used to treat complex aortic pathology and is associated with significantly worse outcomes than TEVAR alone. As fenestrated endovascular technology to treat the aortic arch emerges, the outcomes of open surgical debranching in this study constitute an important benchmark for comparison.

Table 1. Post-operative outcomes

<table>
<thead>
<tr>
<th>Outcomes</th>
<th>TEVAR only N=2,979 (%)</th>
<th>TEVAR + 1 bypass N= 281 (%)</th>
<th>TEVAR + 2 bypasses N= 31 (%)</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>Unplanned intubation</td>
<td>189 (6.3)</td>
<td>21 (7.5)</td>
<td>8 (25.8)</td>
<td>&lt;0.01*</td>
</tr>
<tr>
<td>Failed weaning from ventilator</td>
<td>205 (6.9)</td>
<td>22 (7.8)</td>
<td>9 (29)</td>
<td>&lt;0.01*</td>
</tr>
<tr>
<td>Cardiac arrest</td>
<td>100 (3.4)</td>
<td>12 (4.3)</td>
<td>3 (9.7)</td>
<td>0.123</td>
</tr>
<tr>
<td>Bleeding</td>
<td>583 (19.6)</td>
<td>68 (24.2)</td>
<td>15 (48.4)</td>
<td>&lt;0.01*</td>
</tr>
<tr>
<td>Renal failure</td>
<td>33 (1.1)</td>
<td>1 (0.4)</td>
<td>0 (0)</td>
<td>0.410</td>
</tr>
<tr>
<td>Sepsis</td>
<td>130 (4.4)</td>
<td>11 (3.9)</td>
<td>2 (6.4)</td>
<td>0.790</td>
</tr>
<tr>
<td>Stroke</td>
<td>90 (3)</td>
<td>21 (7.5)</td>
<td>4 (12.9)</td>
<td>&lt;0.01*</td>
</tr>
<tr>
<td>Any morbidity</td>
<td>1,177 (39.5)</td>
<td>135 (48)</td>
<td>24 (77.4)</td>
<td>&lt;0.01*</td>
</tr>
<tr>
<td>Overall Mortality</td>
<td>224 (7.5)</td>
<td>19 (6.8)</td>
<td>7 (22.6)</td>
<td>&lt;0.01*</td>
</tr>
<tr>
<td>Re-admission</td>
<td>30 (2.8)</td>
<td>1 (1)</td>
<td>1 (7.1)</td>
<td>0.249</td>
</tr>
<tr>
<td>Hospital length of stay</td>
<td>7.9 ± 0.2</td>
<td>9 ± 0.6</td>
<td>12.6 ± 2.3</td>
<td>0.492</td>
</tr>
</tbody>
</table>

SEM= Standard Error of the Mean.
*=Post hoc analysis showing statistical difference between the groups, TEVAR only 1, TEVAR + 1 bypass2, TEVAR + 2 bypasses3.
Abstract #22: Safety of Perioperative Cerebrospinal Fluid Drain as a Protective Strategy During Descending and Thoracoabdominal Open Aortic Repair

Authors: Mohamed Abdelbaky MD, Dimitra Papanikolaou MD, Maryam Shaikh, Jinlin Wu MD, Mohammad A. Zafar MBBS, Leon Freudzon MD, Hesham Ellauzi MD, Ayman Saeyeldin MD, Thais Faggion Vinholo BS MSc, Joelle Buntin MSN RN RN-BC, Bulat A. Ziganshin MD PhD, Sandip Mukherjee MD, John A. Elefteriades MD PhD(hon)

Objective
Despite advances in surgical techniques, paraplegia continues to be one of the most feared complications of open descending (DTAA) and thoracoabdominal aortic aneurysm (TAAA). Perioperative cerebrospinal fluid drainage (CSFD) is one of few acknowledged strategies for spinal cord protection. We present our experience with routine application of CSFD during open repair.

Methods
We retrospectively reviewed 100 patients with DTAA and TAAA who underwent CSFD insertion prior to open repair between 2006 and 2017. All CSFD were inserted by cardiovascular anesthesia team. The goal was to keep ICP <10 mm Hg during the surgical procedure through draining CSF at a rate of 20-30 cc ml /hour. Postoperatively, CSFD was set to keep the lumbar pressure at 5-12 mm Hg to reduce the risk of postoperative paraplegia. This was part of our standard cord-protection regimen.

Results
Mean patient age was 65.4±11.7, and 60 (60%) were male. CSFD was successfully inserted in all patients. Beside CSFD, other intraoperative protection strategies included left atrial- femoral bypass in 96 (96%), preoperative radiological detection of anterior spinal artery (ASA) in 67 (67%), and motor evoked potential monitoring in 67 (67%). Mean hospital stay after surgery was 11.9±11.8 days and hospital mortality was 6%. Postoperative transient paresis was observed in 4 patients (4%), and permanent paraplegia in 2 patients (2%). CSFD related complications were reported in 14 patients (14%). Complications included persistent CSF leakage, blood tinged CSF with and without intracranial hemorrhage and spinal cutaneous fistula in 7 (7%), 9 (9%), 1 (1%) respectively (Table 3). Long-term survival was excellent (70% at 10 years).

Conclusion
CSFD is a safe practice when applied routinely as an adjunct strategy to prevent paraplegia when in surgical management of DTAA and TAAA. We feel this contributed to good early and late survival.

Kaplan-Meier analysis of survival for the overall cohort
Abstract #23: “Retrosternal Sponge” Re-Entry Technique Avoids Pre-Sternotomy Cardiopulmonary Bypass in Complex Redo Cardiac Surgery

Authors: Stefanie C. Rohde, Mohammad A. Zafar, Bulat A. Ziganshin, John A. Elefteriades

Objective: To assess the safety of the “retrosternal sponge” technique for re-sternotomy. In this technique, we divide the outer table by oscillating saw and inner table by curved Mayo scissors; however, we always “lead” inner table division by first threading a tape sponge under each cutting zone from xiphoid to sternal notch. This permits avoidance of pre-sternotomy cardiopulmonary bypass.

Methods: We queried one surgeon’s consecutive re-sternotomy cases over five years. We retrospectively assessed perioperative outcomes by record review.

Results: We included 80 “retrosternal sponge” re-sternotomy cases (57.5% male, mean age 61.4±13.7 years [range 24-88], mean time from previous sternotomy 13.3±9.9 years [range 0.4-56]). Indications were for aortic surgery (n=58) or other cardiac surgery (n=22). Re-sternotomy was carried out without aortic injury or entry into other cardiac chambers in all 80 cases. Five cases were aborted after re-sternotomy, including one for diffuse bleeding after safe re-sternotomy and one after inability to advance the retrosternal sponge. Four cases required post-operative re-exploration for bleeding. Stroke rate was 1.25% (n=1). Thirty-day mortality rate was 3.75% (n=3).

Conclusions: The “retrosternal sponge” re-entry technique is safe and effective, permitting avoidance of the risks of pre-sternotomy cardiopulmonary bypass.

<table>
<thead>
<tr>
<th>Outcome</th>
<th>Indication: Aortic Surgery (n=58)</th>
<th>Indication: Non-Aortic Surgery (n=22)</th>
<th>Total (n=80)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Aortic injury or entry into cardiac chambers during re-sternotomy</td>
<td>0 (0%)</td>
<td>0 (0%)</td>
<td>0 (0%)</td>
</tr>
<tr>
<td>Aborted case</td>
<td>3 (5.2%)</td>
<td>2 (9.1%)</td>
<td>5 (6.25%)</td>
</tr>
<tr>
<td>Post-operative re-exploration for bleeding</td>
<td>4 (6.9%)</td>
<td>0 (0%)</td>
<td>4 (5%)</td>
</tr>
<tr>
<td>Perioperative stroke</td>
<td>1 (1.7%)</td>
<td>0 (0%)</td>
<td>1 (1.25%)</td>
</tr>
<tr>
<td>Death within 30 days</td>
<td>1 (1.7%)</td>
<td>2 (9.1%)</td>
<td>3 (3.75%)</td>
</tr>
</tbody>
</table>

Authors: Makoto Mori MD, Thomas JS Durant MD, Chenxi Huang PhD, Bobak J. Mortazavi PhD, Andreas Coppi PhD, Raymond A Jean MD, Arnar Geirsson MD, Wade L. Schulz MD PhD, Harlan M. Krumholz MD SM

Introduction: Intraoperative data may improve post-operative prediction models. Using the national clinical registry for coronary artery bypass graft (CABG), we evaluated the effect of incorporating intraoperative variables to the existing preoperative model on the predictive performance of the model.

Methods: We used the national Society of Thoracic Surgeons Adult Cardiac Surgery Database between 2014-2016 and analyzed 378,834 isolated CABG cases performed across 1,083 centers. Outcomes included operative mortality, 5 complications, and composite event. We fitted models by LR or XGBoost. For each modeling approach we used preoperative only, intraoperative only, or pre+intraoperative variables, with or without an additional variable selection by support vector classifier. We developed a total of 84 models with unique combinations of the 3 variable sets, 2 variable selection methods, 2 modeling approaches, and 7 outcomes. Each model was tested in 20 iterations of 30:70 random splitting into development/testing samples. Model performances were evaluated using c-statistics, precision-recall curve (AUPRC), Brier score, reliability, and resolution.

Results: The mean patient age was 65.3 years and 24.7% were women. Operative mortality, excluding intraoperative death, occurred in 1.88%. In all outcomes, models using pre+intraoperative variables had better c-statistics compared with respective models using either intraoperative or preoperative variable sets alone. This relationship also held true for Brier score and AUPRC in all outcomes, except for deep sternal infection. XGBoost without prior variable selection had the best c-statistics, Brier score, and AUPRC values in 4 of the 7 outcomes (mortality, renal failure, prolonged ventilation, and composite) compared with LR models with or without variable selection. Risk restratification for mortality showed that LR model underestimated the risk in 11,114 patients (9.8%) and overestimated 12,005 patients (10.6%). In contrast, XGBoost model underestimated the risk in 7,218 patients (6.4%) and overestimated 0 patients (0%).

Conclusions: In isolated CABG, addition of intraoperative variables to preoperative variables resulted in improved predictions of all 7 outcomes. Risk models based on XGBoost may further improve prediction of adverse events to guide clinical care.

Figure: Mortality model performances for 3 metrics

Figure shows mortality model performances. Circled red triangles represent the baseline Society of Thoracic Surgeons model. XGBoost models with pre+intraoperative variables showed best performances.
Abstract #25: Does initial unilateral cleft lip width predict final aesthetic outcome?
Authors: Yang JF, Smetona JT, Harirahan A, Peck CJ, Pourtaheri N, Steinbacher DM

Background/purpose
A natural aesthetic appearance of the lip and a favorable scar are essential goals of cleft lip repair. It seems intuitive that the wider the cleft, the more difficult it is to repair, consequently leading to poorer results. This belief, however, has not been directly examined. The aim of the current study is to evaluate whether a wider cleft lip indeed correlates with poorer aesthetic outcome.

Methods/description
A retrospective cohort study was conducted on 17 consecutive unilateral cleft lip patients who underwent primary repair within a 2-year period by the senior author using a modified fisher technique. Pre-operative molds were taken and cleft width at the white roll was determined. Subjects were divided into three groups: wide complete clefts that underwent lip adhesion before definitive repair (5 patients), wide complete clefts who did not have lip adhesion (6 patients), and incomplete clefts (6 patients).

Patients were followed for at least 12 months, and aesthetic outcomes were rated by 24 blinded observers, including 5 with plastic surgery training and 19 without. Aesthetics were rated on a subjective 7-point likert scale based on seven outcome measures including scar width, shape, contour, overall appearance, and lip contour, fullness, and symmetry.

Results
Patients who initially had wider clefts with lip adhesions had significantly higher aesthetic scores in all scar-related outcomes compared to those who had wide clefts without lip adhesion and those who had incomplete clefts. There was no significant difference in scar aesthetic scores between patients with wide clefts without lip adhesion and incomplete clefts.

While laypeople found that patients with wide clefts and lip adhesions had better lip contour than those with wide clefts without lip adhesions, PRS trained individuals did not. There was no significant difference in lip fullness or lip symmetry between any of the groups.

Conclusions
The current study suggests that consistent results can be obtained despite the width of the cleft, and that the use of a staged lip adhesion approach in wider clefts can be useful for achieving the desired outcome.
Abstract #26: Combined Valve Operations in the Aortic and Mitral Positions With or Without Added Tricuspid Valve Repair

Authors: Thais Faggion Vinholo BS MSc, Makoto Mori MD, Syed Usman Bin Mahmood MBBS, Clancy W. Mullan MD, Gabe Weininger BS, Sameh Yousef MD, Arnar Geirsson MD

Introduction: There is limited clinical evidence on when to address tricuspid regurgitation in patients with aortic and mitral valve disease requiring surgical intervention. In this study, we aimed to investigate the potential added value of performing a tricuspid valve repair concomitantly in patients requiring double valve surgery of the aortic and mitral valves.

Methods: We reviewed 223 cases of multi-valve surgery from 2011 to 2016. In this single-institution series, 190 underwent double valve surgery (DVS) in aortic and mitral positions and 33 had triple valve surgery (TVS) in aortic, mitral, and tricuspid positions. Preoperative and postoperative echocardiograms were evaluated to determine changes in valve function. A logistic regression model was performed to assess relationship of patient comorbidities and type of valve operations to perioperative adverse events.

Results: Mid-term survival was similar between the two groups (p=0.541). Compared to DVS, TVS was not associated with an increased risk of perioperative adverse events, including need for pacemaker or mortality on multivariable analysis. Within the DVS subgroup, 19.8% of patients experienced improvement in tricuspid valve function with decrease in the degree of tricuspid regurgitation within a 6-month postoperative follow-up.

Conclusion: Our study indicates that repairing the tricuspid valve while addressing the aortic and mitral valves does not pose significant additional risk. The observed improvement of the degree of tricuspid regurgitation without tricuspid operation suggests the need to further define subpopulations of patients with multivalvular disease.

Kaplan-Meier curve showing mid-term survival following DVS (blue) and TVS (red). Log-rank, p=0.541.
Abstract #27: Neurologic functional connectivity in unilateral coronal craniosynostosis: a side-based comparison

Authors: Anusha Singh BS, Kitae E. Park BA, Cheryl Lacadie BS, Omar Allam BS, John Smetona MD, Michael Alperovich MD MSc, John A. Persing MD

Introduction
Unicoronal synostosis has been associated with impaired reading, language, and social function. Functional MRI (fMRI) can evaluate brain connectivity in targeted brain regions to compare imaging analysis to previously published clinical performance. fMRI was used in this study to compare brain function connectivity in unicoronal synostosis (UCS) and compare outcomes by cerebral dominance (left versus right-sided UCS).

Methods
Twelve adolescents with surgically treated UCS, 7 right-sided and 5 left-sided, were individually matched to age, gender and handedness controls. Resting state fMRI was acquired in a 3T Siemens TIM Trio scanner (Erlangen, Germany). Data was collected with intrinsic connectivity distribution and seed-connectivity analysis with BioImage Suite (Yale School of Medicine). Region of interest (ROI) analysis was performed based on Brodmann’s areas (BA) related to emotional, executive, language, motor and visuo-spatial function, left BA5, 6, 7, 18, 19, 37, 39, and 44. BA5, 6, 7 are areas of the frontal and parietal cortex important for visuomotor coordination and complex movement. BA18, 19 are areas of the occipital lobe related to visual information processing. BA37, 39, and 44 are areas of the fusiform, angular gyri and temporal lobe important for language function. P<0.05 was significant.

Results
Compared to controls, all UCS patients demonstrated decreased connectivity in left BA7, bilateral BA39, and right BA41 (p<0.01), which are areas of the parietal and temporal cortices responsible for vision, language function, and motor coordination. Right UCS patients demonstrated increased connectivity in right BA17, BA18, BA19, BA20, BA36 when compared to controls (p<0.05). In the ROI analysis, right UCS exhibited decreased connectivity between the anterior cingulate cortex and right BA18, 19, and 37 compared to controls (p<0.05). The increased connectivity in BA17-20 (visual processing regions) supports our previous neurocognitive study results of increased visual perception abilities in right UCS patients. The subsequent decreased connectivity between BA18-19 and the anterior cingulate cortex (a section of which is implicated in complex motor coordination) is supported by neurocognitive data that shows decreased visual-motor integration ability in right UCS. This decreased connectivity between the aforementioned areas and the anterior cingulate gyrus despite increased intrinsic connectivity may also imply discordance in connecting emotion and executive function to language and visual information in right UCS patients. Connectivity between the left parahippocampus and right BA36, 37, and 54 was increased (p<0.05). Compared to controls and right UCS, left UCS demonstrated decreased connectivity between left BA6 and left BA17, 18 (p<0.05). Left UCS patients did not demonstrate significantly different intrinsic or seed-based connectivity to right UCS or controls otherwise.

Conclusion
Unilateral coronal synostosis had decreased connectivity and greater potential for neurocognitive dysfunction in regions associated with memory, visual information processing, and motor function. Moreover, left-sided UCS had decreased connectivity in circuits crucial in complex motor movement when compared to right-sided UCS. This study provides data suggestive of long-term sequelae of UCS that varies by sidedness, which may underlie the different phenotypes of neurocognitive impairment found in previous cognitive analyses.
Abstract #28: Impact of Medicaid Expansion Under the Affordable Care Act on Stage at Diagnosis of Breast Cancer

Authors: Justin Le Blanc MD, Danielle Heller MD MHS, Ann Friedrich MD, Donald Lannin MD, and Tristen Park MD

Introduction: Breast cancer remains the most commonly diagnosed cancer among American women, with an estimated 234,190 new cases and 40,920 cancer-related deaths in 2018. The expansion of Medicaid under the Affordable Care Act (ACA) sought to fill gaps in insurance coverage among low-income Americans to allow better access to diagnosis and treatment. While coverage has certainly improved, little is known about the relationship between Medicaid expansion and breast cancer stage at diagnosis across states.

Methods: This was a retrospective review utilizing National Cancer Data Base (NCDB) public benchmark reports via the American College of Surgeons to characterize the relationship of breast cancer stage with race, age, and insurance status over time. Pre-expansion years (2012-2013) were compared with post-expansion years (2015-2016), with use of Kaiser Foundation data to determine which states had expanded Medicaid by 2014. Women living in states that had previously expanded Medicaid coverage before ACA expansion in 2014 were excluded from the analysis (District of Columbia, Delaware, Massachusetts, New York, and Vermont).

Results: Of the 874,903 patients with primary breast cancer, 71,236 were either uninsured or had Medicaid, 27,959 lived in non-Medicaid expansion states and 43,277 lived in expansion states. Expansion states saw a reduction of uninsured patients from 23% to 14% (p<0.00001), while non-expansion states saw no statistically significant change. Additionally, across all races, expansion states saw a reduction in advanced stage disease from 21% to 19% (p=0.00001). The benefit was particularly striking in African American patients, where incidence of advanced disease decreased from 25% to 21% (p<0.01) in expansion states and remained steady at 27% in non-expansion states (p=0.939). Additionally, patients in expansion states under the age of 50 had a statistically significant reduction in late stage disease from 23% to 21% (p<0.01) compared to non-expansion states which remained at 26% (p=0.639). Further analysis demonstrated that the improvement in stage at diagnosis is secondary to a reduction in stage 3 diagnoses.

Conclusion: Expansion of Medicaid after institution of the ACA was associated with reduced incidence of advanced-stage breast cancer. African Americans and patients under the age of 50 experienced particular benefit. While granular data on screening and diagnostic practices are unavailable in this dataset, these data suggest that increasing access to health care resources via insurance coverage alters the distribution of breast cancer stage at diagnosis.
**Abstract #29:** Digital Inference of Immune Microenvironment Reveals Low-Risk Subtype of Early Lung Adenocarcinoma

**Authors:** Vadim Kurbatov MD MHS, Agshin Balayev, Aree Saffarzadeh MD, Danielle Heller MD, Justin Blasberg MD, Daniel Boffa MD, Jun Lu PhD, Sajid Khan MD

**Background:** Classification of lung adenocarcinoma (LUAD) currently relies on the TNM pathological staging system, which cannot fully account for the variability in postsurgery overall survival (OS). Despite the advances in immunotherapy and increased appreciation of the involvement of cancer immune microenvironment (IME) in cancer progression, the contribution of IME to postsurgery LUAD prognosis is not well understood.

**Methods:** We digitally inferred the contribution of 22 immune cell types or activation states to the tumor IME using CIBERSORT (Celltype Identification By Estimating Relative Subsets Of RNA Transcripts) analysis in an exploratory metadataset of 581 patients with early-stage LUAD. Patients were arranged based on similarity in IME using k-means clustering. Relationship to postsurgical OS was tested in univariable and multivariable models using Kaplan-Meier analysis and Cox proportional hazards modeling, respectively. To confirm survival relationships, a support vector machine classifier was constructed from a comparison of low-risk and high-risk IME groups. The classifier was applied to a the Cancer Genome Atlas LUAD validation dataset of 394 patients.

**Results:** Patients with an inferred IME enriched in resting mast cells and depleted of macrophages represented a low-clinical-risk group in both exploratory and validation cohorts.

**Conclusions:** Variability in the digitally inferred composition of the tumor IME contributes to heterogeneity in postsurgical OS. Our data suggest that low inferred macrophage content and inferred resting activation state of intratumor mast cells are associated with improved clinical outcome. Computational inference can be used to define LUAD risk groups and help guide clinical decision making.

![Figure 2](image_url)

**Figure 2.** (A) Heatmap demonstrating 5 patient clusters organized by similarity in the composition of the inferred immune microenvironment (IME). (B) Patients in the low-risk group ($n = 74$) had a median overall survival (OS) of 20.8 years, compared with 5.8 years for patients in the high-risk group ($n = 95$) (log-rank $P < .001$). (C) M0, M1, and M2 Macrophages were inferred to be depleted in the low-risk group ($P < .001$).
Abstract #30: Calling for More Research, Education, and Innovation in Plastic Surgery: A Five-Year Analysis of Physician-Industry Payments Using the Open Payments Database

Authors: Sumun Khetpal BS BA, Elbert Mets BA, Neil Pathak BS, John Persing MD, Michael Alperovich MD MSc

INTRODUCTION: Industry financial relationships represent an important part in plastic surgery practice that have historically been difficult to study. As mandated by the Physician Payments Sunshine Act (PPSA) of 2013, the Open Payments Database (OPD) has increased transparency in physician-industry transactions. However, it remains unclear how industry payments to plastic surgeons have changed in light of this act. Therefore, this study aims to characterize trends in industry payments since passage of this legislation.

METHODS: Using the OPD, industry payments to plastic surgeons from 2014 to 2018 were examined. Median payments in 2015-2018 were compared to those from 2014 for all plastic surgeons, as well as for the top 5% of highest-grossing surgeons and the remaining 95% of surgeons. Payments were further characterized by recipient census region (e.g., Northeast), type of payment (e.g., education), and company. Finally, payments were grouped into five distinct categories (e.g., speaker fees, education, research, innovation, and ancillary) in order to assess distribution.

RESULTS: The median general payment to plastic surgeons increased from $236 in 2014 to $327 in 2018 (p < 0.001). The distribution of general payments was heavily weighted towards the top 5% of highest-grossing plastic surgeons, with this subset of surgeons receiving over 80% of payment volume. Despite this group receiving the majority of industry payments, no significant increase in the median payment to the top 5% of compensated surgeons was seen from 2014 to 2018. However, the remaining 95% of compensated surgeons saw significant increases in median general payments from $222 in 2014 to $294 in 2018 (p < 0.001).

Payments were further analyzed by census region. Surgeons in the South received the greatest number of payments across all five years studied. Considering payment trends within each region, there were significant increases in median general payments in the West, South, and Midwest, but not the Northeast, where there were notable decreases (p < 0.001).

Payment type and company type were also evaluated. Food and beverage represented 82% of the total industry payment value, but only accounted for 10% of total payment volume. On average, the twenty companies which represented the greatest percent of total industry dollars given to plastic surgeons, accounted for 94% of total payment volume, the top 10 companies for 81%, and the top 5 companies for 64%.

In order to further assess distribution, payments were then grouped into five distinct categories (e.g., speaker fees, education, research, innovation, and ancillary). Overall, there was a great skew of percentage of payment volume towards speaker fees (53%), specifically for consulting and non-educational purposes, and for ancillary payments (31%), which include food and beverage, travel and lodging, gifts, and entertainment. In contrast, education, research, and innovation-related payments comprised 3%, 0.6%, and 13% of payment volume respectively.

CONCLUSION: With the increased transparency of industry-to-physician payments brought about by the PPSA, industry payments to plastic surgeons were expected to decrease in value and volume. This study provided a comprehensive analysis of payments, by subtype, regional distribution, and physicians. The main takeaway lies in the heavy skew of payments towards speaker fees and ancillary payments, as opposed to payments within research, education, and innovation. This finding raises questions about the continued influence of physician-industry relationships on clinical practice, and the need for a greater prioritization of research and education to fuel the field of plastic surgery and its advancement.
Abstract #31: Complication Burden and Healthcare resource utilization after pediatric gastrostomy tube placement

Authors: W. W. Fu, N. Munoz, D. Ozgediz, D. Stitelman, R. Cowles, M. Caty, D. Solomon, E. Christison-Lagay

Introduction: Gastrostomy tube (G tube) placement for enteral nutrition is one of the most common procedures performed in the pediatric population. The rate of resource utilization and the care burden of gastrostomy tubes on the healthcare system and families has not been fully characterized.

Methods: This study is a single-center retrospective cohort study of pediatric patients at a tertiary referral children’s hospital. The electronic medical records of all pediatric patients who underwent G tube placement between March 2013 and February 2018 were obtained. Data was manually extracted from chart review and billing records. Data abstraction is ongoing, with results from all patients with at least 5 years of follow-up who underwent G tube placement between March 2013 and December 2015 presented here.

Results: Of the 101 cases reviewed, 17 (60%) were male, 53% were insured by Medicaid; median age at time of placement was 11.3 months (mean 3.4 years) and median weight was 7.7 kg (mean 13 kg). Sixty-three (62.4%) were laparoscopic, 25 (24.8%) were percutaneous endoscopic gastrostomies, and 13 (12.8%) were open. Seventy (70.7%) experienced at least one minor complication (granulation tissue, tube displacement, cellulitis, significant leakage, or failure of gastrocutaneous fistula to close); 9 (8.9%) experienced at least one major complication requiring hospitalization or return to the OR (gastric perforation, tube migration or displacement with inability to replace bedside, tract revision, or gastric mucosa prolapse). Over 267 patient-years, there were 523 inpatient/ED consults or planned surgical clinic visits, and 115 phone calls/emails for medical advice. The median number of outpatient surgical encounters per patient was 3 (range 0-13) and the median outpatient surgical charge per patient was $1,271 (range $0-$7,270). Fourteen patients (13.8%) required more than 10 follow-up surgical consultations, although the majority of these required no intervention.

Conclusion: Gastrostomy tube placement and subsequent minor or major complications can impose a significant resource burden on families and the healthcare system. This burden may be minimized with improved patient and caregiver education, standardized care pathways, more streamlined access to outpatient gastrostomy tube management, and identifying high system utilizers for targeted interventions aimed at optimizing healthcare use.
Abstract #32: Geographic Variations of Surgical Therapy for Hepatocellular Carcinoma in the United States: A SEER-Medicare Study
Authors: En Cheng, MD MSPH, Peiyin Hung MSPH PhD, Shi-Yi Wang MD PhD

Introduction: Surgical therapy for hepatocellular carcinoma (HCC) contains transplantation, surgical resection, radiofrequency ablation, and percutaneous ethanol injection, and it is generally considered as curative treatment for HCC patients, particularly at early stage. With the increasing incidence of HCC, it is critical to investigate geographic variations in HCC surgical therapy and their associations with survival among HCC patients.

Methods: Analyzing the Surveillance, Epidemiology, and End Results (SEER)-Medicare database, we identified 6,782 patients with HCC during 2004-2011. We created quartiles by the proportions of patients undergoing surgical therapy per hospital referral region (HRR). Hierarchical Cox proportional-hazards models were used to examine the association between regional surgical therapy patterns and survivals across quartiles.

Results: An average of 16.9% of HCC patients underwent surgical therapy during 2004-2011, varying substantially from 0% to 34.5% across HRRs. Compared to patients residing in the lowest-quartile regions, patients in the highest-quartile regions were more likely to be other races (vs. White or Black), be infected with Hepatitis B, and have more comorbidities. The 5-year survival was 4.7% in the lowest-quartile regions and 11.4% in the highest-quartile regions (P-value <0.001). After controlling for confounders, patients in the highest-quartile regions had a lower risk of mortality (hazard ratio: 0.78; 95% confidence interval: 0.72-0.85).

Conclusions: HCC patients who resided in HRRs with higher proportions of surgical therapy had better survivals. Given its proven survival benefits, prompt clinical and policy actions are needed to reduce variations in the utilization of surgical therapy.

Figure 1. Quartiles of proportions of taking surgical therapy by hospital referral regions
Legend: Darker regions correspond to higher utilization of surgical therapy
Abstract #33: The Unintended Consequences of Non-operative Management for Acute Appendicitis

Authors: K.D. Oliveira, R. A. Jean, R. Maduka, R. Gonsai, A.S. Chiu, V. Ahuja

Introduction:
Appendicitis is common in the US and has traditionally been thought of as a surgical disease. In recent years, this tradition is coming into question, with many recommending non-operative management as a viable alternative to the traditional operative approach. As non-operative management becomes more common, this raises the question of what the unintended consequences of this management paradigm with respect to cost and patient burden are.

Methods:
National Readmissions Database was queried between 2010 to 2014. Patients who were admitted with acute appendicitis between January and June of each year were identified with an ICD-9 code primary diagnosis of acute appendicitis. Patients who underwent appendectomy were compared to those who did not undergo operative intervention. Six-month all-cause readmission rates and aggregate costs between index hospitalization and readmissions were calculated.

Results:
We identified 438,995 adult admissions for acute appendicitis during the study period. Majority of the cases were managed with appendectomy (95.2%). There was a significant increase in the non-operative management of appendicitis, from 3.6% of discharges in 2010 to 6.8% of discharges in 2014 (p-value for trend <0.0001). Discharges receiving non-operative management tended to be older and have greater comorbidities. Furthermore, 43% of non-operative discharges were identified with an associated abscess, in comparison to 10% discharges in the operative cohort (p<0.0001). There was a 59% decreased adjusted odd (OR 0.41, 95% CI 0.39-0.44) of readmission within 6 months among patients receiving appendectomy (readmission rate 7.1%) in comparison to those managed without appendectomy (readmission rate 19.5%; p<0.0001). Despite this, in comparing the aggregate cost of index hospitalizations and readmissions, there was an adjusted $2,881 cost increase associated with appendectomy over non-operative discharge (p<0.0001).

Conclusion:
This study shows that non-operative management is increasing over time. Patients treated with non-operative management may have an increased risk of readmission within 6 months, but average adjusted total costs are reduced by nearly $2900. Despite this decrease in cost, these increased readmission rates shed light on the increased and durable readmission risk incurred by these patients. Given this, it is important that surgeons critically assess patients who are being considered for non-operative management of appendicitis.
Abstract #34: In-transit Merkel Cell Carcinoma: Yale Cancer Center Experience 2002-2019

Authors: Andrew Esposito MD, Daniel Jacobs BA, James Clune MD, Stephan Ariyan MD MBA, Anjela Galan MD, Harriet Kluger MD, Sarah Weiss MD, Kelly Olino MD

Background: Merkel Cell Carcinoma (MCC) is a rare and aggressive skin cancer with a disease specific mortality of 40% and is commonly found in older, white, or immunocompromised patients.1,2 Historically, treatment of in-transit and metastatic MCC was limited to radiation and chemotherapy with short lived therapeutic responses.3 Recently, immune check point inhibitors have shown promise in these patients.4 The incidence is rising making the study of this rare tumor increasingly important. Upwards of 7.5% of patients will develop in-transit disease. 2 We reviewed 17 cases of in-transit disease in a contemporary cohort of patients treated with novel immunotherapeutic agents at a single institution.

Methods: This was a single-center retrospective review of all patients with biopsy confirmed MCC between 2002 and 2019. The medical records system was queried for all ICD-9 and ICD-10 codes corresponding to MCC. Only patients with biopsy confirmed in-transit MCC were included.

Results: Of the 165 patients treated for MCC at Yale-New Haven Hospital 17 (10%) developed in-transit disease. Of these 17 patients, 5 (29%) presented with in transit disease. The median age at diagnosis was 82 years (51-91 years), 11 males (65%), 17 white (100%), and 1 with a history of lymphoma (5%). Surgical resection of the primary lesion was performed in 15 patients (88%). Metastatic disease developed in 5 (29%) patients. The median time from primary tissue diagnosis to diagnosis of in-transit disease was 6 months (0-120 months). The overall mortality was 35% (6/17) with 24% (4/17) disease-specific mortality. Sentinel lymph node biopsy was performed in 7 (64%) patients with an average of 2.3 lymph nodes (LN) evaluated. Positive LN were detected in 2 (29%) who both subsequently underwent complete LN dissection. Radiation therapy was completed in 14 (82%) patients. Immunotherapy was given to 7 patients (41%) for both adjuvant therapy and after recurrence, with 1 receiving Avelumab (anti-PD-L1) and 6 receiving Pembrolizumab (anti-PD-1). Of those patients treated with immunotherapy, 2 (29%) had stage IV, 5 (71%) were stage IIIB, and death occurred in 1/7 (14%) patients. Of those patients not treated with immunotherapy 3 (30%) were stage IIB, and death occurred in 1/7 (14%) patients. For those patients not treated with immunotherapy 3 (30%) were stage IV, 7 (70%) were stage IIIB, and 5/10 (50%) expired. Intra-lesional talimogene laherparepvec (TVEC) in combination with pembrolizumab was used to treat 2 patients refractory to monotherapy with PD-1.

Conclusions: Immune therapy was recently approved for the treatment of metastatic and in-transit MCC and this is an early report of a single institution experience. Given the high mortality associated with in transit disease we report our early results using immunotherapy. We feel the use of systemic immunotherapy holds promise for future treatment and should be considered in the front-line setting. In patients with treatment refractory to standard radiation and systemic immunotherapy approaches, the addition of intralesional T-VEC should be further explored.


Authors: Michael Shang, Cornell Brooks II, Makoto Mori, Julia Chen, Michael Najem, Arnar Geirsson

Introduction: Volume concentration of complex non-cardiac operations to high-volume centers has been observed. However, contemporary trends in market share and outcomes in cardiac surgery are unknown. We examined the relationship between volume concentration and mortality rates for valve surgery and coronary artery bypass graft surgery (CABG) between 2005-2016 in New York (NY) State.

Methods: We analyzed publicly available, hospital-level case volume and risk-adjusted mortality rate (RAMR) between 2005-2016 for isolated coronary artery bypass graft (CABG) and isolated or concomitant valve operations performed in NY. Data were aggregated into 3-year increments. RAMR was calculated from a risk model using 40 patient factors. We identified hospitals in top and bottom volume quintiles for each procedure type and defined market share as the proportion of cases performed by top and bottom quintile hospitals among the statewide case volume for the corresponding time periods. Gaussian regression was used to evaluate the statistical significance of the temporal trend.

Results: 37 of the 40 centers had complete data for the study period. Total CABG procedures performed across all hospitals decreased by 27.6% (33,750 to 24,430 triannual cases) across the study period while valve cases increased by 3.4% (20,574 to 21,280 triannual cases). Percent market share by the top quintile hospitals steadily increased for valve cases from 45.7% to 48.8% (0.31% increase per 3 years, p<0.001) while CABG share remained stable from 35.9% to 35.8% (p=0.47). There were no significant changes in percent market share for the bottom volume quintile for valve or CABG operations. Statewide, mean RAMR for valve procedures decreased by 43.0% over the study period. Mean RAMR for valve procedures performed in the top quintile decreased linearly by 40.1% over the study period (4.0% decline per 3 years), whereas the bottom quintile only decreased by 23.8% (2.3% decline per 3 years).

Conclusions: In NY, over the last decade, highest-volume hospitals increased their market share for valve operations, and their RAMR decreased at a rate higher than that of lowest-volume hospitals. This trend was not observed for CABG procedures. Valve volume is regionalizing and outcome gap is widening between the highest and lowest-volume hospitals. These differential outcomes suggest that volume-based referrals for specialized cardiac procedures may improve surgical mortality.
Abstract #36: Readmissions Following Distal Radius Fracture Open Reduction Internal Fixation: An Analysis of 11,124 patients

Authors: Rohil Malpani, BS, Tamara S. John MD, Michael R. Mercier BA, Taylor D. Ottesen BS, Afamefuna M. Nduaguba MD, Matthew L. Webb MD, Jonathan N. Grauer MD

Introduction: Distal radius fractures (DRF) represent one of the most common types of fracture, comprising 18% of all fractures. In fact, there are over half a million DRFs in the US per year. A subset of these fractures is considered for open reduction and internal fixation (ORIF), with the percentage growing every year, especially for the elderly population. As such, optimizing the outcomes of such procedures is a priority. Prior studies investigating the incidence and risk factors for readmission after ORIF of DRF have used limited patient populations. With readmission becoming an adverse outcome receiving greater attention, understanding the risk factors and reasons for readmission after ORIF of DRFs may aid in patient selection, preoperative optimization, and postoperative management.

Methods: Adult patients undergoing DRF ORIF were identified in the 2011-2016 American College of Surgery- National Surgical Quality Improvement Program (ACS-NSQIP) database. Patient demographics, comorbidity status, hospital metrics, and 30-day perioperative outcomes were tabulated. Readmission, time to readmission, and reason for readmission were assessed. Risk factors for readmission were assessed with multivariate analyses. Reasons for readmission were categorized.

Results: Of 11,124 patients who underwent DRF ORIF, 196 (1.76%) were readmitted. Based on multivariate analysis, predictors of readmission (p<0.05) were: ASA class > 3 (Odds ratio [OR]=2.87), functionally dependent status (OR=2.25), diabetes with insulin use (OR=1.97), and staying in hospital after the index surgery (inpatient procedure, OR=2.04). Perioperative outcomes that were predictors of readmission by chi-squared analysis were: major (36.73% v. 1.13%), minor (12.76% v. 0.87%) and any adverse events (44.39% v. 1.89%) (p<0.001 for each). Of the DRF ORIF readmissions, 59.18% were unrelated to the surgical site, 18.88% were related to the surgical site, and 21.94% were unknown if related to the surgical site. The average time to readmission was 13.42+/–8.77 days (mean +/- standard deviation) and was defined for different etiologies.

Conclusion: The current study found the rate of 30-day unplanned readmissions following ORIF of DRF to be 1.76%. Demographic, comorbid, and perioperative outcome factors predictive of readmission, as well as reason and timing for readmission, were defined. The majority of postoperative readmissions were unrelated to the surgical site and occurred at an average of approximately two weeks postoperatively. Understanding these factors may aid in patient counseling and quality improvement initiatives.

| Table 4: Multivariate analysis of factors associated with readmission after distal radius fracture repair |
|---------------------------------------------------|----------------------|------------------|------------------|
| **Type** | **Total Cases (N= 11,124)** | **Likelihood of Readmission** | **OR** | **95% CI** | **P-value** |
| **Demographic and Comorbidity Variables** | | | | | |
| Male | 1.04 | 0.72–1.51 | 0.833 |
| Age | 1.01 | 1.00–1.02 | 0.219 |
| BMI | 1.00 | 0.98–1.02 | 0.849 |
| ASA Class of 3 or 4 | 2.87 | 2.02–4.08 | <0.001 |
| Functionally Dependent status | 2.25 | 1.28–3.94 | 0.005 |
| Diabetes without Insulin Use | 1.18 | 0.708–2.09 | 0.954 |
| Diabetes with Insulin Use | 1.97 | 1.18–3.29 | 0.009 |
| **Surgical and Post-operative Variables** | | | | | |
| Inpatient Procedure (Length of Stay ≥ 1 day) | 2.04 | 1.47–2.82 | <0.001 |
| Regional Anesthesia | 0.74 | 0.48–1.14 | 0.168 |
| Prolonged Operative Time | 1.13 | 0.77–1.67 | 0.528 |
| Discharged to Home | 0.67 | 0.42–1.08 | 0.099 |

Factors in Model: Age, Sex, BMI, Functional Status (independent vs. dependent), ASA, Hospitalization Status, Anesthesia, Operative time, Discharge Location, Fracture Type.
Abstract #37: Risk factors for progression of claudication to chronic limb-threatening ischemia following revascularization

Authors: Tanner I Kim, Alaa Mohamedali, Gathe Kiwan, Yawei Zhang, Alan Dardik, Raul J Guzman, Cassius Iyad Ochoa Chaar

Introduction: Claudication has a relatively benign natural history associated with low risk of limb loss. Recent reports raise concerns about accelerated disease progression after lower extremity revascularization (LER). This study examines the long-term outcomes and risk factors associated with progression to chronic limb-threatening ischemia (CLTI) after LER for claudication.

Methods: A single center retrospective review of patients undergoing LER for claudication was performed from 2013-2016. Patients were stratified based whether they progressed to CLTI.

Results: There were 448 patients (503 limbs) treated for claudication and 57 (12.7%) progressed to CLTI. Among patients who progressed, 23 developed tissue loss and 34 developed rest pain. Five patients who progressed to rest pain subsequently developed tissue loss. The mean time of progression to CLTI was 1.6 ± 1.5 years after index LER. Patients who progressed to CLTI were more likely to have a history of congestive heart failure and prior open revascularizations compared with those who did not progress. There was no difference in type or level of index revascularization between the two groups and no difference in perioperative complications. Patients who developed CLTI had significantly higher rates of reinterventions and mean number of reinterventions after index LER prior to developing CLTI compared to those who did not progress. Patients who progressed to CLTI had significantly higher rates of major amputation and mortality. (Table) However, the overall major amputation rate of the total patient population was low (1.2%). Multivariable logistic regression demonstrated that history of congestive heart failure (OR:2.8 [1.2-6.7]), stroke (OR:2.5 [1.1-5.9]), prior open procedure (OR:2.8 [1.4-6.0]) and multiple reinterventions (OR:2.9 [1.4-5.7]) were independently associated with progression to CLTI.

Conclusion: Patients with symptomatic atherosclerosis in the coronary and cerebrovascular beds are more likely to have progression of claudication to CLTI after LER. Initial LER for claudication is associated with a low overall rate of major amputation. However, performing multiple reinterventions for claudication is associated with progression to CLTI.

Table. Characteristics and outcomes of patients treated for claudication by progression to chronic limb-threatening ischemia

<table>
<thead>
<tr>
<th></th>
<th>Claudication without progression N=391</th>
<th>Progression to CLTI N=57</th>
<th>P value</th>
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<tbody>
<tr>
<td>FOLLOW UP</td>
<td></td>
<td></td>
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<tr>
<td>Mean follow up time (years)</td>
<td>3.7 ± 1.5</td>
<td>3.6 ± 1.5</td>
<td>0.671</td>
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<tr>
<td>Time to progression to CLTI (years)</td>
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<td>1.6 ± 1.5</td>
<td></td>
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<tr>
<td>Mean number of Reinterventions (prior to CLTI)</td>
<td>1.7 ± 1.0</td>
<td>2.3 ± 1.4</td>
<td>0.004</td>
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<tr>
<td>Number of Reinterventions (prior to CLTI)</td>
<td></td>
<td></td>
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<tr>
<td>1 reintervention</td>
<td>81 (20.7%)</td>
<td>12 (21.05%)</td>
<td>0.001</td>
</tr>
<tr>
<td>≥ 2 reinterventions</td>
<td>60 (15.4%)</td>
<td>20 (35.1%)</td>
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<tr>
<td>LONG-TERM OUTCOMES</td>
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<tr>
<td>Major amputation</td>
<td>0</td>
<td>6 (10.5%)</td>
<td>&lt;0.001</td>
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<tr>
<td>Mortality</td>
<td>64 (16.5%)</td>
<td>16 (28.1%)</td>
<td>0.034</td>
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</table>

CLTI: chronic limb-threatening ischemia, ABI: ankle-brachial index, TASC II: Inter-Society Consensus of the Management of Peripheral Artery Disease
Abstract #38: Airway volume is restricted by subcranial skeletal structural development in Apert syndrome

Authors: Xiaona Lu MD PhD, Antonio Jorge Forte MD PhD, Alexander T. Wilson BS, Kitae Eric Park BA, Omar Allam BS, Mohammad Ali Mozaffari MD, Michael Alperovich MD, Derek M. Steinbacher MD DMD, Nivaldo Alonso MD PhD, John A. Persing MD

Introduction
Apert syndrome is frequently combined with respiratory insufficiency, because of the midfacial deformity which, in turn, is influenced by the malformation of the skull base. Respiratory impairment resulting from Apert syndrome is caused by multilevel limitations in airway space. Therefore, this study evaluated the segmented nasopharyngeal and laryngopharyngeal anatomy to clarify subcranial anatomy in children with Apert syndrome and its relevance to clinical management.

Methods
In total of 112 patients (Apert syndrome, n = 49; control, n = 63) were included, and divided into 4 subgroups by age. All of the computed tomographic scans were obtained from the patients preoperatively. Craniometric data relating to the midface, airway, and subcranial structures were analyzed using Materialise software.

Results
Distance between nasion and posterior nasal spine (PNS) of patients with Apert syndrome was shorter than normal before 6 months of age, but then improved gradually, which is synchronous with the reduced nasal airway volume (47%, p<0.001). There are significantly reduced sphenethmoid-to-PNS, sella-to-PNS, and basion-to-PNS distances initiated prior to 6 months, 6 months-2 years, between 2-6 years of age, by 16% (p=0.003), 15% (p=0.004) and 19% (p=0.002), respectively. The distances between bilateral condylions and gonions were decreased before 6 months of age, by 12% (p<0.001) and 14 percent (p<0.001), respectively. The pharyngeal airway volume surprisingly greater than normal by 114% (p=0.014) prior to 6 months of age, followed by gradual reduction to its volume at 6 years of age, and 45% less than normal (p=0.026).

Conclusion
The airway compromise seen in patients with Apert syndrome is attributable more to the nasal cavity in infants but in the older child, it is the pharyngeal region. The pharyngeal airway restriction is gradually worsened from the anterior to the posterior airway with age, resulting in a significantly reduced volume of the hypopharynx.
Abstract #39: A Craniomorphometric Comparison Analysis Distinguishing Unilateral Lambdoid Craniosynostosis from Deformational Plagiocephaly

Authors: Omar Allam BS, Kitaе Eric Park BA, Maham Ahmad BA, Mohammad Ali Mozaffari MD, John Smetona MD, Navid Pourtaheri MD Ph.D, Xiaona Lu MD, John A. Persing MD, Michael Alperovich MD

Background: Differentiating between positional posterior plagiocephaly (PPP) and unilateral lambdoid craniosynostosis (ULC) has historically been difficult due to overlapping clinical findings. This distinction is important as only ULC requires surgical intervention. Ear position has been shown to be a distinguishing feature in ULC, classically describing a posterior and inferior displacement of the ear on the synostosed side. The aim of this study was to perform an extensive craniomorphometric analysis in the largest series of infants with non-syndromic ULC to date to help develop a more robust diagnostic measure.

Methods: Morphometric analysis using Materialise Mimics was performed retrospectively on craniofacial computed tomographic scans of infants with non-syndromic ULC and PPP by two independent reviewers. Inter- and intra-rater reliability was established. The differences between the contralateral (nonsynostosed) and ipsilateral (synostosed) petrous ridge (PR) and greater sphenoid wing (GSW) angle, and the external acoustic canal (EAC) were measured. Anterior, middle, and posterior cranial fossa areas were measured and the percent difference between each side was calculated. Posterior fossa deflection from midline, anterior-posterior displacement and relative vertical height of the ears were measured. Mastoid bulge and position were also assessed bilaterally. Results were analyzed using a two-tailed t test (p<0.05 was significant). Patients were subdivided into two groups: age <6 months (group 1) or older (group 2).

Results: 27 ULC patients were included with a mean age of 6.6 months, the majority male (75%) with left-sided lambdoid synostosis (71%). There were 14 patients in group 1 and 13 in group 2. For group 1, the PR angle was 13.8 degrees larger on the nonsynostosed side (p<0.001). The middle and posterior cranial fossa areas were significantly larger on the nonsynostosed side, 38.0% and 13.5% (p<0.001) respectively. The posterior fossa was rotated on average 14.3 degrees (+/- 3.6) towards the synostosed suture. There was an 8.9mm (+/- 2.3) anterior and 2.8mm (+/-2.4) inferior displacement of the ipsilateral EAC versus the contralateral side. Trends were comparable in the older cohort. Compared to ULC subjects, PPP subjects had a significantly smaller percent difference between bilateral petrous ridge angles, indicating a smaller degree of middle cranial fossa asymmetry (p<0.001). Posterior fossa deflection angle was significantly smaller in PPP than ULC, suggesting less severe posterior fossa deviation (p<0.001). The EAC was on average 0.03mm (+/- 3.05) posterior and 0.29mm (+/- 1.75) superior on the flattened side in PPP. The most sensitive (100%) and specific (97%) radiographic finding in ULC was the presence of an ipsilateral mastoid bulge and mastoid cant.

Conclusions: Contrary to published dogma, the EAC is more anteriorly and inferiorly displaced on the synostosed side in 100% of cases of ULC. Anterior ear position alone is not a reliable indicator for differentiating between PPP and ULC, as 33% of PPP also had anterior EAC displacement. Mastoid bulge can be identified on plain film x-ray and serves as a more reliable distinction of ULC.

Figure 1: Mastoid cant and mastoid bulge in a patient with unilateral lambdoid craniosynostosis. A) Scout image frontal view demonstrating a mastoid cant relative to the orbitale line. B) 3D CT demonstrating mastoid bulge on the synostosed side.
Abstract #40: An ACS NSQIP Analysis of Surgical Outcomes for Intraductal Papillary Mucinous Neoplasms of the Pancreas

Authors: Samuel M. Miller MD, Joseph T. King Jr. MD MSCE, Vanita Ahuja MD MPH MBA, Ronald R. Salem MBChB, John W. Kunstman MD MHS

Introduction: Intraductal papillary mucinous neoplasm (IPMN) incidence is increasing and its status as a pancreatic cancer precursor often complicates management. Guidelines for recommending pancreatectomy are evolving and emphasize resection in cases with invasive disease or high-grade dysplasia (IPMN-I) and forgoing surgery in non-invasive disease (IPMN-NI). We identified national trends in IPMN management and examined outcomes following pancreatectomy for IPMN versus non-IPMN indications.

Methods: The ACS NSQIP general and targeted pancreatectomy datasets were merged to identify subjects undergoing pancreatic surgery from 2014-2018. IPMN-I to IPMN-NI incidence was examined longitudinally using database-defined pathologic categories. These were aggregated as an ‘IPMN’ cohort for comparison to all other cases as a ‘Non-IPMN’ cohort. Outcomes were evaluated with chi-squared tests and Poisson regression. The primary outcome measures were clinically-relevant pancreatic fistula (CR-PF) incidence and overall major morbidity. Secondary outcomes included 30-day operative mortality and length of stay (LOS).

Results: 31,965 subjects were identified; the annual incidence of pancreatectomy increased from 4,702 to 6,547 over the study period. 3,112 (9.7%) cases were performed for IPMN; of these, 852 (37.7%) had IPMN-I. IPMN-I comprised 33.3-42.5% of resected IPMN annually (Figure 1). Patients with IPMN were older (67.4 versus 63.0 years, p<0.001) and less likely to undergo pancreaticoduodenectomy (53.9% versus 62.6%, p<0.001) or vascular resection (4.8% versus 14.9%, p<0.001) compared non-IPMN patients. Those with IPMN experienced fewer major complications (31% versus 39.9%, p<0.001) but similar rates of CR-PF (12.7% versus 13.8%, p=0.09) than the non-IPMN cohort. Mortality was lower (0.8% versus 1.5%, p<0.001) and LOS was shorter (8.8 vs 9.3 days, p<0.001) in those with IPMN compared to non-IPMN patients.

Conclusions: Surgical outcomes for patients with IPMN compare favorably to those undergoing pancreatectomy for non-IPMN indications. However, selecting the appropriate candidates for surgery remains challenging as the majority of IPMN that are resected lack high-grade dysplasia or invasive disease.

Figure 1: Surgical intervention for intraductal papillary mucinous neoplasms of the pancreas
Abstract #41: Prevalence of Aortic Arch Anomalies and Congenital Variants in the General Population and Associated Thoracic Aortic Aneurysm Disease

Authors: Sameh Yousef MD, Saket Singh MD, Makoto Mori MD, Clancy W. Mullan MD, Cornell W. Brooks II BA, Roland Assi MD, Peter J. Gruber MD, Arnar Geirsson MD, Prashanth Vallabhajosyula MD, MS

Objective: To identify and categorize congenital variants and anomalies of the aortic arch and the associated thoracic aortic aneurysm disease in a large population database.

Method: CT scans of patients aged 50-85 years performed at single institution from 2013 to 2016 were included. Characteristics of patients with and without arch anomalies were compared by t-test and Fisher exact tests.

Results: Of 21,336 CT scans, 603 reports (2.8%) described arch anomalies. Of these, bovine arch (n=354, 58.7%) was most common, followed by aberrant right subclavian artery (n=147, 24.4%), and aberrant left vertebral artery (n=95, 15.8%). These patients were more likely to be female (p<0.001), non-Caucasian (p<0.001), and hypertensive (p<0.001). Higher prevalence of thoracic aneurysm disease occurred in arch anomalies group (10.8% vs. 4.1%, p<0.001), with significant association on logistic regression (OR=2.85[2.16-3.75]).

Conclusions: In the older adult general population, Prevalence of aortic arch anomalies is ~3% and is significantly associated with aortic aneurysm disease. Imaging surveillance for aortopathies may be warranted in later adulthood in these patients.

Figure. Independent risk factors of thoracic aortic aneurysms.
Abstract #42: Tracing the Course of the Cervical Branch of the Facial Nerve

Authors: Scott Persing MD, Ean Saberski MD, Beecher Watson BA, John Persing MD

BACKGROUND: Concern has been raised that some facial palsies may be due to damage to branches of the cervicofacial nerve during routine operations. This study examines the anatomy of the cervicofacial nerve in relation to readily identifiable mandibular landmarks in order to provide a safer operative outcome.

MATERIALS AND METHODS: Eleven fresh, adult cadaver hemi-neck dissections were performed under loupe magnification, identifying the peri-mandibular branch of the cervicofacial nerve. The distances between the gonion and the ante-gonial notch, and the ante-gonial notch and the pgonion were measured. Measurements were then taken of the cervical branch’s distance below the mandible at 25%, 50%, 75%, and 100% of the distances between these points.

RESULTS: The average gonion to ante-gonial notch distance was 3.1 cm. The branch’s distance below the mandible at 25%, 50%, 75%, and 100% of the distance from the gonion to the ante-gonial notch was 1.1 cm, 1.3 cm, 1.6 cm and 1.8 cm, respectively. The average distance from ante-gonial notch to pgonion was 7.8 cm. The branch’s distance below the mandible at 25%, 50%, and 75% of that distance was 2 cm, 2.2 cm, and 2.2 cm, respectively. The cervical nerve could not be reliably dissected anterior to 75% of this distance.

CONCLUSION: The peri-mandibular branch of the cervical branch of the facial nerve ran a progressively caudal course from the gonion to the pgonion, within 2.5 cm below the mandible. The course of the cervical branch, and its fine arborizations became imperceptible under loupe magnification as it approached the pgonion.

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<th>Cadaveric Hemi-Neck Dissection</th>
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<th>Average (in cm)</th>
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<tr>
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<td><strong>Ante-Gonial Notch to Pgonion Distance (in cm)</strong></td>
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Table 1. Cervical Branch Anatomical Measurements – all measurements in centimeters
Abstract #43: Treatment of HPV Positive Oropharyngeal Cancer: Predictors and Outcomes

Authors: Amrita Singh, Daniel Jacobs, Benjamin Judson

Introduction: The relationship between clinical outcomes of HPV positive oropharyngeal cancer and socioeconomic status is not well understood. We hypothesize 1) that socioeconomic status (SES) and other demographic factors are associated with choice of treatment plan (i.e. surgical or non-surgical care), and 2) that socioeconomic status (SES) is associated with patient survival in patients with HPV positive oropharyngeal cancer.

Methods: The Surveillance, Epidemiology, and End Results Program (SEER) database from 2010-2016 was queried for patients with non-metastatic HPV-positive oropharyngeal cancers. The American Joint Committee on Cancer (AJCC) 8th Edition Cancer Staging Manual was used to determine staging. We used simple and multivariable binary logistic regression to assess the impact of patient demographic, clinical and tumor factors on receipt of surgical management. Cox proportional hazards regression was subsequently performed on a propensity score matched sample to identify factors associated with overall survival.

Results: We identified 1,793 patients with early-stage and 521 patients with late-stage non-metastatic HPV-positive oropharyngeal cancer. We did not find an association between SES group and treatment selection for the early-stage or late-stage groups (p-values 0.62 and 0.48, respectively). The only factor that was associated with treatment selection (i.e. receipt of surgical management compared to radiation therapy alone for the early-stage group or chemoradiation for the late-stage group, respectively) was age. Increasing age was associated with decreased likelihood of surgical management in both early-stage and late-stage groups (OR 0.98, 95% CI: 0.97, 0.99; and OR 0.96, CI: 0.93, 0.98, respectively). Next we assessed the impact of SES on overall survival. Patients in the lowest SES group had worse overall survival compared to those in the highest SES group in a 1:1 propensity score matched analysis of patients with either early-stage or late-stage disease (HR 1.52, CI: 1.17, 1.97; and HR 2.03, CI: 1.29, 3.21, respectively). Other demographic variables associated with worse overall survival in the early-stage group included marital status (single vs. married: HR 1.43, CI: 1.08, 1.89), and radiation therapy alone compared to surgery with radiation therapy (HR 1.55, CI: 1.26, 1.90).

Conclusion: We did not find an association of SES with treatment selection in patients with early- and late-stage non-metastatic HPV positive oropharyngeal cancer. However, SES was associated with worse overall survival in these patients.
Abstract #44: A Novel Mouse Arteriovenous Fistula Model Recapitulates Central Venous Stenosis

Authors: Ryosuke Taniguchi, Shun Ono, Toshihiko Isaji, Jia Liu, Luis Gonzalez, Arash Fereydooni, John Langford, Jolanta Gorecka, Shin Rong Lee, Xixiang Gao, Mingjie Gao, Weichang Zhang, Hao Liu, Yutaka Matsubara, Bogdan Yatsula, Alan Dardik

Introduction: To understand mechanisms of arteriovenous fistula (AVF) failure, a reproducible small animal model that recapitulates central venous stenosis (CVS) distal to an AVF is required. We hypothesized that this mouse model will show comparable morphological and physiological properties to that reported in humans with CVS.

Methods: A fistula was created between the distal aorta and IVC; stenosis was then created in the outflow of the fistula via partial IVC ligation. Sham animals, AVF without venous stenosis, and venous stenosis without AVF were used as controls. IVC was harvested at day 21. Physiological properties of the IVC, both upstream and downstream of the stenosis, or the corresponding sites in models without stenosis, were assessed with ultrasound. Spectral broadening was defined as the difference between the maximum velocity and the width of the spectral window; relative spectral broadening was defined as the ratio of spectral broadening to the maximum velocity.

Results: AVF patency significantly decreased with CVS by day 21 (50% vs 90%; p<0.05; n=10-20). Wall thickness increased in groups with AVF compared to other groups (upstream of stenosis: 13.9 vs 11.0 vs 4.5 vs 3.9 µm, p<0.05, n=4-5; downstream of stenosis: 6.0 vs 6.6 vs 4.5 vs 3.8 µm, p<0.05, n=4-5; AVF with stenosis, AVF, stenosis, sham, respectively). The IVC of mice with AVF showed a venous waveform with pulsatility (Figure 1). Relative spectral broadening of the groups showed no difference upstream of the stenosis. However, there was a significant decrease in relative spectral broadening in the AVF with stenosis group compared to the AVF group downstream of the stenosis (1.06 vs 0.78, day 21; p<0.05; n=5-8); mice with stenosis retained disturbed flow whereas mice without stenosis showed laminar flow. Immunofluorescence of Klf2 and phosphorylated eNOS, proteins upregulated with increased shear stress, showed a tendency towards a decrease in the AVF with stenosis group compared to the AVF group downstream of the stenosis (p=0.22 and 0.09, n=4; day 21).

Conclusions: This novel mouse model of CVS distal to an AVF shows similar morphology and physiology as reported in humans with CVS, including continuous disturbed flow. Relative spectral broadening is a feasible index to quantify disturbed flow.
Abstract #45: Matrix Density Dependent Modulation of Secretory Function of iPSC-VSMCs

Authors: Biraja C. Dash, Ocean Setia, Jolanta Gorecka, Hassan Peyvandi, Kaiti Duan, Lara Lopes, James Nie, Alan Dardik, Henry Hsia

Introduction: The application of induced pluripotent stem cells (iPSCs) to generate vascular smooth muscle cells (iPSC-VSMCs) in abundance is a promising strategy for disease modeling and cell therapy. While iPSC-VSMCs have already been utilized for disease modeling, there is a lack of investigations exploring their therapeutic abilities. The objective of this study is to understand how biophysical property of a scaffold dictates changes in the therapeutic potential of iPSC-VSMCs while developing iPSC-VSMC-based therapy for durable regenerative wound healing.

Methods: We investigated the effect of collagen fibrillar density (CFD) on hiPSC-VSMC’s secretory function via the construction of varying concentrations of collagen scaffolds and using plastic compressed dense fibrillar collagen (DC) scaffolds. In vitro conditioned medium (CM) from the scaffold, culture was used to analyze paracrine factors and their bioactivity in vitro. The hiPSC-VSMCs within DC scaffolds were used in the acute wound model in nude mice. Wound closure, cell survival, angiogenesis, and inflammation were measured in addition to collagen synthesis and dermis and epidermis formation.

Results: The CM displayed an enhanced secretion of proangiogenic factors such as VEGF, bFGF and MMP-2 with an increase in density of the collagen scaffolds. However, plastic compression of the collagen scaffold and rolling them increased the fibrillar collagen density multifold. This rolled configures DC scaffolds differentially expressed pro-angiogenic, anti-inflammatory, and tissue remodeling secretory via the upregulation of hypoxia inducing factor (HIF)-1α (Figure 1). The CM of rolled DC scaffolds enhanced proliferation and migration of endothelial cells, keratinocytes, and fibroblasts, and promoted angiogenesis and anti-inflammatory activity in vitro. In vivo application of hiPSC-VSMCs in rolled DC scaffolds accelerated wound closure, increased matrix production, and resulted in thicker epidermis and dermis, in a full-thickness nude mouse wound model. Hypoxia pre-activated hiPSC-VSMCs in the DC scaffolds retained their viability and phenotype in vivo and promoted angiogenesis, via MMP-2 and VEGF positive expression, and reduced inflammation by upregulating expression of IL-10.

Conclusion: Our study demonstrated that collagen fibrillar density is a key scaffold property that modulates the secretory function of iPSC-VSMCs. This study lays the foundation for developing collagen-based scaffold materials for the delivery of iPSC-VSMCs to promote regenerative healing through guiding paracrine signaling pathways.

![Figure 1: A dense collagen scaffold in rolled configuration modulates paracrine function of hiPSC-VSMCs. hiPSC-VSMCs embedded in DC scaffolds in rolled configuration for 72 h exhibited hypoxia and affected the cells' secretory function. Qualitative ELISA was performed on conditioned media collected from flat and rolled scaffolds for (A) VEGF (n=6, Rolled vs Flat p<0.003), (B) IL-10 (n=6, Rolled vs Flat p<0.0001), (C) TGFβ (n=6, Rolled vs Flat p<0.004) and (D) IL-8 (n=6, Rolled vs Flat](image)
Abstract #46: Transcriptomics Reveal Cardioprotective Features of Arteriovenous Fistula-induced Cardiac Hypertrophy

Authors: Shin-Rong Lee, Stephanie Thorn, Nicole Guerrera, Albert Sinusas, Alan Dardik

Introduction: Arteriovenous fistulae (AVF) are surgical shunts created for hemodialysis access. The high shunt rates can result in left ventricular (LV) hypertrophy, which is thought to portend poor cardiac outcomes. Yet, clinical studies point to superior cardiac specific survival for patients with AVF, compared to those with other dialysis modalities. Could AVF-induced cardiac remodeling be cardioprotective?

Methods: 9-11 week C57Bl/6 mice were subjected to sham laparotomy, or AVF surgery (needle puncture (25Ga) of infrarenal aorta into IVC just above aortic bifurcation). Cardiac chamber size and function were assessed with cardiac CTA and echocardiography at 5 weeks postop. Hearts were then sectioned and stained with Masson’s trichrome for histologic analysis. mRNA sequencing was performed from LV of sham/AVF mice at 10 days post-op. Differentially expressed genes were analyzed using Ingenuity Pathway Analysis (Qiagen) to identify affected pathways and predict downstream biological effects.

Results: Mice with AVF had similar body weight (BW) (p=0.9) and wet lung mass (p=0.8), but increased cardiac mass (Δheart/BW=0.2±0.06%, p<0.01) compared to sham. All 4 cardiac chambers were enlarged (ΔRA=21±6.0μl, p=0.02; ΔLA=11±3.6μl, p=0.04; ΔRV=36±9.2μl, p=0.02; ΔLV=35±12μl, p=0.04), without LV wall thickening (p=0.7). AVF increased cardiac output (ΔCO=12±4ml/min, p=0.01) while preserving LV systolic (LVEF 62.8±0.5 (AVF) vs 68.8±2.9% (sham), p=0.1) and diastolic (E/e': 40.7±18 (AVF) vs 56.2±9.8 (sham), p=0.47) function, as well as indices of right heart function (MPAP: 69.7±1.3 (AVF) vs 68.4±0.9 (sham), p=0.47; TAPSE: 0.72±0.1 (AVF) vs 0.94±0.06 (sham), p=0.12). Histology showed preserved collagen density within each of the 4 chambers (collagen area fraction: p>0.25 for each chamber) without areas of fibrosis. RNA sequencing captured 19,384 genes, of which 857 were significantly differentially expressed, including transcripts from extracellular matrix-related genes, ion channels, metabolism, and cardiac fetal genes. Top upstream regulatory molecules predicted include activation of angiogenic (Vegf, Z=6.9; Akt1, Z=3.9), pro-cardiomyocyte survival (Hgf, Z=6.1; Foxm1, Z=4.6; Erbb2, Z=3.9; Lin9, Z=2.9; Areg, Z=2.7), and inflammation-related (CSF2, Z=7.1; Tgfb1, Z=6.5; TNF, Z=5.1; Ifng, Z=4.1; Ccr2, Z=4.1; IL6, Z=3.8) genes, as well as the inactivation of cardiomyocyte antiproliferative factors (Cdkn1a, Z=2.6; FoxO3, Z=2.4; α-catenin, Z=4.9). Predicted downstream effects include reductions to heart damage (Z=2.0), and increased arrhythmia (Z=2.12), angiogenesis (Z=2.5), and cardiogenesis (Z=2.5).

Conclusion: AVF stimulates an adaptive cardiac hypertrophy in mice without heart failure or pathologic fibrosis. Transcriptional correlates suggest AVF-induced cardiac remodeling has some cardioprotective features.
Abstract #47: Cyclic nucleotide phosphodiesterase 10A regulates medial artery calcification

Authors: Yujun Cai, Xue-Lin Wang, Tonghui Lin, Jinny Lu, Raul J Guzman

Introduction: Vascular calcification is highly prevalent in patients with diabetes mellitus and chronic kidney disease. When located in the media, arterial calcification is strongly associated with increased cardiovascular morbidity and mortality. During arterial calcification, vascular smooth muscle cells (SMCs) in the media undergo phenotypic transformation into a more osteogenic cell type showing decreased SMC contractile markers and increased osteogenic markers, which contributes to the development of calcification. Currently, there is no cure for vascular calcification. The second messenger cyclic nucleotides cAMP and cGMP, controlled by distinct cyclic nucleotide phosphodiesterase (PDE) isozymes, play important regulatory roles in a variety of human diseases. 11 families and 21 PDE genes serve to control particular pools of cyclic nucleotides and regulate unique cellular functions.

Methods and Results: Using a qPCR PDE array, we found that PDE10A was the most highly induced among all PDE genes using a rat model of medial artery calcification. PDE10A expression was also markedly increased in calcified arteries from rats with chronic kidney disease and in tibial arteries from patients with peripheral artery disease. Interestingly, it co-localized with osteogenic markers in these specimens. In vitro, knockdown using specific siRNA and inhibition of PDE10A with synthetic inhibitor attenuated high phosphate-induced SMC osteogenic transformation and calcification. In response to high phosphate, the aortic rings from PDE10A knockout mice showed less medial calcification than those from wild-type controls. Ablation of PDE10A in PDE10A knockout mice also reduced medial calcification compared with wild-type controls in a mouse medial calcification model. Mechanistic studies suggest that PDE10A can promote MAPK and AKT and therefore increase MMP3 activity to promote SMC osteogenic transformation and calcification.

Conclusions: These findings suggest that PDE10A plays a critical role in SMC osteogenic transformation and arterial calcification and that targeting it may provide a novel therapeutic strategy for reducing medial calcification and improving outcomes in patients with PAD.
Abstract #48: Evaluating the impact of anatomic variability in kidney cortical wedge biopsies on human organ research results

Authors: C.M. Edwards, J.T. Langford, M. Reschke, J.R. DiRito, D. Mulligan, D. Haakinson, G.T. Tietjen

Introduction: Biopsy collection is a simple and effective method for obtaining information about an organ in human organ experimentation. Single biopsies are used as a metric to assess organ viability and determine effectiveness of diagnostic tools or therapies. Current practices assume that data obtained from a singular biopsy is representative of a kidney as a whole. The purpose of this study is to determine how representative a cortical wedge biopsy is of an entire kidney and investigate how the information obtained from a biopsy can best be used to draw experimental conclusions in human organ research. This will be accomplished by studying non-transplanted human kidney.

Methods: The variability within a singular biopsy and within a kidney was determined using the following methods. Cortical wedge biopsies were taken from transplant-declined human kidney in 5 locations (Figure 1A). The biopsies were fixed in 10% formalin. 4 μm sections were sliced every 200 μm for the length of each biopsy and stained with H&E. The whole sections were imaged using a 20x tiling program. The number of healthy glomeruli were counted, and the total area of each biopsy section was determined. Healthy glomerular density per section was calculated. The H&E 20x images were inputted into our digital pathology tool developed in MATLAB to gather preliminary nuclear density quantification data (Figure 1B and 1C). Biopsy sections were also stained with picrosirius red and imaged at 20x in order to quantify areas of fibrosis.

Results: The density of healthy glomeruli per section was plotted vs. the biopsy location (Figure 1D). The data demonstrate that the density of healthy glomeruli is variable both within a single biopsy and between biopsy locations. The preliminary nuclear density and area of fibrosis data obtained from our digital pathology tool demonstrate similar variability.

Conclusions: The results suggest that biopsy location selection and biopsy sectioning processes appear to contribute to variable characterization of a kidney. Additional kidney will be studied to identify trends and refine methods. Omics analysis will be used to supplement quantitative histological data and enhance our understanding of variability at a molecular level.

![Figure 1: A) Biopsy collection method, B) 20x image of biopsy section stained with H&E, C) quantification of nuclear density using digital pathology tool, and D) plot showing healthy glomerular density as a function of biopsy location](image-url)
Abstract #49: Developing Infrastructure for High Impact Transplant Declined Human Organ Research in the US and Opportunities as a Platform for Surgical Education


Introduction: There is significant organ shortage in the US with unacceptably high waitlist mortality. Our deceased donor pool has increasing marginality with greater burden of medical comorbidities as well as increased frequency of donors resulting from overdose with prolonged periods of hypoxia. Transplant surgeons have limited tools to prognosticate safe use of higher risk organs which leads to organ discard. Many deceased donors consent to use of their organs for research if declined for transplantation. Transplant-declined human organs recovered with research consent are a scarce resource and utilization should be maximized to best respect the gift of donation. Human organ research is a source of impactful translational research in transplant, and this research can also simultaneously provide a platform for residents to develop competency in technical skills by working with the exact organs and tissue they will operate on clinically.

Methods: We have set up a robust multi-disciplinary infrastructure for high-volume transplant declined human organ translational research, developing online tools to allow for rapid organ allocation to relevant protocols. Our research infrastructure models that utilized by our collaborators in the United Kingdom as well as our clinical transplantation workflow in the United States. Additionally, we developed a curriculum for residents participating in human organ research to learn to bench livers for perfusion research on the OrganOx Metra® device. This curriculum isolates components of benching, flushing, and perfusing. It was applied in a series of 7 sequential livers with two residents. Components were taught by a transplant surgeon, performed by residents with feedback, then assessed. Measures included time for completion, surgical technique, anatomic knowledge, and ability to perfuse.

Results: We implemented our research infrastructure in November 2018. As of January 2020, we had accepted a total of 78 kidneys and 25 livers for our research protocols. We have 6 active kidney and 2 active liver protocols available for allocation. These range from characterization of ischemic injury on cold storage or perfusion, developing tools for organ assessment, and delivering targeted therapies on perfusion. This allows for utilization of every research organ offer for translational research protocols as well as surgical education. The isolated steps of liver benching, cannulating, and perfusing were tracked for surgical trainees participating. Total procedure time shortened with repetitions and improved technique was noted by subjective evaluation by the attending surgeon.

Conclusions: Directly evaluating transplant-declined human organs allows for rapid translation of technologies that may have more immediate impact on clinical practice by reducing rates of discard of potentially usable organs, which will help alleviate the organ shortage and waitlist mortality. A high-volume research infrastructure for organ allocation is required to make best use of these discarded organs and honor our donors. Residents involved with human organ research have a platform to learn essential technical skills and anatomy while learning about marginal organ utilization. We can maximize the gift of donation by not only performing impactful translational research with transplant declined human organs, but also supporting surgical education and inspiring generations of future transplant surgeons.

Figure 1
Transplant declined human organ research volume by month since implementation of infrastructure.
**Abstract #50: Title:** Delivery of Induced Pluripotent Stem Cell Derived Smooth Muscle Cells in a Collagen Scaffold Enhances Cell Survival and Accelerates Wound Healing  
**Authors:** Jolanta Gorecka, Xixiang Gao, Jiesi Luo, Biraja Dash, Luis Gonzalez, Shin Rong Lee, Ryosuke Taniguchi, Yutaka Matsubara, Yibing Qyang, Henry Hsia, Alan Dardik

**Aim:** We have previously shown that delivery of mesenchymal stem cells (MSC) in a collagen scaffold promotes cellular retention *in vivo* and accelerates wound healing in a diabetic mouse model. Induced pluripotent stem cells (iPSC) are a revolutionary cell type in regenerative medicine, secondary to their abundance, ease of harvest, and pluripotency. We hypothesized that similar to MSC, human induced pluripotent stem cell derived smooth muscle cells (hiPSC-SMC) are activated by a hypoxic environment, accelerate diabetic wound healing, and are protected by delivery in a collagen scaffold.

**Materials & methods:** *In vitro*, the characterization of MSC and hiPSC-SMC were evaluated by cell morphology and VEGF expression. *In vivo*, biomimetic collagen scaffolds containing MSC or hiPSC-SMC were used to treat splinted full thickness excisional back wounds on diabetic athymic nude mice. Wound healing and skin morphology were subsequently evaluated.

**Results:** *In vitro*, hiPSC-SMC were activated by hypoxia and secreted increased concentrations of 31/37 analyzed pro-angiogenic cytokines, as compared to MSC. Topical delivery of one million hiPSC-SMC in a collagen scaffold accelerated wound healing in diabetic mice to a greater extent than MSC containing scaffolds and direct cellular injection. Histological analysis revealed improved skin morphology with increased proliferation, VEGF, and angiogenesis in the hiPSC-SMC treated group. This was also associated with an increase in M2 type macrophages. Cells were retained in the wound 7 days post treatment, with a higher concentration of hiPSC-SMC cells in the collagen scaffold group, as compared to direct cellular injection.

**Conclusions:** Delivery of hiPSC-SMC in a collagen scaffold activates the cells, leading to improved angiogenesis, accelerated wound healing, and improved *in vivo* survival. This data suggests that hiPSC-SMC are a reasonable choice to evaluate for translational therapy in treatment of human diabetic wounds.
Abstract #51: Rouleaux Formation in Human Livers During Normothermic Machine Perfusion
Authors: Matthew Harris, Siavash Raigani, Claire Albert, Melanie Reschke, Cailah Carroll, John Langford, Christopher Edwards, Danielle Haakinson, Korkut Uygun, Heidi Yeh, Gregory Tietjen

Introduction: We recently discovered that red blood cells (RBCs) form rouleaux plugs in human kidney vasculature during normothermic machine perfusion (NMP) and are associated with poor perfusion (DiRito et al, manuscript in review). Since in-vivo, rouleaux formation is typically mediated by hepatic fibrinogen, we sought to determine if fibrinogen release is associated with rouleaux formation during NMP of human livers.

Methods: Transplant-declined human livers underwent NMP on the OrganOx or LiverAssist perfusion devices. Perfusate was collected prior to perfusion and after 2-4 hours of NMP. Wedge or core needle biopsies were H&E stained and imaged at 20x magnification. After qualitative analysis, rouleaux plugs were identified and quantified using custom Matlab code that relies on user defined training images to characterize positive and negative features in each organ. Serum fibrinogen concentration was measured prior to and after initiation of NMP using ELISA and correlated with perfusion flow rate data.

Results: Serum fibrinogen concentrations varied between livers, but most serum fibrinogen concentrations increased during perfusion. Increased levels of fibrinogen seem to correlate with increased levels of rouleaux and vascular plugging as identified by quantitative analysis of biopsies (Fig.1 A&B). Representative images of an H&E stained liver biopsy from after NMP demonstrates rouleaux and congestion identified by the image analysis Matlab code (Fig. 1C). Across all livers, increasing levels of perfusate fibrinogen were positively correlated with hepatic arterial resistance (r(8)=0.7524, p=0.0120).

Conclusions: RBCs form rouleaux during NMP of livers and fibrinogen concentration in perfusate increases in most liver perfusions over time. These levels may provide a marker of viability and further elucidation of these pathways could lead to treatments to rescue injured grafts for transplant.

Figure 1
Abstract #52: Transcription Factor Profiling Identifies Spatially Heterogenous Mediators of Follicular Thyroid Cancer Invasion

Authors: Norman G. Nicolson, Johan Paulsson, C. Christofer Juhlin, Courtney E. Gibson, Tobias Carling, Reju Korah

Introduction: Follicular thyroid cancer (FTC) generally has low risk of recurrence or death, but some cases are encapsulated angio-invasive (eaFTC) or widely invasive (wiFTC) histological subtypes, with significantly worse prognosis. Drivers of invasion are incompletely understood. We elected to profile the transcription factor expression in FTC to better elucidate the mechanism of invasive behavior.

Methods: Tissue samples including minimally invasive FTC (miFTC), eaFTC, and wiFTC tumors, as well as histologically normal thyroid adjacent to benign follicular adenomas, were selected from a cohort (n=21) of thyroid tumor patients. Extracted total RNA was subjected to a quantitative PCR array containing 84 transcription factor probes. Genes differentially expressed in invasive FTC were determined, and then explored via in silico network analysis. Invasion-relevant spatial expression patterns of selected transcription factors were characterized with immunohistochemistry.

Results: Of the 84 genes interrogated, 23 were differentially expressed between FTC and normal, or between subtypes. E2F1 was over-expressed in all 3 subtypes (p<0.01). SP1 was differentially expressed in eaFTC and wiFTC compared to normal (p=0.01 and 0.04, respectively). TCF7L2 was significantly upregulated in wiFTC specifically (p<0.05). Immunohistochemistry revealed differential transcription factor expression along the tumor invasive front relative to the central tumor (Figure).

Conclusions: WiFTC is rare but has a high risk of recurrence and death relative to miFTC. This study identifies differential transcription factor expression associated with invasive subtypes of FTC, possibly localized to the invasive component of the tumor specifically. Our study may have significant implications for the interpretation of bulk gene expression analysis of thyroid tumor samples.
Abstract #53: Biodistribution of Nanoparticles in Fetal Lung after IV Injection

**Authors:** Sarah Ullrich, Mollie Freedman-Weiss, Samantha Ahle, Adele Ricciardi, Hanna Mandl, Alexandra Piotrowski-Dapsit, Mark Saltzman, David Stitelman

**Purpose:** In utero delivery of nanoparticles loaded with drugs or gene editing reagents has potential to treat pulmonary diseases such as congenital diaphragmatic hernia and cystic fibrosis early in their pathogenesis. This study aims to show the impact of nanoparticle size and chemistry on their biodistribution in the fetal mouse lung after IV injection.

**Methods:** Fluorescently labeled 150nm PLGA (n=7), 250nm PLGA (n=5), PLA-PEG (n=3), PACE (n=5) and PACE-PEG (n=4) nanoparticles were intravenously injected into B6 mice at e15. Dams were sacrificed 3-hours post injection and lungs were harvested from the pups. Confocal microscopy and flow cytometry with staining for EpCAM, PECAM and CD45 were used to assess particle delivery to the lungs.

**Results:** Smaller sized particles (150nm PLGA) were delivered more efficiently to epithelial cells and leukocytes (p<0.05). PEGylation of particles (PLA-PEG and PACE-PEG) improved their delivery to both endothelial cells and leukocytes(p<0.05). PACE nanoparticles were exhibited the highest level of delivery to lung epithelial cells (p=<0.05).

**Conclusion:** Composition effects the biodistribution of nanoparticles in the fetal mouse lung after IV injection and should be taken into consideration when developing particle based therapy.

A. Flow cytometry from fetal lung cells injected with Dio-loaded nanoparticles and stained for EpCAM, PECAM and CD45

B. DAPI stained confocal images of fetal lungs injected with Dio loaded nanoparticles
Abstract #54: Human Organ Culture: A Novel Method for Evaluation of Reperfusion Injury in Human Kidney

Authors: John Langford MD, Chris Edwards SCB, Jenna DiRito BS, Matthew Harris MD, Jordan S. Pober MD PhD, Dani Haakinson MD, Gregory Tietjen PhD

Introduction
Ischemia reperfusion injury remains a critical determinant of graft function in renal transplant. It is a determinant in both delayed graft function and graft rejection. The underlying pathophysiology of this injury mechanism is still being understood. We recently discovered fibrinogen is synthesized during cold ischemia and secreted during normothermic perfusion (manuscript in review). Currently we are limited to biopsies from kidneys during transplantation for evaluation of the pathophysiology. This severely restricts the sample size with usually only one experiment per biopsy. We hypothesized that human organ culture (HOC) could be used to simulate the function of renal cells during reperfusion injury and measure fibrinogen production.

Methods
Biopsies are obtained from transplanted-declined human kidneys after varying cold storage times. These biopsies are then dissected into 1 mm³ samples and placed in culture media (without fetal bovine serum) for incubation at 37°C. Cultured media and tissue samples are then collected at specific time points during the 37°C incubation period. Fibrinogen content in the media was evaluated by ELISA.

Results
Dissected tissue samples were placed into wells containing media for each warm incubation time point (n=3). Fibrinogen levels appear to increase from 1 hour, 2 hours too 4 hours of incubation after both 24 hour cold ischemic time (34.6 ± 17.5, 249.5 ± 66.0, 498.1 ± 175.4, respectively) and 48 hours cold ischemic time (249.1 ± 61.4, 418.4 ± 180.2, 468.8 ± 288.1, respectively). There also appears to be an increased starting fibrinogen based on the 1 hour incubation in the 48 hours of cold ischemic time (249.1 ± 61.4) compared to the 24 hours of cold ischemic time (34.6 ± 17.5).

Conclusions
HOC allows small samples of tissue to potentially function as they would during reperfusion. Using this technique we were able to replicate known effects of fibrinogen production during cold ischemia and secretion in a normothermic setting. We will be able to expand this assay to look for other products of reperfusion injury and test therapeutics such as small molecule drug inhibitors as well.
Abstract #55: Inhibition of PD-L1 reduces regulatory T-cells and M2 macrophages and inhibits vascular wall thickening during AVF maturation

Authors: Yutaka Matsubara, Luis Gonzalez, Jia Liu, Arash Fereydooni, John Langford, Shin Rong Lee, Jolanta Gorecka, Mingjie Gao, Xixiang Gao, Ryosuke Taniguchi, Yatsula Bogdan, and Alan Dardik

Introduction: Vascular remodeling during arteriovenous fistula (AVF) maturation is characterized by infiltration of T-cells and macrophages. Although helper T-cells (Th) and M1 macrophages are associated with classical inflammation, regulatory T-cells (Treg) and M2 macrophages reduce inflammation and promote wall thickening during AVF maturation. We have previously shown that inhibition of T-cells reduces M2 macrophage and vascular wall thickening in AVF. However, it is still not known how T-cells are regulated during AVF maturation. Programed death ligand 1 (PD-L1) suppresses T-cells such as Th and induces Treg. Since vascular endothelial cells express PD-L1, we hypothesized that PD-L1 induce Treg to promote vascular remodeling and allow M2 macrophage accumulation, leading to vascular wall thickening.

Methods: We used the mouse aorta-inferior vena cava AVF model. PD-L1 antibody (200 mg/kg, intraperitoneal injection, 3 times/week) was used to inhibit PD-L1. Control mice were treated with matched IgG2 isotype antibody. Th1, Th2, Treg, M1 macrophage and M2 macrophage infiltration was assessed by immunofluorescence. Vascular wall thickening was assessed by elastin van Gieson stain.

Results: PD-L1 antibody significantly increased infiltration of Th1 (15.9 vs 8.6 cells/hpf; n=3; p<0.05) and Th2 (18.0 vs 9.7 cells/hpf; n=3; p<0.05), but decreased Treg (3.8 vs 11.2 cells/hpf; n=3; p<0.05) compared with control (day 7). PD-L1 significantly inhibited accumulation of TGM2+ macrophages (5.8 vs 15.7 cells/hpf; n=3, p<0.01) and CD206+ macrophages (2.6 vs 13.2 cells/hpf; n=3; p<0.01), but not iNOS+ macrophages (8.8 vs 10.0 cells/hpf; n=3, p=0.23) or TNF-α+ macrophages (9.8 vs 12.3; n=3; p=0.29). At day 21, there was less wall thickening in AVF treated with PD-L1 antibody compared with control AVF (8.2 µm vs. 17.55 µm; n=4-5; p<0.01; t-test, Figure). Patency of PD-L1 Ab treated group was significantly reduced compared with control (28.2% vs 80.0%; n=16-17; P=0.0396; Figure)

Conclusions: Inhibition of PD-L1 is associated with reduced vascular wall thickening as well as less Treg infiltration and M2 macrophage accumulation in the vascular wall during AVF remodeling. These results suggest that PD-L1 may induce Treg to promote M2 macrophage accumulation and vascular wall thickening during AVF maturation.
Abstract #56: Bile at strongly acidic pH potentiates the NF-κB activation and its related anti-apoptotic pathway in human hypopharyngeal squamous cancer cells

Authors: Michael Hajek, Sotirios G. Doukas, Clarence T. Sasaki, Dimitra P. Vageli

Background: Prognosis for hypopharyngeal cancer is usually poor, and recurrence is common. Identifying new factors or related mechanisms that promote its progression may have clinical implications. Though recent studies support the role of acidic bile reflux as a risk factor for hypopharyngeal carcinogenesis, it remains to be explored how bile and its related NF-κB activated pathway may further affects its progression in already established hypopharyngeal cancer.

Methods: Human hypopharyngeal squamous cell carcinoma (SCC) cell lines, FaDu and UMSCC11A, both negative for HPV, were repetitively exposed to bile acids (400 μM) at variable pH points (4.0, 5.5 and 7.0). Immunofluorescence, western blotting, luciferase assay, and qPCR were used to detect NF-κB activation, bcl-2 overexpression and gene expression.

Results: Bile at strongly acidic pH (4.0) potentiated the activation of NF-κB and its related mRNA phenotype in HSCC cells (Table 1). IL-6, TNF-α, and BCL2 were found among the highest overexpressed genes as was previously found in HSCCs excised from patients with documented biliary reflux (Table 1). An enhanced transcriptional activity of EGFR, RELA, STAT3, and WNT5A and higher survival rates were observed in human hypopharyngeal SCC cells exposed to acidic bile compared to those exposed to bile at weakly acidic or neutral pH.

Conclusion: Our novel findings support the observation that bile reflux has the potential for actively influencing the progression of hypopharyngeal cancer, mediated by NF-κB. In patients with hypopharyngeal cancer and known gastroesophageal reflux disease, antacid therapy may exert a role in furthering control of disease recurrence and progression.

Table 1. Similarities between mRNA oncogenic phenotypes related to exposure to bile in human hypopharyngeal SCC cell lines and excised HSCCs

<table>
<thead>
<tr>
<th></th>
<th>*Human Hypopharyngeal SCC cell lines</th>
<th>**Bile-related HSCCs</th>
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<tbody>
<tr>
<td></td>
<td>FaDu</td>
<td>UMSCC11A</td>
</tr>
<tr>
<td>TNFα</td>
<td>++</td>
<td>++++</td>
</tr>
<tr>
<td>IL6</td>
<td>++</td>
<td>+++</td>
</tr>
<tr>
<td>BCL2</td>
<td>+</td>
<td>++</td>
</tr>
<tr>
<td>RELA</td>
<td>+</td>
<td>+</td>
</tr>
<tr>
<td>EGFR</td>
<td>+</td>
<td>+</td>
</tr>
<tr>
<td>STAT3</td>
<td>+</td>
<td>+</td>
</tr>
</tbody>
</table>

*Acidic bile induced molecular changes in human hypopharyngeal cancer cells (SCC) lines (FaDu and UMSCC11A); **Molecular changes in bile (+) versus bile(-) human hypopharyngeal squamous cell carcinomas (HSCCs) [ref 4].

+++ 10-100; ++++ 100-1000; ++++>1000

Abstract #57: *In vivo* temporal characteristics of NF-κB inhibition in bile-induced early oncogenic molecular events in murine hypopharyngeal mucosa

**Authors:** David Kasle, Sotirios G. Doukas, Clarence T. Sasaki, Dimitra P. Vageli

**Background.** Biliary supraesophageal reflux at acidic pH promotes tumorigenic processes in exposed hypopharyngeal mucosa (HM)\(^1\)-3. Topical simultaneous co-application of NF-κB inhibitor BAY 11-7082 with bile can block its effect in upregulating an NF-κB-related oncogenic phenotype4. We hypothesize that *in vivo* topical application of BAY 11-7082 either pre- or post- bile exposure, is capable of inhibiting bile-induced oncogenic molecular events in exposed HM, as similarly found *in vitro*.

**Methods.** We topically applied BAY 11-7082\(^4\) on hypopharyngeal mucosa of C57BL/6J (Mus, Musculus; Jax mice, Jackson Laboratory USA) 15 min before or 15 min after acidic bile exposure *in vivo*. Specifically, 20 males and 20 females were randomly divided in the following groups [8 mice (4 males+4 females) per group]: (i) acidic bile-treated group (pH 3.0), at concentrations previously described\(^1,4\) (ii) pre-treated group (treatment of HM with BAY 11-7082\(^4\) 15 min before acidic bile exposure), and (iii) post-treated group (treatment of HM with BAY 11-7082\(^4\) 15 min after acidic bile exposure), (iv) saline-DMSO (pH 7.0) treated HM, and (v) an untreated control group (negative control). The HM of treated groups was exposed two times per day (with an interval of 6 hours during which animals had access to drinking water, ensuring adequate wash out between treatments) for 10 days (20 applications), using a plastic feeding tube\(^1,4\). Immunohistochemical and gene expression analyses were performed to evaluate NF-κB activated levels and its related mRNA oncogenic phenotype in experimental HM compared to controls.

**Results.** We document that *in vivo* pre- or post-application of BAY 11-7082 on murine HM can effectively inhibit the effect of acidic bile, eliminating NF-κB activation and preventing transcriptional activation of Bcl2, Rela, Stat3, Egfr, Tnf, Wnt5a, that exert central roles in head and neck cancer (Table 1). On the other hand, pre-application of BAY 11-7082 but not its post-application significantly reduces the transcriptional activation of Il6 and prostaglandin H synthases 2 (Ptgs2), supporting the observation that bile induces a rapid pro-inflammatory effect (Table 1).

**Conclusion.** We provide novel evidence that short-term, topical pharmacologic inhibition of NF-κB, either before or after acidic bile exposure is capable of successfully preventing its mRNA oncogenic phenotype in HM, supporting the observation that NF-κB inhibition may be clinically feasible in preventing the biliary oncogenic effects creating a strong basis for further translational exploration.

**Table 1: Relative expression changes of acidic bile-related mRNA\(^1\) oncogenic phenotype in topically pre- and post-treated murine HM with NF-κB inhibitor (BAY 11-7082).**

<table>
<thead>
<tr>
<th>Gene</th>
<th>ACIDIC BILE vs. CNTL</th>
<th>*PRE-BAY vs ACIDIC BILE</th>
<th>**POST-BAY vs ACIDIC BILE</th>
</tr>
</thead>
<tbody>
<tr>
<td>Stat3</td>
<td>186.2</td>
<td>-3336.0</td>
<td>-39.9</td>
</tr>
<tr>
<td>Rela</td>
<td>37.1</td>
<td>-555.5</td>
<td>-18.6</td>
</tr>
<tr>
<td>Il6</td>
<td>5.3</td>
<td>-2.8</td>
<td>1.2</td>
</tr>
<tr>
<td>Ptgs2</td>
<td>5.0</td>
<td>-1.9</td>
<td>1.0</td>
</tr>
<tr>
<td>Wnt5a</td>
<td>4.0</td>
<td>-57.4</td>
<td>-4.2</td>
</tr>
<tr>
<td>Tnf</td>
<td>2.0</td>
<td>-21.5</td>
<td>-6.7</td>
</tr>
<tr>
<td>Egfr</td>
<td>1.5</td>
<td>-1779.7</td>
<td>-16.7</td>
</tr>
<tr>
<td>Bcl2</td>
<td>1.6</td>
<td>-56.5</td>
<td>-4.6</td>
</tr>
</tbody>
</table>

\(^1\)Normalized mRNA levels, by qPCR; *Pre-BAY: pre-application of BAY 11-7082; **Post-application of BAY 11-7082*

Abstract #58: Intravital imaging of cellular-level interactions at multiple metastatic organ sites
Authors: Andrew Daniels, Irina Krykbaeva, Maor Sauler, Kelly Olino, Marcus Bosenberg

Melanoma is the deadliest form of skin cancer. The American Cancer Society estimates that it will cause 7,230 deaths in 2020. In the past, treatment options for metastatic melanoma were limited, however the introduction of immunotherapies has drastically changed outcomes, increasing 2 year overall survival from 20% with prior therapies to 64% with combined CTLA4 and PD-1 checkpoint inhibitors (CPI). Importantly though, this benefit has not been the case for most cancers in which CPIs have been evaluated. Many tumor-intrinsic factors have been associated with the likelihood of a tumor’s responsive to CPI, but for the most part the molecular and immunologic underpinnings of successful CPI have yet to be elucidated. The importance of better understanding the immunologic-oncologic interactions in the setting of metastasis is paramount.

In order to achieve this goal, we have created a technique that allows for the intravital imaging of metastatic tumors at multiple sites. Utilizing a set of mouse melanoma lines, YUMMER, developed by our lab that are derived from mutations reflective of human disease, cells are injected into the left ventricle and allowed to spread hematogenous to distant sites, as shown by luminescence imaging (Fig. 1a). Ultimately, using a set of complex intravital imaging techniques are able to track the immunologic-oncologic of tumor cells in multiple metastatic organ sites including brain, lung and subcutaneous tissue (Fig. 1b,c). These techniques, while honed in melanoma, are broadly applicable and provide an essential tool for the study of metastatic disease across cancer types.

Figure 1: (A) Luminescence imaging of left metastatic tumor dispersal. (B, C) Intravital imaging two photon imaging of brain tumors (gfp) and blood vessels (rfp) in the same mouse at over 24 hours.
**Abstract #59: Macro-Patch Studies on Outer Hair Cell Nonlinear Capacitance**

**Authors:** Joseph Santos-Sacchi and Winston Tan

Prestin (SLC26a5) underlies outer hair cell (OHC) mechanical activity (electromotility, eM). The protein’s voltage-dependent conformational changes couple into length changes of the cell. These conformational changes are measurable as an electrical correlate of eM, i.e., nonlinear capacitance (NLC), which is maximal at $V_h$, the voltage where prestin charge is distributed equally across the OHC lateral membrane.

We have recently shown that NLC and eM display low pass behavior that counters current dogma. NLC and eM exhibit multi-exponential or stretched exponential components, and the frequency response is dependent on holding voltage relative to $V_h$; that is, it is voltage-dependent (Santos-Sacchi and Tan, JNeuro, 2018). Furthermore, we have shown that NLC is not stationary in time following voltage steps (Santos-Sacchi et al., JPhysiol, 1998). Most of these studies have been done on whole cell preparations. Whole cell behavior can be influenced by internal and external mechanical impediments, and since prestin is mechanically sensitive its response characteristics conceivably could be altered to provide an inaccurate picture of intrinsic prestin kinetics. Here we evaluate NLC in membrane macro-patches to reduce extraneous (though likely physiologically important) influences to confirm the low pass, stretched-exponential nature of prestin kinetics.

We utilized macro-patches (~4 µm inner pipette tip diameter; seal > 5 GΩ, on-cell and excised) of guinea pig OHC lateral membrane under voltage clamp, where voltage control is excellent. Voltage chirp arrays (32 contiguous chirps, 4096 pts each at 10 µs sampling; 10 mV peak) were summed with 20 mV step offsets from -160 to +160 mV), for total step durations of about 1.5 s. Stray and linear capacitive currents were removed by subtracting the AC response at +160 mV, where NLC is absent. The resulting nonlinear capacitive currents were used to solve for membrane capacitance with dual-sine and single-sine techniques (Santos-Sacchi, JBiophys, 2004) at frequencies from 390 to 20000 Hz.

We find that NLC extends beyond our highest measurement frequency, but exhibits continuous low pass behavior that can be fit either with multi-Lorentzian or power functions, confirming our whole-cell observations on eM and NLC. Additionally, the voltage and frequency dependence of NLC changes over the course of step durations. Notably, a low frequency component of NLC diminishes over time, and $V_h$ shifts positively across all frequencies, but is fairly stable across frequency. Importantly, our data illustrate that experimental approaches that average eM, NLC, or possibly even in vivo electrophysiological correlates of OHC activity in order to enhance signal-to-noise may miss important aspects of OHC performance.

(Supported by NIH-NIDCD R01 DC016318 and R01 DC008130)
Abstract #60: Microtubule-Associated Protein 1S (MAP1S) is Required for Normal OHC Electromotility and Hearing

**Authors:** Winston Tan, Jun-Ping Bai, Alexei Surguchev, Joseph Santos-Sacchi, Dhasakumar Navaratnam

Prestin (SLC26a5) is a motor protein within the lateral membrane of outer hair cells (OHCs) of the cochlea. Changes in OHC membrane voltage drives molecular conformational changes in prestin that couple into robust cell length changes termed electromotility (eM), a key element for mammalian cochlear amplification. Earlier studies by our group showed that prestin interacts with microtubule-associated protein 1S (MAP1S), a protein that also binds actin and tubulin. We also demonstrated expression of MAP1S in OHCs and co-localization of MAP1S with prestin. Furthermore, coexpression of MAP1S with prestin enhanced the surface expression and function of prestin as confirmed by biochemical and electrophysiological means. These data led us to hypothesize that MAP1S links prestin to the underlying cytoskeleton in OHCs and modulates prestin activity. To study the role of MAP1S in OHC and hearing function, we used a MAP1S knockout (MAP1S KO) mouse model. We demonstrated using ABR and DPOAE measurements that MAP1S KO mice have significantly reduced hearing sensitivity and OHC function respectively. However, patch-clamp recording showed that OHC nonlinear capacitance (NLC), an electrical correlate of eM, remained normal. These results indicated that the hearing loss is associated with OHC dysfunction but is not related to changes in NLC.

Here, we sought to investigate the underlying basis of the hearing phenotype by measuring OHC eM. Single isolated OHCs were whole-cell voltage clamped and stimulated with a hyperpolarising voltage ramp (100 to -120 mV), superimposed with summed AC voltages at harmonically related frequencies from 195.3 to 6250 Hz. The ramp-induced eM was recorded with a fast video camera (Phantom 310, Vision Research) at a frame rate of 25 kHz and measured by tracking the cuticular plate of the OHC using a shape tracking algorithm that provides sub-pixel resolution of movements. Our results showed that the average eM gain was significantly reduced in both young and old MAP1S KO mice by 30% and 44% respectively relative to age-matched WT controls. Interestingly, there was no significant age-dependent change of eM in both WT and KO mice. Furthermore, using super-resolution imaging (dSTORM), we localized MAP1S along the OHC lateral membrane in close proximity to both prestin and actin at sub-diffraction resolution (nanoscopic level). In addition, we confirmed interactions between MAP1S, prestin and actin using co-immunoprecipitation.

In conclusion, our findings suggest that MAP1S, through its interactions with prestin and the underlying cytoskeleton, plays a key role in modulating the active mechanical properties of the OHC, and that this is critically important for normal hearing. These data for the first time implicate the cytoskeleton in eM that was thought to be primarily a membrane-based phenomenon.

(Supported by NIH-NIDCD R01 DC000273, R01 DC016318 and R01 DC008130)
**Abstract #61:** Bioadhesive nanoparticles as a delivery vehicle in pancreatic cancer epithelial cells and pancreatic fibroblasts

**Authors:** Nesrin M. Hasan, Hee Won Suh, Paulomi Aldo, W. Mark Saltzman, Nita Ahuja

Pancreatic cancer, referred to as pancreatic ductal adenocarcinoma (PDAC), is characterized by high lethality and limited treatment options. PDAC is generally diagnosed at a later stage and is resistant to chemotherapy and radiation therapy. Therefore, there is an urgent unmet need for novel treatment options to improve the survival of patients. PDAC is characterized by dense solid tumors that hinder drug penetration and novel treatment technologies should be utilized to improve drug access to cancer cells. Nanoparticle-based compounds have been shown to improve site specific targeting, intracellular penetration, and circulation time therefore can be used for therapeutic delivery to solid tumors.

In our study, we performed in vitro characterization studies of non-bioadhesive nanoparticles (NNPs) and bioadhesive nanoparticles (BNPs) in pancreatic cancer epithelial cells and pancreatic fibroblasts. NNPs are polylactic acid-hyperbranched polyglycerol (PLA-HPG) nanoparticles and BNPs are obtained through conversion of HPG to an aldehyde-rich corona which increases the bioadhesive property through formation of linkages with proteins.

The aim of our study was to characterize the internalization of nanoparticles in vitro in different pancreatic cell lines. We incubated pancreatic cancer epithelial cells (PANC-1 and MIA PaCa-2) and pancreatic fibroblasts with fluorescent DiO-loaded NNPs and BNPs to assess internalization. Both DiO-NNPs and DiO-BNPs were internalized by PANC-1, MIA PaCa-2 and pancreatic fibroblasts as determined by both flow cytometry and fluorescence microscopy. The nanoparticles were internalized in a dose- and treatment time-dependent manner. Although both nanoparticles were internalized, due to their increased bioadhesive properties BNPs had 1.7 fold higher internalization compared to NNPs. Viability of the cells following DiO-NNPs and DiO-BNPs treatment was assessed through both acridine orange staining and flow cytometry analysis. DiO-NNPs and DiO-BNPs treatments did not affect the viability of the cells. Similar results were obtained with Dil-loaded nanoparticles.

In summary, our study shows that nanoparticles can be internalized by pancreatic cancer epithelial cells and pancreatic fibroblasts and do not cause any loss of viability. Our results demonstrate the potential applicability of nanoparticles, especially bioadhesive nanoparticles, for synergistic therapeutic targeting of different cell types in pancreatic cancer to improve treatment outcomes.
Abstract #62: External Validation of Gene Expression-based Predictive Model for Lymph Node Metastasis in Papillary Thyroid Cancer

Authors: G. Linderman, N. Nicolson, T. Carling, Y. Kluger, R. Korah

Introduction
Papillary thyroid cancer (PTC) often spreads to the regional lymph nodes. The frequency of central neck metastases is high, but the impact of such metastases is controversial. In addition, they are frequently undetectable on pre-operative imaging studies, so many centers perform routine “prophylactic” central neck dissections (CND). However, many patients who undergo CND are subjected to the additional risks of the procedure without any of the benefits, as a significant fraction will not be found to have central neck metastases. Our group explored whether the RNA-seq gene expression profile of the primary tumor can identify patients who are at higher risk of PTC lymph node metastasis and therefore most likely to benefit from CND.

We previously trained an elastic-net regularized logistic regression model to predict the binary outcome of lymph node metastasis using the papillary thyroid cancer dataset from the Cancer Genome Atlas (TCGA). When evaluated on a held-out validation set of the TCGA data, the model had an area under the curve of 0.77. In the present work, we sought to validate the model in an external dataset.

Methods
The original model was trained on 501 primary papillary thyroid cancers obtained from TCGA. Cases were randomly divided into training (75%) and validation (25%) cohorts. On the training set, an elastic-net regularized logistic regression model was trained to predict the binary outcome of lymph node metastasis using the expression levels of 20,531 genes. The resulting model was then evaluated on 74 PTC samples published in Yoo et al. 2017, an unrelated cohort of papillary thyroid cancers.

Results
The final logistic regression model consisted of 24 genes with non-zero regression coefficients. Evaluating the previously developed model on the Yoo et al. dataset revealed an area under the curve of 0.65.

Conclusion
Using RNA-seq gene expression data for 24 genes, the model is able to delineate a higher-risk and lower-risk set of patients for lymph node metastasis in PTC, and was validated in an external data set. Translating this risk modeling approach to the clinic could permit selection of higher-risk patients for prophylactic central neck dissection, while helping to avoid the additional morbidity of the procedure for those less likely to benefit.
Abstract #63: Progress in SLC26A6 (A6) structural studies by Cryo-EM

Authors: Alexei Surguchev, Alberto Rivetta, Kirill Grushin, Jun-Ping Bai, Frederick Sigworth, Dhasakumar Navaratnam and Joseph Santos-Sacchi

Introduction: SLC26A6 (A6) a member of the SLC26 family of anion transporters, is responsible for transporting oxalate, sulfate, and bicarbonate. A6 is an anion-exchanger/transporter expressed in the apical membrane of the kidney proximal tubule. The molecular mechanism which allows it to transport anion is currently unclear. The current 7+7 inverted repeat model is based on homology modeling of three distant family members SLC26Dg, UraA, and AE1, however a better structural information is long overdue in order to get a clearer understanding how it functions as a transporter on a molecular level. Here we discuss our continuous efforts in optimizing expression, purification, and ultimately interrogating the feasibility of using SLC26A6 for structural studies by Cryo-EM.

Methods: SF9 insect cells infected with A6-GFP baculovirus were used for expression. Membranes were extracted and A6-GFP was subjected to a two-step purification procedure of affinity and SEC chromatography in the presence of the non-ionic detergent DDM. SEC peak fractions were analyzed by negative staining (NS) EM. A6-GFP from the peak fractions were loaded on holey carbon grids, vitrified, imaged on a FEI Glacios Cryo-EM microscope, and analyzed using Relion single particle software package.

Results and conclusions: A6-GFP eluted as a single monodisperse peak in DDM. Its monodispersity was confirmed by negative staining. Cryo-EM micrographs showed the presence of protein particles resembling A6 trimers. Relion analysis of Cryo-EM data sets offers the possibility to classify particles in 20 2D classes and build an initial 3D model, however a larger and more homogeneous data set is required in order to attempt high resolution reconstruction.

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Abstract #64: Long-term exposure of laryngopharyngeal mucosa to acidic bile is carcinogenic

Authors: Dimitra P. Vageli, Sotirios G. Doukas, Jose Costa and Clarence T. Sasaki

Background. There is growing epidemiologic evidence linking biliary esophageal reflux to cancers of the upper aero-digestive system 1,2. During esophageal reflux bile frequently reaches the upper aero-digestive tract potentially exerting its carcinogenic effect on pharyngeal mucosa 3. We have previously demonstrated that exposure of murine laryngopharyngeal mucosa to acidic bile for 45 days induces epithelial dysplasia and that these changes are associated with activation of the NF-κB oncogenic pathway 4-8. To buttress the role of acidic bile reflux we extended the exposure in the in vivo mouse model to elucidate whether the lesions of dysplasia progressed to fully invasive carcinoma under continued intermittent exposure to acidic bile.

Methods. In Mus Musculus, mouse strain C57Bl6J (Jax mice, Jackson Laboratory USA) [24 males + 24 females (8 males + 8 females/group)] we performed repeated topical application on laryngopharyngeal mucosa, two times per day for 100 days, using a mixture of conjugated bile salts (~4 μmoles/day) at acidic pH 3.0, at molar concentration as previously described 4, based on the concentrations found in esophageal aspirates of patients with gastroesophageal reflux disease (GERD) 2. The experimental and control groups included (i) bile at acidic pH 3.0, (ii) an acid alone, without bile salts, (buffer saline; pH 3.0), and (iii) a saline-treated control group at pH 7.0 (approved protocol 11039 by IACUC, Yale University). Histologic evaluation, immunohistochemical, AQUA, gene expression and miRNA analyses were performed in laryngopharyngeal mucosa tissue specimens from animals of each group.

Results. We show that acidic bile progressively promotes malignant lesions characterized by increasing: i) oxidative DNA damage; ii) p-γH2AX expression consistent with DNA double-strand breaks (DSBs); iii) NF-κB pathway activation, and iv) elevated p53 expression. The histologic demonstration of invasive cancer of the hypopharynx observed in mice exposed to acidic bile is preceded by elevated transcriptional levels of cancer-related cytokines, Tnf and Il6, anti-apoptotic Bcl2, and other oncogenic factors such as Egfr, Rela and Stat3, as well as deregulation of cancer-related miR-21, -155, -192, -34a, -375 and -451a.

Conclusion. We provide new evidence that long-term exposure of laryngopharyngeal mucosa to acidic bile is carcinogenic and worthy of our consideration as an independent risk factor in the development of supraesophageal malignancies. As importantly, we also reproduce the role of several biomarkers of progression that can serve as valuable indicators of early neoplasia in our experimental model. These findings provide a sound basis for proposing translational studies in the human by exposing new opportunities for early detection and prevention.

Abstract #65: Altered Hemodynamics During Arteriovenous Fistula Maturation Leads to Reduced Fistula Patency in Female Mice

Authors: Arash Fereydooni, Tambudzai Kudze, Shun Ono, Luis Gonzalez, Ryosuke Taniguchi, Jun Koizumi, Toshiya Nishibe, and Alan Dardik

Introduction: The arteriovenous fistula (AVF) is the preferred method of dialysis access due to its proven superior long-term outcomes. However, women have lower rates of AVF patency and utilization than men. We used a novel mouse AVF model that recapitulates human AVF maturation to determine if there are differences in AVF patency in female and male mice.

Methods: Aortocaval fistulae were created in female and male C57BL/6 mice (9-10 weeks). At days 0, 3, 7 and 21, infrarenal IVC and aortic diameters and flow velocity were monitored by Doppler ultrasound and used to calculate the vessel diameter, blood flow and shear stress. AVF were harvested and proteins were examined using proteomic analysis and immunofluorescence, and mRNA by qPCR.

Results: At baseline, female mice weighed less and had lower IVC velocity (41.87±13.18 mm/s vs 28.5±10.3 mm/s, p=0.0002) and smaller magnitudes of shear stress (10.94±3.715 dyn/cm² vs 6.971±2.284 dyn/cm², p=0.0003), but there was no significant difference in IVC diameter (1.188±0.3077 mm vs 1.194±0.1857 mm; p=0.9503) and thickness (3.20±0.44 µm vs 4.15±0.7 µm; p=0.9128). After AVF creation, both female and male mice had similar IVC dilation (p=0.682) and thickening with no significant differences in IVC wall thickness (10.85±3.244 µm vs. 14.40±9.937 µm; p=0.2931) at day 42. However, female mice had diminished AVF patency (25.7% vs. 64.3%, p=0.039). During fistula maturation, female mice had lower IVC mean velocity and shear stress magnitude and increased spectral broadening (p=0.0376). mRNA and protein expression of KLF2, eNOS and VCAM-1 was similar at baseline in female and male mice, but increased in the AVF only in male (p<0.001), but not in female mice. Proteomic analysis of female and male mice detected 56 proteins expressed at significantly higher levels in the IVC of female mice and 67 proteins expressed at significantly higher levels in the IVC of male mice; function-specific analysis showed that the IVC of male mice overexpressed proteins that belong to pathways implicated in the regulation of vascular function, thrombosis, response to flow and vascular remodeling (p<0.05).

Conclusion: AVF in female mice have diminished patency, preceded by lower velocity, reduced magnitudes of shear stress and less laminar flow during maturation. There is also sex-specific differential expression of proteins involved in thrombosis, response to laminar flow, inflammation and proliferation. These findings suggest that hemodynamic changes during fistula maturation may play an important role underlying the diminished rates of AVF utilization in women.
Abstract #66: Whole exome sequencing of atrioventricular septal defect demonstrates key contributions from Plexin-Semaphorin, Hedgehog and cilia signaling in cardiac development

Authors: Lalita Wadwha, Holly Corbitt, Hannah Lester, Kevin McDonnell, Thibault Vernier, Charles D. Fraser, James O’Brien, David Craig, Stephen B. Gruber, Cheryl Maslen, Ivan Moskowitz, and Peter J. Gruber

Introduction
Congenital heart disease (CHD) is the most common birth defect, affecting >40,000 births per year. One of the most severe forms of CHD is atrioventricular septal defect (AVSD). Most AVSDs are associated with genetic syndromes, such as Trisomy 21, though they can also occur sporadically. While some genetic risk factors have been identified, the cause of the majority of sporadic, non-syndromic AVSD cases remains unknown. To expand our understanding of the genetic underpinnings of AVSD, and specifically to understand the differences between syndromic and non-syndromic AVSD beyond large structural defects, we used whole exome sequencing (WES) to define the genetic variation in a cohort (n=228) of both syndromic (n=67) and non-syndromic (n=161) AVSD cases. By applying parallel strategies of case-control gene burden analysis and a deleterious rare variant filtering strategy, we:

1) confirm genes previously suspected to play a role in AVSD
2) identify novel genes and pathways
3) uncover unanticipated risk alleles that underscore syndromic and non-syndromic AVSD

Methods
Whole exome sequencing was conducted on 228 patients and 429 controls. Library capture was performed with the Niblegen V2 kit and WES completed with Illumina HiSeq 2000. Variant calling employed Picard, Samtools, and GATK. Data cleaning and filtering was performed using PLINK v1.90b3g, providing a total genotyping rate of 0.99997. Principal component analyses (PCA) were performed on alignment, variant, and population level data using the prcomp package in R. SKAT-O was used to test for the association with AVSD as a dichotomous variable. Variants were interrogated in the 1000 Genomes, ExAC browsers, and Genome Aggregation Database. The integrated gene signal processing (IGSP), was used as one of two rare-variant approaches to prioritize risk genes.

Results
SKAT-O identified ITGA5, FGF10, and TNFSF9 as genes associated with non-syndromic AVSD (see figure). IGSP prioritized an additional 25 risk genes, three of which were also identified in the SKAT-O analysis. These top 25 risk genes were significantly enriched for genes in cardiac development, including ZFPM2, MAP2K1, ITGAV, CXCL12, JAM2, and GATA6.

Conclusions
This large sequencing study of AVSD used parallel approaches to discover risk genes for AVSD. Some of the genes we discovered confirm prior studies demonstrating the critical role of the second heart field and SHH signaling in the formation of the atrioventricular septum (GATA6, ZFPM2, FGF10; and ciliome genes GLI3, GLI1, PTHC1, SMO). Additionally, we identified genes involved in novel signaling pathways, trafficking, cell adhesion, and transcription factor networks (e.g. ATF1 and MYC), signaling regulators (e.g. COP3, ERN1, GNG3, and P2RX3). Furthermore, we identify similar risk alleles in both syndromic and non-syndromic patients, suggesting that Trisomy 21 may not be a sufficient genetic explanation for AVSD in syndromic patients.
Abstract #67: Bio-distribution of Microparticles in Mice following Intra-placental Injection
Authors: Nathan Maassel, Douglas Wu, Sarah Ullrich, Nicholas Yung, Mark Saltzman, David Stitelman

Introduction: Placental insufficiency is seen in up to 8% of pregnancies and is responsible for 16% of maternal deaths, and 20-30% of fetal deaths due to pre-eclampsia and pre-maturity respectively. Placentas of growth restricted fetuses are shown to be deficient in multiple growth factors including VEGF and IGF-1. Several studies have demonstrated correction of intrauterine growth restriction by viral vector delivery of these growth factors, however inflammation produced by these therapies prohibits translation to clinical use at this time. We propose direct injection of microparticles loaded with growth factor to target this pathology, and here present preliminary data in mice regarding biodistribution of 3 particle types.

Methods and Materials: On gestational day 15 (20 is term), pregnant dams were anesthetized, and a laparotomy was performed to expose the uterine horns. Mice placentae were individually injected with 15 uL of a 20mg/ml dose of microparticles. After injection, mice were either euthanized immediately, or at 3 hours to determine particle biodistribution. Three microparticles were tested: 2.5 uM Alginate (V-Alginate), 5 uM Alginate(X-Alginate), and 3 uM Poly (lactic-co-glycolic acid) (PLGA). For immediate harvests, placenta only were harvested, while 3-hour harvests included fetus and maternal liver for evaluation. Specimens for both experiments were flash frozen, then later sectioned at 14 uM and stained with DAPI for histologic evaluation using confocal microscopy. Un-injected mice placentae for each respective gestational day were used as control tissue.

Results: In total 6 dams were used – two for each particle type (immediate and 3-hour harvest). In total there were 27 placentae injected. V-alginate was readily visualized at immediate harvest but was not visualized in placental tissue, maternal liver, or fetal liver at 3 hours. X-alginate was readily visualized in placenta harvested immediately but appeared degraded within the placenta and mom liver at 3 hours, with none seen in the fetal liver at 3 hours. PLGA MP was well visualized immediately within the placenta, and again found at 3 hours in placental tissue, mom liver, and fetal liver.

Conclusion: Alginate microparticles appear to quickly degrade in placental tissue and do not show any signs of transfer to the fetus. PLGA microparticles appear to be more resilient within the placenta at delayed harvest and additionally show robust uptake in the maternal liver and some evidence of transfer to fetal liver at 3 hours. PLGA microparticles could be a vehicle for growth factor to correct placental insufficiency in rodent models with eventual translation to an off-the-shelf human therapy.
Abstract #68: Bio-Functional Collagen Matrix Scaffold Composition Differentially Promotes Paracrine Activity in Human Induced Pluripotent Stem Cell Derived Vascular Smooth Muscle Cells  
Authors: Kaiti Duan, Biraja Dash, Henry Hsia MD

Purpose: Induced-pluripotent-stem-cell-derived-vascular smooth muscle cells (iPSC-VSMC) have the potential to treat chronic wounds by secreting proangiogenic factor vascular endothelial growth factor (VEGF) (1). However, little is known how the extracellular matrix (ECM) composition may impact the cells’ paracrine secretion profile. In this study, our objective was to understand the effects of ECM density and functionalities on the secretory profile of human iPSC-VSMCs.

Methods: Type-I collagen was used as the material for the scaffolds and were incorporated with hyaluronic acid (HA), fibronectin, and laminin functional biomolecules to fabricate different functionalities of collagen scaffolds. The functionalities were used in combination with three different density of type-I collagen (1.25mg/ml, 2.5mg/ml, and 5mg/ml) to study iPSC-VSMCs viability and paracrine secretion profile. Several pro-angiogenetic factors included VEGF, Stromal cell-derived factor (SDF), platelet derived growth factor (PDGF), basal fibroblast growth factor (bFGF), angiopoietin 1 (ANG-1), IL-8, and transforming growth factor (TGF) were investigated. Anti-inflammatory factor IL-10 was also evaluated.

Result: Human iPSC-VSMCs functional biomolecules-collagen scaffolds showed an increase in cell viability across all the collagen densities compared to the non-functional collagen scaffolds. 1.25mg/ml scaffolds displayed the greatest significant level of cell proliferation (P-value=0.0001). Enhanced VEGF was observed in all three of the functionalized scaffolds in 1.25mg/ml (P value=0.0086) and in 2.5mg/ml collagen with HA(p value=0.0026), whereas no significant difference in VEGF level was found among 5mg/ml functionalized scaffold group. Interestingly, fibronectin-functionalized 5mg/ml collagen scaffold exhibited substantially elevated bFGF secretion (P value=0.0049). There was also a positive correlation of increasing amount of fibronectin embedment with increasing bFGF paracrine secretion (P value=0.0001). Furthermore, recent preliminary data showed an upregulation of IL-8, and IL-10 secretion in fibronectin-functionalized collagen scaffolds in 1.25mg/ml and 2.5mg/ml, respectively.

Conclusion: These results suggested that functionalization along with density differentially regulate paracrine function of Human iPSC-VSMCs. Future studies in elucidating the underlying signaling pathways and mice model experiments will further deepen our understanding of the interaction between ECM and Human iPSC-VSMCs. This will ultimately optimize Human iPSC-VSMCs as a viable therapeutic agent for chronic wound healing.

Reference:
Abstract #69: Inhibition of NLRP3 inflammasome derived interleukin 1β during normothermic machine perfusion of human kidneys


Introduction: Post-transplant renal ischemia reperfusion injury (IRI) can result in acute kidney injury manifested as delayed graft function. A critical mechanism in IRI is the intracellular assembly and activation of the NLRP3 inflammasome, which triggers production of inflammatory caspases and the maturation of the prototypic inflammatory cytokine IL-1β. MCC950 has been shown to be a potent NLRP3 inhibitor in experimental autoimmune conditions. In this study, we delivered MCC950 to human kidneys during normothermic machine perfusion (NMP) and assessed the response using an organ culture model.

Methods: Human kidneys declined for transplantation were studied. An MCC950 dose-response study was performed using cold stored kidneys (n=4). Subsequently, kidneys were randomly allocated to NMP alone (n=4) or NMP plus MCC950 (n=4). NMP was performed using a red cell-based perfusate at 36-37°C. After 4 hours of NMP sections of renal cortex were divided into 1 mm³ samples and placed in M199 media for 4h at 37°C. Triplicate samples were then transferred to a hypoxic chamber for 2h at 37°C and finally transferred back into normal media and incubated at 37°C for 2h to simulate reperfusion. Following the reperfusion period, tissue and media were collected and analyzed for IL-1β levels via ELISA (Figure 1A).

Results: Exposure of human renal cortex to MCC950 in concentrations ranging from 0-100 µM demonstrated a clear dose-response relationship between NLRP3 inhibitor concentration and IL-1β levels (Figure 1B). NMP administration of MCC950 at 100 µM (the most inhibitory concentration) led to a highly significant reduction, and in some cases complete inhibition, of IL-1β secretion after subsequent organ culture (Figure 1C; p < 0.0001).

Conclusions: NMP provides a highly effective platform for the targeted delivery of pre-transplant therapies. Blockade of the NLRP3 inflammasome and downstream IL-1β production is suggested as a therapeutic opportunity in the search for interventions that may improve early allograft function.
Abstract #70: Targeting the Intestinal Microbiome to Promote Intestinal Mucosal Growth in Mice

Authors: Matthew P. Shaughnessy, Christine J. Park, Lilly H. McCarthy, Natasha A. Barry, Andrew L. Goodman, Robert A. Cowles

Background: Previous work demonstrated enhanced enterocyte proliferation and mucosal growth in gnotobiotic mice colonized with a limited microbiome, supporting the notion that intestinal flora participate in mucosal homeostasis. Furthermore, broad spectrum enteral antibiotics are known to induce near germ-free (GF) conditions in mice with conventional flora (CF). We hypothesized that inducing near GF conditions with broad spectrum enteral antibiotics (eAbx) would result in ordered small intestinal mucosal growth in CF mice but similar treatment would have no effect in GF mice with no inherent microbiome.

Materials and Methods: C57BL/6J CF mice were allowed ad libitum access to either an antibiotic solution (eAbx: Ampicillin, Ciprofloxacin, Metronidazole, Vancomycin, Meropenem) mixed in artificial sweetener (n=3-6) or artificial sweetener alone (n=3-4) for 1, 2, or 4 weeks. After treatment, the small intestine was harvested, fixed, sectioned and stained with H&E. Villus height (VH) and Crypt Depth (CD) were measured and mucosal surface area (MSA) was calculated. The small intestinal mucosa was further assessed for crypt proliferation index (CPI), degree of apoptosis, and villus and crypt cellular profiling. CPI was determined by intraperitoneal bromodeoxyuridine (BrdU) injection one hour prior to harvest and expressed as the percentage of BrdU-positive cells per crypt. Villus apoptosis was assessed using deoxynucleotidyl transferase dUTP nick end labeling (TUNEL) assay. Cellular composition of villi and crypts was investigated by standard immunofluorescent staining for chromogranin A and lysozyme. Enterochromaffin cells (ECC), Goblet Cells (GC), and Enterocytes (EC) were counted and calculated as a percentage of total cells per villus, and number of Paneth Cells (PC) per crypt was assessed. The experiment was repeated in C57BL/6J GF mice (n=6 GF-eAbx, n=6 GF-vehicle) for a duration of 2 weeks to test whether any observed changes could be attributed to alterations within the intestinal microbiome. Reversibility of the eAbx treatment effect was evaluated by comparing the mucosa of CF mice having received 2 weeks of eAbx followed by 2 weeks of vehicle (n=4CF) to that of CF mice treated with vehicle alone for 4 weeks (n=4CF). Data were analyzed within Prism V8.0.0 using Student’s t-test (Mean±SEM) and significance assumed for p<0.05. All animal protocols were approved by Yale University’s Institutional Animal Care and Use Committee.

Results: Antibiotic-treated CF (Abx-CF) mice had taller villi (415.5±19.6μm vs 270.9±8.9μm, p<0.0001), deeper crypts (78.8±2.4μm vs 73.1±2.4μm, p=0.09), increased CPI (39.2±0.56% vs 26.9±0.52%, p<0.0001), increased degree of apoptosis (1.9±0.16cells vs 1.1±0.14cells, p<0.001), and greater MSA (1195±166cm² vs 663±83.3cm², p=0.01) compared to vehicle-treated CF mice at both 2 and 4 weeks (2 week data listed). No significant differences in mucosal growth parameters were noted at 1 week of treatment. Abx-CF mice had significant increase in total cells per villus along the entire small bowel (p<0.05). The proportion of EC, ECC, and GC in villi and PC in crypts was unchanged in Abx-CF mice compared to vehicle-treated CF mice (p>0.05). Following the cessation of antibiotic therapy for 2 weeks, Abx-CF mice demonstrated persistent increases in VH, CD, and MSA (p>0.05). When GF mice were treated with eAbx for 2 weeks, no significant increases in VH or MSA occurred when compared to vehicle-treated GF mice (p>0.05).

Conclusion: Enteral administration of broad-spectrum antibiotics to mice with a conventional microbiome stimulates ordered and prolonged small intestinal mucosal growth, resulting in taller villi with increased proliferative markers and retention of normal cellular composition. Mucosal growth was not seen in germ-free mice treated with antibiotics, suggesting that the microbiome is the target for the stimulatory effects of antibiotics on intestinal mucosal growth. The relationship between the microbiome and mucosal growth warrants further study and may provide guidance for development of future therapies for patients with malabsorptive disorders.
Abstract #71: Development of an Organoid–based Model System for Intraductal Papillary Mucinous Neoplasia of the Pancreas

Authors: Nicholas Peters, Prashanth Gokare, Nesrin Hasan, Paulomi Aldo, Anup Sharma, Nita Ahuja, John W Kunstman

Introduction. Intraductal papillary mucinous neoplasms (IPMN) of the pancreas are mucin-producing cystic lesions that arise from the pancreatic ductal epithelium. IPMN are pre-malignant and are thought to cause 10-20% of pancreatic ductal adenocarcinoma (PDAC). Interest in IPMN is high as it is both detectable and treatable prior to the development of invasive PDAC. However, most IPMN do not progress to PDAC and the underlying molecular determinants remain undefined, largely due to the lack of a suitable model system. To address this, we sought to assess the feasibility of creating a well-characterized, genetically tractable model derived from human IPMN tissue utilizing an organoid-based cell culture approach.

Methods. Patients undergoing pancreatectomy for cystic lesions were consented for multi-region tissue harvesting (HIC#1203009817). Following resection, aliquots were enzymatically digested to oligo-cell clusters and single cells. The resultant milieu was then embedded in a solubilized preparation of basement membrane proteins resembling the in vivo environment (Matrigel; Corning, New York, USA). Permissive media promoting epithelial growth was utilized to enrich for the ductal cellular fraction. Resulting spheroid organoids recapitulating source tissue architecture were characterized by microscopy. Subject to availability, specimens with sustained growth were genotyped via Sanger sequencing of known IPMN somatic mutational loci. Expression of typical IPMN proteins was characterized via immunohistochemistry (IHC).

Results. During the 12-month study period, 8 patients underwent harvesting of 19 unique tissue samples. Of those, 5 patients were found to have confirmed IPMN by clinical pathologic analysis. Ultimately, 5 viable cultures with microscopic evidence of organoid formation and sustained growth (defined as 2 de novo passages through fresh Matrigel) were isolated from 4 unique patients (Fig. 1A). Compared to fully permissive media, organoid growth was inhibited in the absence of growth factors Wnt3A, R-spondin, or EGFR and enhanced in the absence of MAPK inhibitor SB202190. Ongoing analysis of recurrent IPMN mutations (KRAS G12x, KRAS Q61x, GNAS R201x) reveal the presence of at least 1 mutation in 3 of 4 assessed organoid samples (75%). Similarly, IHC staining of 1 organoid sample for IPMN-defining protein markers (CEA, MUC2, CDX2, MUC5AC; Fig. 1B) mirrored expression of the clinical tissue of origin.

Conclusion. Human IPMN tissue can be successfully established, passaged, and maintained in a three-dimensional organoid culture model. Available data suggests these organoids are representative of bona fide IPMN tissue by both genetic analysis and protein expression.

Figure 1 – (A) Phase contrast microscopy of IPMN organoid cultures. (B) Immunohistochemical evaluation of formalin-fixed paraffin-embedded organoid derived from an intestinal-subtype IPMN. All recapitulate the expression pattern of the source tissue.

Abstract #72: SLU7 regulates cardiac developmental programs and contributes to the pathogenesis of hypoplastic left heart syndrome

Authors: Yujia Yang, Zhe Han, Lia Crotti, Markus Krane, Neil Bowles, Gabriel Baccam, Hannah Lester, Zhiheng He, Lutz Hein, Thomas Meitinger, Karl Laugwitz, Alessandra Moretti, and Peter J. Gruber

Introduction

Hypoplastic left heart syndrome (HLHS) is a severe form of congenital heart disease characterized by underdevelopment of the left ventricle. There are conflicting theories regarding the pathogenesis of this disease. We sought to further define the genetic landscape of HLHS through exome sequencing and mechanistic interrogation using a novel, functional genomics approach (fly, mouse, human). We sequenced a cohort of patients with HLHS identifying the mutational landscape in this cohort. Using a Drosophila screen, we unified the pre-mRNA-splicing factor slu7 as one mechanism for the development of HLHS. We generated Slu7 gene-targeted mice, identifying its essential role in development. Using RNASeq in human cells, we further explored the transcriptional and alternative splicing consequences of SLU7K302R. This study demonstrates the profound genetic diversity of HLHS, emphasizing the need for multiple approaches and patient-specific, individualized analyses to understanding the pathogenesis of HLHS.

Methods

Whole exome sequencing was conducted on 87 patients with HLHS. Exome-enriched indexed libraries were constructed and paired-end sequenced on an Illumina HiSeq4000 instrument. Read-mapping was performed with the Burrows-Wheeler Aligner (BWA) and SAMtools. Single-nucleotide variants and indels were called with GATK and PINDEL. Variants were interrogated in the 1000 Genomes, ExAC browsers, and Genome Aggregation Database. The predicted functional effect of a coding variant was surveyed using Polyphen2, SIFT, and CADD. Variants were functionally screened using siRNA knockdown and rescue experiments in mef2-lacZ transgenic flies. Immunohistochemistry (IHC) was conducted using standard techniques. Murine gene targeting of Slu7 was performed using an IGTC gene trap and standard techniques. Human cardiac myocytes (HCM) were transfected with SLU7 siRNA and collected for RNASeq; this was analyzed using custom R scripts, DESeq2, JunctionSeq, and RMATs. GSEA was performed to analyze expression datasets and annotate the enrichment results.

Results

In humans, we identified 94 non-synonymous de-novo mutations (81 missense, 7 frameshift, 3 nonsense, 2 splice variant and 1 in-frame deletion) in a cohort of 87 HLHS trios, one of which is SLU7K302R. In Drosophila, slu7 knockdown with SLU7K302R and SLU7WT human rescue experiments demonstrate a critical role for SLU7 in heart tube formation. In mice, SLU7 IHC demonstrated cardiac-specific expression in the developing heart. Homozygous Slu7 murine gene-targeted mice were embryonic lethal, demonstrated an essential role for Slu7 in mammalian development. SLU7 knockdown resulted in defects in transcriptional and alternative splicing of developmental programs, many of which are essential for cardiac embryogenesis. One of the aberrantly spliced products is the chromatin-modifying gene KMT2D, one of the most common genes mutated in HLHS.

Conclusions

These findings expand our knowledge of the genetic landscape of HLHS, emphasizing the need to go beyond in silico analyses to understand the mechanism. Furthermore, our studies demonstrate slu7/Slu7/SLU7 as a critical factor in RNA processing and cardiac development in fly, mouse, and human. These pathways include novel, as well as known (KMT2D), genes, building a knowledge base to enable the development of rational therapeutic and counseling strategies for this complex set of patients.
Abstract #73: New strategy to maximize nanomedicine delivery during ex vivo perfusion

Authors: C. Albert, L. Bracaglia, A. Koide, T. Lysyy, J. Langford, C. Edwards, J.S. Pober, W. M. Saltzman, S. Koide, G. Tietjen

Introduction: One solution to the severe lack of transplantable organs is the development of new therapeutic strategies to render marginal organs more resistant to injury, enabling their use without sacrificing the patient outcome. In this context, normothermic machine perfusion (NMP) can be used to deliver targeted nanoparticles (NPs) to potentially protect marginal organs from post-transplant reperfusion injury by providing a prolonged release of an encapsulated therapeutic without off-target toxicity. The standard targeting approach uses chemical conjugation to bind antibodies (Ab) directly to the surface of NPs. These chemistries have two major drawbacks: 1) too generic to control the final orientation of the Ab, which compromises targeting efficacy, or 2) so specific as to require different conditions for coupling of every different targeting Ab. To overcome these limitations, we designed a novel linker technology based on a synthetic binding protein called “Monobody” (Mb) [Sha et al., 2017, Protein Sci, 26:910].

Methods: We developed Mbs that potently and selectively bind to the Fc region of a specific IgG subtype. A unique cysteine was engineered in the otherwise cysteine-free Mbs to enable a single conjugation site to PLA-PEG-mal NPs (poly lactic acid-polyethylene glycol terminated maleimide) using thiol chemistry. The Mbs then function as linker to connect the NP to the Ab, forming Ab-Mb-NPs. The efficiency of binding of Ab-Mb-NPs to endothelial cells was characterized and compared with that obtained with PLA-PEG NPs directly conjugated with Ab using the amine-based chemistry (Ab-NPs).

Results: The Ab-Mb-NPs display a dramatic enhancement of binding efficiency compared to Ab-NPs using the exact same core PLA-PEG NPs, same anti-human-CD31 Ab, and same concentrations. The binding of Ab-Mb-NPs to human umbilical vein endothelial cells (HUVECs) is up to 300x better in vitro static culture (measured by flow cytometry after 2h incubation with the NPs), up to a 1300x better in vitro under flow (measured by quantitative fluorescence microscopy after 1h of constant flow) and up to 20x better ex vivo in a single vessel perfusion system (measured by flow cytometry after the injection of a bolus followed by 1h of perfusion). The Mb-NP system is readily adaptable to coupling with different Abs without re-engineering of Abs or NPs. Specifically, we showed that we can easily change 1) the targeting antibody (from mouse IgG1 anti-human-CD31 to mouse IgG1 anti-human-ICAM2) and 2) the species of the targeting antibody (from mouse IgG1 anti-human-CD31 to mouse IgG1 anti-pig-CD31).

Conclusion: In short, we have developed a new way to conjugate nanoparticles to antibodies that dramatically improves the efficiency of cell targeting, most likely due to improved orientation of the antibodies. The system is modular and easily adapted to different targeting antibodies. Thereby our Mb-linker technology combined with NMP will allow us to develop the formulation directly for the treatment of human organs and then switch the Ab in order to use the pig transplantation model to evaluate the long-term efficacy of the formulation.
Abstract #74: Elucidating the cells and pathways driving fibrosis in the intestine
Authors: Blackburn HN, Roulis M, Flavell RA

Introduction: Fibrosis/scarring is a complication associated with numerous chronic inflammatory diseases involving the skin, liver, kidneys, etc. Crohn's disease (CD) is a type of inflammatory bowel disease which exhibits chronic transmural inflammation and a high prevalence of clinically relevant complications like fistulae, strictures, bowel obstructions, and bowel perforations. Despite advancements in anti-inflammatory treatment, strictureing (a fibrotic complication) is often seen as an inevitable and irreversible cause of morbidity or mortality in CD patients. Unfortunately, there are currently no animal models with robust intestinal stricturing to study this disease in vivo. As such, little is known about which pathways or even which cells drive fibrosis in the intestine. Recent work has revealed that mesenchymal cells (aka “fibroblasts”) in the colon are a heterogeneous group of at least 4-5 different cell types. To better elucidate the driving forces of intestinal stricturing in CD, we propose to 1) assess the heterogeneity of human fibroblasts and activated transcriptional profiles across healthy, inflamed, and strictured tissue, 2) develop a novel stricturing CD model by combining a genetic CD mouse with a mechanical disruption (enterotomy and repair), and 3) confirm the results of our human studies by integrating up/downregulated pathways into our stricturing CD model through genetic knockouts. The goal of this work is to identify previously undiscovered mechanisms driving human fibrotic complications in the abdomen and establish a novel mouse model to study these candidate molecular and cellular pathways in vivo.

Methods: 1) To understand the diversity of fibroblasts in humans, we will use full thickness specimens from CD patients undergoing bowel resection for stricture. Specimens will be compared via histology, immunofluorescence, immunohistochemistry, and RNA sequencing across “normal,” “inflamed,” and “strictured” tissue (determined grossly) from the same resection. 2) To develop a novel stricturing model, we will perform an enterotomy and repair (and sham control procedures) on wild type versus TNFαARE/+ mice, which exhibit transmural inflammation of the terminal ileum. 3) To confirm the results of our human studies, once pathways are identified we will develop knock out or conditional knockout mice to be used in the stricturing model.

Results: 1) We identified two areas of collagen deposition in our first strictured specimen (submucosa and serosa) compared to normal. While the strictured submucosa showed a large population of myofibroblasts (αSMA+), the correspondent serosa lacked these cells. The strictured serosa was noted to have more active procollagen 1 producing cells compared to the submucosa. 2) Model is in process. At present mice of varying initial age (6 weeks old, 8 weeks old, 10 weeks old) are being aged postoperatively and will be evaluated at varying time points (4 weeks, 8 weeks, 12 weeks post op) to optimize stricture formation. 3) Pending results of (1).
Abstract #75: CD40 agonist in combination with checkpoint inhibition boosts anti-tumor immunity to melanoma

Authors: Irina Krykbaeva, Koonam Park, Andrew Daniels, Harriet Kluger, Marcus Bosenberg, Kelly Olino

Introduction: Melanoma is the deadliest skin cancer and is estimated to cause 6850 deaths this year. Checkpoint inhibitor treatment is currently frontline therapy for stage IV melanoma, and the overall response rate for dual therapy with αPD1 and αCTLA4 inhibitors is 57.6%. However, many patients either do not respond to checkpoint inhibition or develop resistance and ultimately experience disease progression. Options for these patients are limited and there is a critical need for new therapies to adequately treat αPD1 non-responders. The tumor microenvironment (TME) plays an important role in determining the efficacy of various treatments. Tumors that are resistant to checkpoint blockade are characterized by a non-inflamed TME with poor CD8+ T cell infiltration and CD8+ T cell exhaustion, an abundance of immune suppressive myeloid populations such as tumor associated macrophages (TAMS) and myeloid-derived suppressor cells (MDSCs), regulatory T cells, and loss of MHCI expression leading to inefficient antigen presentation. All of these changes are heavily based on innate immune dysfunction that results in an inability to activate T cells. Therefore, we hypothesize that agents targeting innate immunity, specifically agonistic CD40 antibodies, should synergize with checkpoint blockade to overcome resistance and produce a higher overall response rate. CD40 is a costimulatory receptor found on antigen-presenting populations such as dendritic cells, myeloid cells, and B cells. CD40 activation results in increased MHCI presentation, recruitment of CD4+ and CD8+ T cells, and CD8+ T cell activation.

Methods: We test a triple combination of αPD1 and αCTLA4 blockade together with CD40 agonist in a mouse melanoma cell line, YUMMER1.7, that can be used in immunocompetent mice and has a primary resistance to αPD1 similar to human melanoma. We evaluate treatment efficacy in both subcutaneous and metastatic models of melanoma. We use a Luminex assay on peripheral blood of treated and untreated mice to investigate the changes in the cytokine milieu induced by triple therapy.

Results: We treated mice with large, well established subcutaneous tumors with either triple therapy or dual checkpoint blockade. 75% of mice treated with triple therapy experienced complete tumor regression compared to only 12.5% of mice treated with dual αPD1 and αCTLA4. Importantly, we also show that triple therapy induces complete regression in 80% of mice with widespread YUMMER1.7 metastases compared to only 50% of mice treated with dual αPD1 and αCTLA4, even though a high dose of αCTLA4 was used for this experiment (Figure 1). Furthermore, rechallenging survivors with YUMM1.7, a melanoma cell line that is more aggressive and less responsive to immunotherapy than YUMMER1.7, also resulted in complete regression even without further treatment. This suggests that triple therapy leads to the development of a robust memory T cell response and truly durable survival. Cytokine profiling of peripheral blood from triple therapy treated mice reveals a high concentration of type 1 cytokines such as IL-1α, IL12, IFNγ, as well as myeloid associated cytokines TNFα and G-CSF, indicating a strong Th1 T cell response with involvement of inflammatory myeloid populations. Triple therapy also induces chemokines CXCL9 and CXCL10, which are directly responsible for CD8+ T cell recruitment into the TME.

Conclusion: Overall, this study demonstrates that taking advantage of innate mechanisms of T cell stimulation is a promising strategy to augment checkpoint inhibitor treatment in patients that do not respond to checkpoint inhibition alone. Future work will focus on further characterization of the changes to the TME induced by triple therapy, as well as determination of the mechanisms responsible for tumor regression.

Figure 1. Triple therapy results in improved survival compared to dual checkpoint inhibition. Metastatic YUMMER1.7 tumor bearing mice treated with a combination of anti-CTLA4, anti-PD1, and CD40 agonist antibodies show 80% survival at 45 days post tumor injection. Mice treated with anti-CTLA4 and anti-PD1 that did not receive CD40 agonist show 50% survival at 45 days post tumor injection.
Abstract #76: Surgeons’ Financial Relationships with Industry: The First Five Years of Open Payments
Authors: Christopher T. Breen AB and Saral Mehra MD MBA

Introduction: Industry payments to physicians are controversial and have been discussed in academic literature and popular media. It is important for surgeons to be aware of the state of financial relationships between industry and the various surgical fields. Our objective is to describe industry payments made to surgeons from 2014 to 2018 and identify trends during this time period. We hypothesize that there has been no meaningful change in industry payments to surgeons in the years studied.

Methods: Retrospective cross-sectional study (2014-2018) utilizing the Open Payments database. Surgeons receiving non-research industry payments (n = 184,106) as identified in the 2014-2018 Open Payments databases were included.

Results: There were 184,106 surgeons who received a collective 7,861,670 payments during the five-year study period, with 122,695 to 126,968 surgeons receiving 1,530,956 to 1,621,442 payments in any given year. The total value of payments ranged from $789 million in 2014 to $847 million in 2018 for a total of $4.0 billion over the study period. The median total payment per compensated surgeon per year varied by specialty, with obstetrics & gynecology (range of $133 in 2017 to $150 in 2018) most consistently near the low end of specialties and thoracic surgery (range of $567 in 2018 to $813 in 2016) consistently at the top.

Conclusions: Industry payments to surgeons have largely remained constant from 2014 to 2018, the first five years of available Open Payments data, suggesting that national public reporting requirements have not decreased financial ties between surgeons and industry, as some had expected.

Figure 1. Trends in Total Payment per Compensated Surgeon. Each line shows the total payment received by the median surgeon in that specialty in constant 2014 dollars.
Abstract #77: Assessment of Resident Cost Consciousness for Common Operating Room Expenses

Authors: Alee Hernandez, Erin White, Ashwini Paranjpe, Susanna Gallani, Peter Yoo

Introduction: In the face of rising healthcare spending, there is a heightened interest in managing costs. In teaching hospitals, interventions to increase cost-consciousness among residents may decrease spending overall, however there is limited knowledge of residents’ baseline insight into healthcare costs. This study presents the effort of a single university-based general surgery residency to evaluate trainees’ level of understanding regarding costs incurred in surgical care.

Methods: Qualitative and semi-quantitative data was collected using an iterative process including resident interviews and beta testing, during which we developed an online survey tool to probe multiple dimensions of cost-awareness. Questions examined familiarity with terminology, general and contextual understanding, and prior training regarding health care costs. We then utilized a new cost transparency tool, developed by our institutions’ perioperative information service and accessible within the electronic medical record, to identify the supply cost of 20 single-use items commonly used in general surgery procedures. This included various sutures, surgical energy devices, staplers, disposable laparoscopic tools, etc. We then assessed resident knowledge using a three-minute worksheet which asked them to estimate the costs of these items; this was distributed during weekly resident didactic time.

Results: Twelve residents participated in qualitative interviews. 62 of 75 residents responded to the online survey (82.7%), and 45 of 75 (60%) responded to the cost estimate worksheet. Several themes emerged from our qualitative interviews. Respondents endorsed that cost was frequently discussed in the operating room and expressed interest in knowing the supply cost of surgical tools. Although residents were frequently able to identify the costliest items for most operations, few had a basis for estimating the actual cost of the items used. Commonly, residents suspected that most attendings likely had a similar level of understanding. These data was corroborated by survey results. Only two-thirds accurately identified the definition of “cost”, 23.0% stated that they “understand health care costs,” and 13.1% had ever taken a formal finance or accounting course. However, 91.9% of respondents believed it important for physicians to understand costs, with 79% recommending formal didactic sessions in resident education. Figure 1 shows a comparison between actual costs and residents’ cost estimates for 20 commonly used single-use surgical tools. Residents tended to dramatically overestimate the costs of most items, but greatly underestimated the three highest-cost items.

Conclusions: This mixed-methods study demonstrated that surgical residents lack knowledge regarding health care costs, particularly regarding itemized costs. However, they are aware of what items carry high costs, place importance on understanding costs, and are eager to learn more. Cost-transparency tools, such as the one described here, alongside formal resident education initiatives, may allow residents to be more active participants in decision-making and discussion surrounding the costs for the care they deliver.
**Abstract #78: Protocolized Management of Abscess Drains Safely Reduces Resource Utilization in Complicated Pediatric Appendicitis**

**Authors:** Lindsay Eysenbach MSIV, Brian Dillon MD, Michael Caty MD MMM, Emily Christison-Lagay MD, Robin Goodman MBBChir MBA, Doruk Ozgediz MD, David Stittleman MD, Daniel Solomon, MD

**Introduction:** Clinical protocols for diagnosis and treatment of pediatric appendicitis have improved process measures and outcomes. However, a paucity of data exists evaluating standardized management strategies for percutaneous drains placed for appendiceal abscesses in children. We hypothesized that a drain management protocol based upon clinical factors instead of routine drain interrogation: 1) would reduce the need for interventional radiologic (IR) procedures, decreasing anesthetic and radiation exposure; 2) would not adversely impact clinical outcomes.

**Methods:** A standardized drain management protocol advising appendiceal abscess drain removal if the patient was afebrile and clinically well following 48-hours of <20cc/day drain output was uniformly adopted by pediatric surgeons at a tertiary-care children’s hospital in April, 2016 (Figure 1). A retrospective chart review was conducted for all patients with an appendectomy requiring abscess drainage by IR for 3-years preceding and 3-years following protocol adoption (2013-2019).

**Results:** Fifty-nine patients (pre-protocol=40, post-protocol=19) underwent abscess drainage by IR, of whom 52 (pre-protocol=34, post-protocol=18) had a drain placed. Baseline demographics, initial presentation, and management strategy were similar across groups. Following protocol implementation, total number of IR procedures decreased (p=0.0047), including CT-guided and fluoroscopic interventions (Table 1). There was no statistically significant difference in number of diagnostic imaging studies, readmissions, or length of stay.

**Conclusion:** Implementation of a standardized protocol for abscess drain management in pediatric complicated appendicitis reduced the number of IR procedures without a negative impact on clinical outcomes or increase in alternative imaging studies. Thus, this treatment approach decreased radiation exposure, anesthetic administration, and resource utilization.

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**Figure 1: Drain Protocol**

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<table>
<thead>
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<th>DRAIN PLACED</th>
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<tr>
<td>Inpatient: Daily rounding with monitoring of output</td>
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<tr>
<td>Outpatient: Weekly clinic visit with drain output diary</td>
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Yes / No

> 14 Days post drain placement?

Yes / No

> 20mL/day for last 2 days?

Yes / No

Discontinue Drain

Drain Study

Inpatient: Daily rounding with monitoring of output

Outpatient: Weekly clinic visit with drain output diary

Yes / No

Fistula?

Yes / No

Fistula Management

Seroma/Lymphocele management

No

Residual Collection?

Yes / No

Residual Collection with Fistula

Residual Collection with Seroma/Lymphocele

No

Drain Appropriately Positioned/and Patent?

Yes / No

Drain Change or New Placement

Ultrasound

Contrast Study

No

Ultrasonic
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Abstract #79: Improving long term outpatient vascular follow-up among patients undergoing lower extremity revascularization in Patients with lower extremity revascularization

Authors: Tanner Kim, Vanessa Baratta, Jolanta Gorecka, Shin Rong Lee, Cassius Iyad Ochoa Chaar

Background: Appropriate follow-up with a vascular specialist after lower extremity revascularization (LER) is important to assess the patency of revascularization and avoid limb-loss. Loss to follow-up after LER is associated with worse outcomes and higher mortality rates. We sought to identify all patients lost to follow-up at a single institution and to intervene with physician-delivered telephone calls and informative letters. Our primary outcome was to improve outpatient vascular compliance following the intervention and our secondary outcome was to identify barriers to follow-up in this patient population.

Methods: Patients who underwent LER at the Yale New Haven Hospital Heart and Vascular Center in 2016 and who did not have a record of follow-up in Epic® were identified. Patients who died, moved, transferred care, or who were currently seeing a vascular specialist were excluded. The remaining patients were contacted by telephone by surgical residents and were sent letters to encourage appropriate medical care. Vascular appointments were then tracked over a three-month period to determine the efficacy of the interventions.

Results: Of the 125 patients initially flagged as lost to follow-up in Epic®, 54 (43.2%) patients were included in the study; 26 patients had died, 42 had appropriate follow-up, and 3 moved away. At least three attempts were made to contact all 54 patients. Nine patients (17%) were successfully contacted via telephone and completed a resident-distributed survey. Four additional patients were deceased and two had moved, leaving 48 patients without appropriate follow-up. Of those patients, 85% were discharged on an antiplatelet and 81% were discharged on a statin medication. Several patients expressed difficulty traveling to appointments given their frail condition or a lack of transportation. Letters encouraging follow up were then sent to all 48 patients, and vascular follow up is currently being tracked over a three-month period.

Conclusion: Loss to follow-up after LER is a common problem among vascular patients. Assessing determinants for loss to follow-up is an important quality initiative in order to more effectively improve outpatient compliance with a vascular specialist. Telephone calls have low rates of success, suggesting that an inability to contact patients may contribute to poor follow up. While the effectiveness of letters is still being assessed, establishing other means of communication with patients may improve follow up rates.
Abstract #80: Utilization of an Ultrasound Template for Evaluation of Pediatric Appendicitis at Bridgeport Hospital

Authors: Sarah Ullrich, Nathan Maassel, Nicholas Yung, Matthew Shaughnessy, Justin LeBlanc, Daniel Solomon

Introduction: Currently there is no set template used by radiology technicians or radiologists at Bridgeport Hospital while evaluating pediatric patients for appendicitis with ultrasound (US). We are seeking to implement at least 50% utilization of a validated template for diagnosis that has been demonstrated to improve the diagnostic accuracy of US and decrease CT scan usage.

Methods: We retrospectively reviewed all patients who were evaluated for appendicitis over a two year period, from November 2017 through November 2019. US reads were evaluated for template usage, appendix visualization, whether or not the scan was diagnostic and the reporting of ancillary findings. Rates of CT scan usage were also evaluated.

Results: We identified 662 patients who were evaluated for appendicitis during the study period. Of those, 89% of patients were evaluated with an US, of which 12% then underwent a CT scan for further evaluation, and 11% of patients were evaluated with a CT scan only. The template was used 0% of the time. The appendix was visualized 21% of this time, 80% of US reports commented on ancillary findings and the US was considered diagnostic 15% of the time. These figures are compared to adult and pediatric radiologists using the template at YNHH after this same template was introduced in Fig 1.

Conclusions: Among pediatric patients evaluated for appendicitis at Bridgeport Hospital, few ultrasounds are diagnostic and there are high rates of CT scan usage. We propose that the implementation of a template for US reads will improve diagnostic performance of US and decrease CT Scan utilization.

Fig 1: Rates of follow up CT scan usage and of having a diagnostic US and YNHH vs Bridgeport Hospital
Abstract #81: Augmenting Breast Nutrition: Pre-op Nutritional Screening in Breast Surgery Patients
Authors: John Langford, Michelle Salazar, Vadim Kurbatov, David Tsai, John Smetona, Henry Hsia

Introduction
The nutritional status of patients has a significant impact on their outcomes. Malnourished patients have increased rates of wound healing problems and can have a mortality of up to 50% three years after discharge from the hospital (Lim, 2012). Furthermore, it has been shown that up to 45% of patients admitted to the hospital (Allard, 2016) and 15% of those undergoing outpatient elective surgery are malnourished (Roy, 2017). Given the impact of nutritional status on outcomes, more specifically wound healing, and the high proportion of patients at risk for malnourishment, we sought to develop a screening tool to preoperatively evaluate the nutritional status of patients undergoing mastectomies with reconstruction.

Methods
Patients undergoing partial or total mastectomy with reconstruction from February 2020 to April 2020 will be included in the study. A nutritional screening questionnaire will be implemented in the pre-operative history and physical, which then will be uploaded to EPIC. Patients’ nutritional status based on the questionnaire will be assessed through EPIC.

Results
Our goal is to increase pre-operative nutrition screening in mastectomy patients with reconstruction from the baseline of 0% to 50% by April 2020.

Conclusions
We anticipate this study will allow us to identify patients that are malnourished that would have otherwise not been identified. Using this preliminary data we will design a protocol to optimize the nutritional status of these patients prior to surgery, with the ultimate goal of decreasing wound healing adverse outcomes.
Abstract #82: Examining the Last 24 Hours: An Opportunity to Reduce Excessive Opioid Prescriptions at Post-Operative Discharge

Authors: Erin M. White MD MBS, Alex S. Chiu MD MPH, Peter S. Yoo MD

Introduction: In response to the ongoing opioid crisis, there is increasing evidence that post-operative inpatients who require no opioids in the last 24 hours of admission do not require additional opioids after discharge. Providing these patients with opioid prescriptions increases the possibility of diversion or abuse. Baseline prescribing patterns are unreported, therefore we undertook a mixed-methods study of provider beliefs and prescription practices at time of discharge for post-operative inpatients on general surgery teaching services.

Methods: In August 2019, Yale general surgery residents received an electronic survey asking them to report on a 5-point (Never to Always) scale: 1) How often they look at the medication administration record (MAR) to see how much pain medication patients received in the 24 hours prior to discharge 2) How often they believe post-operative inpatients who receive no opioids in this 24-hour period should still be prescribed opioids. This self-reported data was then compared to electronic medical record data. We reviewed all elective inpatient cases in the Yale New Haven System between November 1, 2017 and August 30, 2019. By screening for cases done at three clinical teaching sites and admitted to 92 attendings-of-record in general surgery subspecialties, we excluded all patients for whom a general surgery resident was unlikely to be involved in their care. In addition to basic demographic data, we recorded morphine milligram equivalents (MMEs) administered in the 24 hours prior to discharge, and MMEs of all discharge medications prescribed.

Results: 61 of 75 residents (81.3% response rate) responded to the survey. Both questions yielded a bimodal distribution with 55.7% of residents reporting they look at the MAR most of the time, while 42.6% of residents believe post-operative inpatients who receive 0 MME should still regularly receive opioid prescriptions. Regression analysis showed no correlation between the frequency residents reported consulting the MAR and how frequently they felt opioids should be prescribed. Review of practice patterns documented in the medical record demonstrated even higher rates of opioid prescribing than what was self-reported. Electronic medical record review of the 22-month study period yielded 26,950 elective inpatient operations, of which 5,890 patients were admitted to a general surgery teaching service. At the time of discharge, 1,952 (33.1%) patients had received 0 MMEs in the final 24 hours of admission, however 1,534 (78.6%) of these patients still received a prescription for opioids at the time of discharge. Under the proposed recommendations, this represents 223,613 MMEs in inappropriately prescribed opioids.

Conclusions: Based on self-reported data, a large number of general surgery residents at our institution believe that most post-operative patients should receive opioid prescriptions at discharge, even if the patient has not required any MMEs in the last 24 hours prior of admission. This was corroborated by medical record review, showing that over 3/4 of such patients received opioid prescriptions at discharge – prescriptions which the literature suggests are unnecessary and potentially harmful. The Yale New Haven Hospital Opioid Stewardship Committee and the Department of Surgery are collaborating to develop a 2-pronged approach to improve this practice pattern: 1) A brief education session for attending, resident, and advanced practice providers will be delivered during departmental Grand Rounds and 2) A Best Practices Alert within Epic will alert providers if they are ordering a potentially inappropriate opioid prescription based on a patient’s 24-hour pre-discharge MME. By decreasing this common practice of excess opioid prescribing there is potential to keep the equivalent of over 1.3k tablets of 5mg oxycodone out of our local community on a monthly basis.

Abstract #83: Assessment of Institutional Practices to Guide Implementation of a Colorectal Clean Closure Tray

Authors: Matthew Harris, Erin White, Nicholas Peters, Jianliang Man, Kathleen O’Neill, Holly Blackburn, John Morton, Kevin Schuster

Introduction: Colorectal surgical site infections (SSIs) are a significant source of morbidity and mortality. National guidelines describe use of clean instruments for closure in these cases as a “common-sense practice”, and published literature demonstrates bundled interventions with clean instruments, reduce risk for SSIs. Higher than expected rates of SSIs at our institution motivated evaluation of current practices and development of a standardized approach to closure in colorectal cases. Here we describe the project’s initial phase where we assessed staff sentiments about closure and current practices at our institution.

Methods: Surgery residents conducted this project as part of a quality improvement education course. Using a standardized survey and observation form designed in Qualtrics, the resident team interviewed OR staff and surgeons while observing 7 colorectal cases between December 2019 and January 2020. This data was presented to a multidisciplinary infection committee with surgical faculty and OR staff to discuss current barriers and potential strategies to implementing a standardized clean closure tray (CCT).

Results: Attendings and OR staff report multiple strategies to maintain sterility. Both groups report using a clean closure tray less than half of the time (Figure 1A), however, attendings felt more frequently that dirty instruments are isolated during the case (Figure 1B). Glove changes was the technique most commonly utilized, while drape and gown changes were less common (Figure 1C). Respondents raised concerns about case time, attending buy-in, and staff education as potential barriers to CCT use. Case observations revealed lack of awareness regarding current practices and lack of consensus identifying “dirty” instruments. Though all OR staff believed they were using techniques without contamination, potential contamination events were observed in 5 out of 7 cases. Only 3 of the 7 observed cases used a CCT with variable impact of its use on case flow. One case suffered an 11-minute delay, while another was associated with no increased operative time. Data from the survey and case observations were discussed in a multidisciplinary surgical infection committee focus group. Consensus was made that using a CCT should be standard protocol across the YNHH system, however, the implementation barriers identified need to be addressed and an EMR tool developed to monitor use.

Conclusions: Closure practices at our institution are not currently standardized. Current barriers to implementation of a clean closure tray include concerns about case complexity and time. Next steps will involve clearly defining the practice with process map development and providing adequate education on the practice. Some best practices have already been identified and these processes mapped. The next step will be process optimization through simulation and staff training to use these appropriately to minimize case disruption and contamination events.