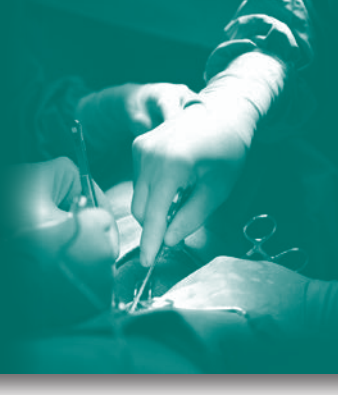
MEDICAL COLLEGE OF WISCONSIN
DEPARTMENT OF SURGERY

SURGERY UPDATE
LEADING THE WAY



WINTER 2017 • VOLUME 8, NUMBER 1

Teamwork

From the Chair

DOUGLAS B. EVANS, MD

We have been very fortunate, in the last two months, to expand our team through the successful recruitments of four senior faculty to the Department of Surgery. Their recruitments were made possible by many dedicated individuals across the medical school and our hospital partners – a few brief words on the talented clinicians and scientists joining us over the spring and early summer:

Paul J. Pearson, MD, PhD

Chief of the Division of Adult Cardiothoracic Surgery, effective March 1.

Dr. Pearson currently serves as Chief of the Division of Cardiovascular Surgery and Co-Director of the Cardiovascular Institute at NorthShore University HealthSystem. Dr. Pearson received his MD and PhD degrees from Mayo Graduate School of Medicine, where he also completed an NIH-sponsored post-doctoral fellowship in the Department of Physiology. Following his surgery residency at the Virginia Mason Clinic in Seattle, he returned to the Mayo Clinic for cardiothoracic surgery training. Dr. Pearson has dedicated the majority of his career to clinical trial and device development, largely in the field of cardiac valve replacement and repair.

Marc A. de Moya, MD

Chief of the Division of Trauma/Critical Care/Acute Care Surgery, effective June 26.

Dr. de Moya is currently Associate Professor of Surgery at Harvard Medical School and Chief of the Churchill Service at Massachusetts General Hospital. Dr. de Moya is also an Associate Program Director for their general surgery residency. He will succeed Dr. John Weigelt, whose contributions to this campus have been invaluable to the success of the Department of Surgery. Dr. de Moya is a graduate of Seton Hall University and Temple University School of Medicine. Following his general surgery residency at St. Barnabas Medical Center, he completed a fellowship in trauma and critical care at the University of Miami, Jackson Memorial Hospital. Dr. de Moya has spent his entire faculty career at MGH and Harvard Medical School where his clinical and translational research has focused on both patient and systems response to injury and critical illness.

Gwen Lomberk, PhD

Inaugural Chief of the Division of Research and Associate Professor of Surgery, effective July 1.

Dr. Lomberk is currently Associate Professor of Medicine at the Mayo Clinic College of Medicine and, in addition to her basic science research program, is actively involved in graduate education. She is a graduate of Boston College and received her PhD in the Cancer Biology Program of the departments of Biochemistry and Molecular Biology at the Mayo Medical School. Her NIH-funded laboratory focuses on many areas of epigenetics, biochemistry and cell signaling; her current R01 grant is in translational science, supporting the study of novel experimental therapeutics for pancreatic cancer. Her leadership role in the Department of Surgery will facilitate faculty and resident career development in basic and translational research.

Raul A. Urrutia, MD

Professor of Surgery and Director of the Human and Molecular Genetics Center at the Medical College of Wisconsin, effective July 1.

Dr. Urrutia is currently Professor of Medicine and Biophysics at the Mayo Clinic College of Medicine and an internationally known expert in the fields of Epigenomics, Personalized Medicine, and Pancreatic Cancer biology. Dr. Urrutia graduated Magna Cum Laude from the University of Cordoba Medical School in Cordoba, Argentina following which he pursued a career in basic research at the NIH before being recruited to the Mayo Clinic. He is past president of the American Pancreatic Association and his textbook entitled *Pancreatic Cancer* is entering its second edition, edited by Dr. Urrutia and an international team of colleagues. His laboratory has made many critically important discoveries in the areas of diabetes, cancer, and epigenetic pathways. He has been continuously funded by the National Institutes of Health for over 20 years.

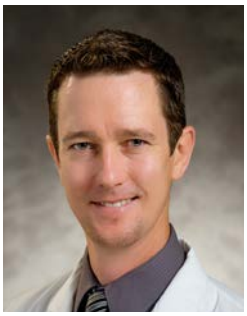
IN THIS ISSUE:

INNOVATION wecare DISCOVERY

We Care Fund Grant Recipients

by Meg M. Bilicki, Director of Development for the Department of Surgery

John E. Baker, PhD



Michael James, PhD

Susan Tsai, MD, MHS

Amy Wagner, MD

The Department of Surgery is pleased to announce the recipients of the **2016 We Care Fund for Medical Innovation and Research** faculty grant recipients. The We Care Scientific Review Committee carefully reviewed a total of 13 exceptional submissions and selected four grant proposals for funding. The awardees and their proposals are:

- John E. Baker, PhD, Professor, Division of Congenital Heart Surgery
  Radiation Fibrosis in Heart: Mechanisms and Mitigation
- Michael James, PhD, Assistant Professor, Department of Surgery
  Mechanisms of CRR9-Mediated Pancreatic Cancer Chemoresistance
- Susan Tsai, MD, MHS, Associate Professor, Department of Surgery
  Quantification of Rare Allelic Cell-Free DNA Mutation in Plasma from Pancreatic Cancer Patients
- Amy Wagner, MD, Associate Professor, Division of Pediatric Surgery
  Gastroschisis Outcomes of Delivery (GOOD) Study Pilot

At its core, the We Care Fund for Medical Innovation and Research in the Medical College of Wisconsin Department of Surgery is about the hope for a future with better treatments. Established in 2010, the We Care Fund has raised more than $500,000 from more than 700 grateful patients, families, friends, faculty, and alumni. Every penny raised for the We Care Fund supports physicians and researchers working on medical research, translational studies, or clinical projects in the fields of cancer, cardiovascular disease, gastrointestinal diseases, organ transplantation, diseases of the newborn/child, or trauma.

Researchers supported by the We Care Fund gather a body of evidence through scientific discoveries that can lead to much larger grants from the National Institutes of Health. Philanthropic support plays a vital role in providing support to get these studies started, especially when promising research cannot wait months or even years for traditional funding.

The We Care Committee, which includes a number of professional, business and community leaders, is the engine that drives fund raising for research and increasing community awareness. Arlene Lee, Committee Chair, notes that "all grant proposals submitted to the committee are peer-reviewed, and I am proud we have been able to award 11 grants in the past four years."

Private gifts from generous donors help sustain the We Care Fund, therefore the grant cycles are not predetermined and will be announced. Philanthropic support plays a vital role in providing seed grants.

If you would like to learn more about the We Care Fund, or are interested in making a gift, please visit the website at www.mcw.edu/wecare or contact Meg Bilicki, Director of Development for the Department of Surgery, at mbilicki@mcw.edu or (414) 805-5731. •

We Care Fund for Medical Innovation and Research Committee, 2016–2017

Arlene A. Lee, *Chair*
Carrie Raymond Bedore
Betsy Evans
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Radiation Fibrosis in Heart: Mechanisms and Mitigation

JOHN E. BAKER, PHD
Professor
Division of Congenital Heart Surgery

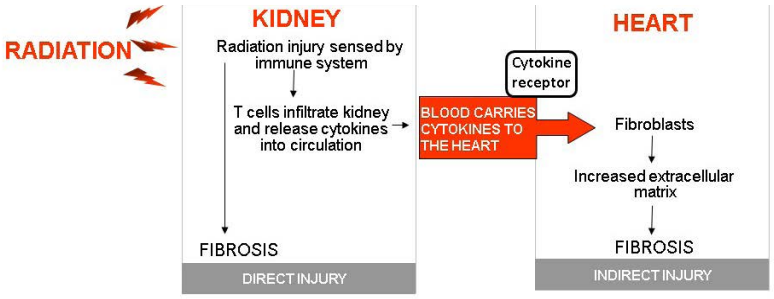


FIGURE 1: Proposed mechanism by which kidney irradiation results in cardiac injury: A role for the immune system in driving this response.

Radiation is a cornerstone of successful cancer treatment, with one-half to two-thirds of all patients currently receiving radiotherapy. Dr. Baker's study is investigating why survivors of cancer, who have been treated with radiation therapy, have a significantly increased risk of dying from heart disease.

In 2011, Dr. Baker and his colleagues identified intestinal microbiota as biomarkers of prior radiation exposure. This particular project aimed to help triage patients after a radiological event, such as the nuclear accident that occurred that very year in Japan. As a result of their work, they were able to establish in an animal model that a survivable dose of radiation would result in injury to the heart later in life; a finding that had significant implications for survivors of childhood and other cancers.

Radiation used to cure cancer oftentimes results in severe health problems, poor quality of life and even early death. Radiation therapy can cause late effect medical complications, the most insidious of which, and the leading cause of non-cancer related death thirty years later, is heart disease. With the survival rates for cancer improving with each decade, Dr. Baker's We Care-funded study aims to prevent these brave survivors from dying early from the very treatments that initially saved their lives.

It is known that exposure to therapeutic radiation increases relative risk for developing heart disease later in life by 2- to 6-fold, compared with non-irradiated individuals. Risk factors for heart disease can be detected at higher rates in survivors of pediatric cancer compared with their healthy siblings. Survivors are 1.9 times more likely than siblings to be prescribed medications for hypertension, 1.6 times more likely to be prescribed medications for hyperlipidemia, and 1.7 times more likely to be prescribed medications for diabetes. Total body irradiation is linked to a 5.5-fold increased risk of clustering of these risk factors for heart disease, and radiation of both chest and abdomen is linked to a 2.2-fold increased risk for heart disease.

Tissue injury in the heart is a major complication of radiation therapy, yet our understanding of the cellular and molecular mechanisms leading to this injury in vital organs such as this are incomplete. Effective strategies for preventing, stopping or reversing this injury are lacking. If the underlying mechanisms can be understood, then therapeutic strategies can be developed. To determine the cause of this damaging effect, Dr. Baker is testing the notion that the kidneys are responsible for the increased risk for heart disease that arises from radiation. Results from this study will be used to develop medical countermeasures.

Present research efforts on radiation injuries are largely focused on an individual organ system, single disease or health condition. Dr. Baker's study breaks the paradigm of confining research to individual organ systems by examining the interactions between kidney and heart after irradiation, and will accelerate the acquisition and validation of scientific knowledge of how this injury evolves in these two organs so that novel treatment strategies can be developed.

Dr. Baker and his colleagues have shown that shielding the kidneys during whole body irradiation prevents heart disease in rats. This is the first time this has been demonstrated. Using an established model of radiation injury in the rat, they will determine whether irradiation of the kidneys alone increases risk for and occurrence of heart disease similar to that observed after irradiation of the whole body. They propose a new research model whereby radiation-induced heart disease is indirect. They will test this notion by incorporating links between changes in kidney to signs of heart disease. Their team has shown that injury to the heart occurs at a distance from the irradiated kidney and is independent of any direct exposure of the heart to radiation. They will then test the notion that an immune system T cell, CD3+, infiltrates the kidney after local irradiation to increase levels of pro-inflammatory cytokines in the circulation. These cytokines travel in the blood to the heart where they are recognized by receptors that send signals inside the heart to cause injury.

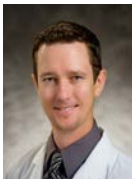
Thus, the proposed studies will determine if the mechanism that causes cardiac disease originates from activation of the immune system after local radiation injury to the kidney. If this is proven to be true, then therapeutics targeting the immune system will be able to decrease injury in the heart following radiation therapy. In collaboration with immunologists, Dr. Baker will determine the ability of antibodies to neutralize inflammatory signals present in the blood in order to treat radiation injury in kidney and heart. If cardiac injury from radiation is indirect, originating from activation of the immune system in response to kidney injury, this finding may open doors to new approaches for the treatment of diseases.

Understanding the way heart disease evolves after therapeutic irradiation is essential for developing medical countermeasures that will enable cancer survivors to lead long and healthy lives. •

Acknowledgement: the author thanks Mary Baker, RN, for assistance with manuscript preparation.

FOR ADDITIONAL INFORMATION on this topic, please visit mcw.edu/surgery, or contact Dr. Baker, 414-955-8706, jbaker@mcw.edu.

CRR9 is a Therapeutic and Chemosensitization



MICHAEL JAMES, PHD
Assistant Professor
Department of Surgery

Pancreatic cancer will soon be the second leading cause of cancer death in the U.S. and at this time has already reached that #2 milestone in Wisconsin.[1] Pancreatic tumors are notoriously resistant to chemotherapy with a tumor response rate of 25-30%.[2] Therefore, there is an immediate need for effective ways to sensitize tumors to chemotherapy.

Altered regulation of homeostasis under cellular stress has been implicated in many cancers and has recently become a therapeutic target of interest.[3] Pancreatic tumors exhibit extensive desmoplasia, resulting in a cellular stress response that is critical for the survival of tumor tissues under these conditions.[4] There is evidence that targeting this survival mechanism is synergistic with genotoxic chemotherapy.[4-7]

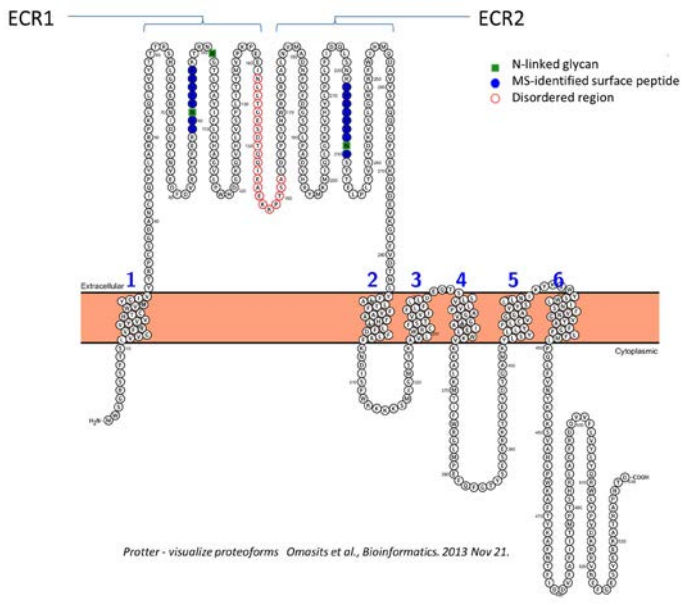


Figure 1: Predicted topology of CRR9 at the plasma membrane of tumor cells. ECR1 and 2 are predicted extracellular globular domains. Generated using Protter (Omasits, 2013; PMID:24162465).

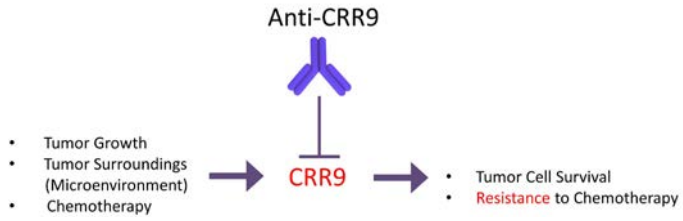


Figure 2: Schematic of the role of CRR9 in stress-induced tumor cell survival and chemoresistance.

We have discovered a specific therapeutic target in pancreatic tumors, Cisplatin Resistance Related Protein 9 (CRR9) (Figure 1), that is implicated in cellular survival under chemotherapeutic and oncogenic stress [8,9](Figure 2). Our data shows that CRR9 is commonly overexpressed at the cell surface in pancreatic adenocarcinoma, and that higher expression of CRR9 is associated with poor outcome.[10] Our prior work showed that CRR9 confers resistance to chemotherapeutics, including gemcitabine and cisplatin. We have developed novel antibody inhibitors of CRR9 function that chemosensitize tumor cells *in vitro* and inhibit transformation by KRas.[10] Targeting this pathway holds promise in combating the significant problem of chemoresistance in pancreatic tumors.

We recently discovered that CRR9 interacts with Glucose Regulated Protein 78 (GRP78) (Figure 3), an HSP70 family protein that regulates the cellular response to stress and the survival of tumor cells, including pancreatic adenocarcinoma cells, under such stress.[11] GRP78 has been shown to be overexpressed and translocated to the cell surface specifically in tumor tissues, to be induced by chemotherapy, and, like CRR9, can promote chemoresistance through PI3K and Akt signaling.[5–7,12] These characteristics represent significant correlation with CRR9 function. However, the relationship between GRP78 and CRR9 function remains to be determined (Figure 3). Importantly, signaling pathways initiated by CRR9/GRP78 interaction may provide a mechanism of chemoresistance and, therefore, a therapeutic target in pancreatic cancer.

Our proposed studies will investigate the precise mechanism of resistance to therapy conferred by CRR9 and the effect of this signaling axis on chemoresistance *in vivo*, which will help us to discover better ways to make therapy more effective for patients and inform the design and development of the drugs against CRR9 that we are currently developing.

Target in Pancreatic Cancer

It is our hope that this work will directly impact patients in the form of better treatments in the near future. To that end, we are working toward follow-up funding to support broader basic science and translational work on this important tumor cell signaling axis as well as preclinical pharmacology/toxicology studies, IND application and first-in-human trials with anti-CRR9 adjunctive therapy. Thanks to the We Care Fund for Medical Innovation and Research, this project will be an important step in that direction. •

FOR ADDITIONAL INFORMATION on this topic, see references below, please visit mcw.edu/surgery, or contact Dr. James, 414-955-7572, mjames@mcw.edu.

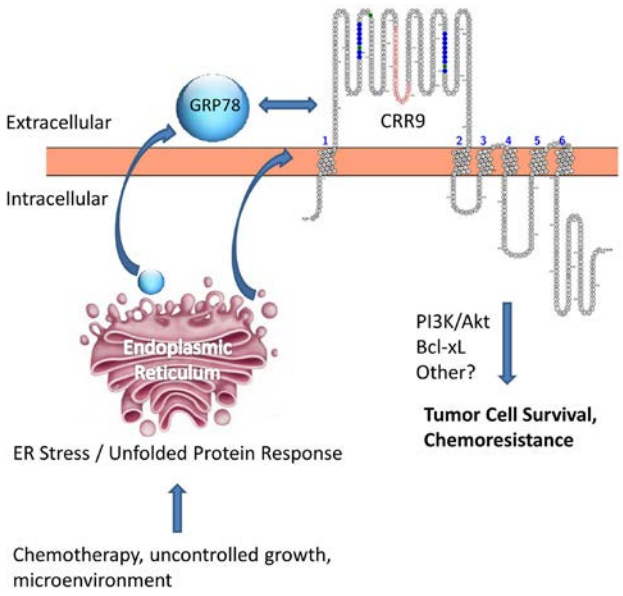


Figure 3: Working model of the CRR9/GRP78 survival signaling axis in cancer.

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Quantification of Rare Allelic Cell-Free DNA Mutation

SUSAN TSAI, MD, MHS
Associate Professor
Division of Surgical Oncology

Increasingly, clinicians and scientists now support the hypothesis that the majority of patients with pancreatic cancer (PC) will have systemic disease at the time of diagnosis, even in the absence of radiographic evidence of distant metastases.[1-3] Radiographic underestimation of metastatic disease is a major impediment in the management of PC. Among patients with localized PC who undergo surgical resection, disease recurrence occurs in up to 60% of patients within 6.9 months of surgery[4] and the median survival is only 24 months, suggesting that radiographically occult metastatic disease is present in many patients at the time of surgery.[5] Furthermore, the delivery of postoperative (adjuvant) therapy for micrometastatic disease is unpredictable due to unanticipated perioperative morbidity and can only be achieved in 50% of patients.[5, 6] Therefore, inaccurate staging has significant consequences, and immediate surgery for presumed localized disease may temporarily or permanently delay access to systemic therapy for patients at high risk for metastatic disease. Furthermore, radiographic imaging also underestimates treatment response and may not necessarily correlate with resectability.[7, 8] As the paradigm begins to shift from postoperative (adjuvant) to preoperative (neoadjuvant) therapy, objective and quantitative methods to assess treatment response and overall extent of disease will be critical to optimize patient selection and oncologic outcomes.

Use of Tumor-Specific Cell-Free DNA as a Treatment Response Biomarker

In recent years, the field of oncology has recognized the potentially revolutionary application of cell-free DNA (cfDNA). Cell-free DNA is a naturally occurring component of plasma that originates from cellular death when cellular DNA is released into free circulation. The utility of cell-free DNA monitoring has seen the greatest success in the detection of fetal DNA in the maternal blood, including point mutations and aneuploidy, and has become part of the standard of care in prenatal assessment in high-risk patients.[9, 10] In oncology, detection of cell-free tumor DNA (ctDNA) may be particularly relevant, as the pathogenesis of many cancers is the result of acquired genetic mutations. Therefore, ctDNA may have exquisite biologic specificity as a biomarker. Especially in PC, monitoring of ctDNA represents a unique opportunity, in that over 90% of PCs have a KRAS oncogene point mutation and therefore a ubiquitous genetic target should exist.[11, 12] We hypothesize that monitoring of KRAS mutations detected in plasma ctDNA may be a clinically useful biomarker.

The use of ctDNA as a biomarker has largely been studied in patients with metastatic lung cancer as a means to both monitor tumor burden and to detect molecular resistance to targeted therapies.[13, 14] The utility of ctDNA has been more limited among patients with earlier stage disease, as current technologies have insufficient sensitivity to quantitate extremely low mutant allelic frequencies. In PC, approximately 59-75% of patients with metastatic disease have ctDNA detectable by PCR-based single gene methods.[15, 16] However, detection of ctDNA is challenging in earlier stage disease. In the largest experience of cfDNA monitoring in patients with PC reported by Takai et al, only 18% and 8% of locally advanced and resectable patients with PC had detectable mutant KRAS, respectively.[15] The inability to detect KRAS mutations from patients with localized PC may be limited by the sensitivity of the assay. Our laboratory has demonstrated the limit of quantification to be 0.4% using next generation sequencing technology (Figure 1).

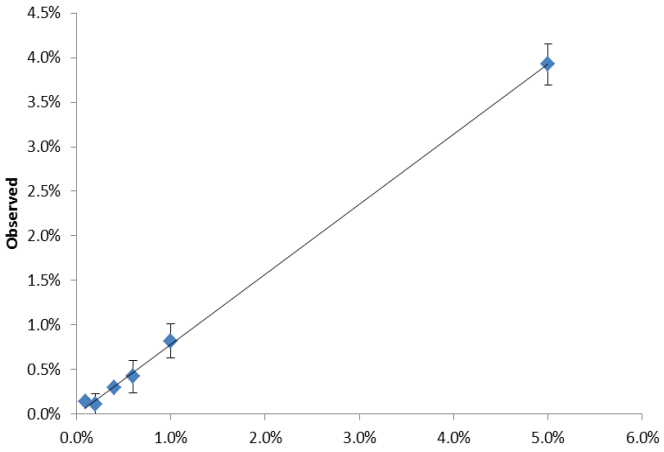

FIGURE 1: Reconstruction experiment for G12D. Purchased wildtype DNA was spiked with 5%, 1%, 0.6%, 0.4%, 0.2% and 0.1% dilutions of KRAS G12D mutant DNA.

Alternative techniques, which provide greater sensitivity, are needed to detect rare mutant allelic frequencies at very low levels (<0.001%). The mismatch amplification mutation assay, PCR assay, was first described in 1992 as a method to detect rare mutations in HRAS.[17] This PCR assay involves the development of primers with a single mismatch corresponding to mutated allele, but a double mismatch corresponding to the wild-type allele. This results in preferential amplification of the mutant allele relative to the wide-type allele. Reconstruction experiments reported the sensitivity to detect 30 copies for c-HRAS in 3 x 106 copies of wild-type allele.

in Plasma from Pancreatic Cancer Patients

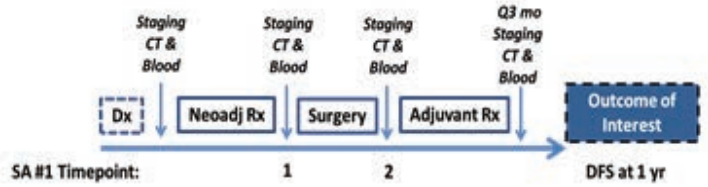

FIGURE 2: Blood collection and staging assessments of patients enrolled in the clinical trial. The ctDNA levels will be determined in pre-operative (1) and postoperative blood (2) to evaluate the primary outcome of disease free survival (DFS) at one year.

We Care Proposal

With our co-investigator, Dr. Aoy Mitchell, we propose to develop a highly sensitive assay to identify rare mutant allelic frequencies from plasma cell-free DNA and correlate quantitative levels of KRAS mutations at two time points (prior to surgery and following surgery) with disease-free survival at one year. We will utilize biospecimens prospectively collected from patients with localized PC who were enrolled in a clinical trial. We will utilize biospecimens collected from patients with resectable and borderline resectable PC who have been enrolled in an investigator-initiated clinical trial (NCI01726582). This trial utilizes immunohistochemical profiling from fine needle aspirate biopsies and surgical specimens to guide chemotherapeutic selection for neoadjuvant and adjuvant therapy, respectively. As a secondary endpoint of the trial, planned blood collection occurred at defined staging intervals. Blood was collected prior to the initiation of any therapy and following neoadjuvant therapy prior to surgery, after surgery, and with every restaging evaluation (Q3 month) until the date of disease progression (Figure 2). Restaging imaging prior to surgery (Figure 2: time point 1) consisted of a dual-phase computed tomography (CT) of the abdomen and pelvis, abdominal magnetic resonance imaging, positron emission test and laboratory tests, including CA19-9. Subsequent restaging evaluations consisted of an abdomen and pelvis CT and laboratory tests. To date, 95 patients have been enrolled and are evaluable for the primary endpoint of the study; 81 (85%) of patients completed all neoadjuvant therapy and surgery and 14 (15%) had disease progression during neoadjuvant therapy. The goal of these studies is to develop a highly sensitive biomarker to improve the clinical management of patients with PC by allowing clinicians to identify patients at high-risk for disease relapse within one year of surgery and to improve assessment of treatment response. •

FOR ADDITIONAL INFORMATION on this topic see references, visit mcw.edu/surgery or contact Dr. Tsai, 414-805-5084, stsai@mcw.edu.

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Gastroschisis Outcomes of Delivery

AMY J. WAGNER, MD
Associate Professor
Division of Pediatric Surgery

Gastroschisis is a congenital birth defect in which loops of intestine herniate through a hole in the abdominal wall during development. Startlingly, the prevalence of gastroschisis is on the rise.[1] Gastroschisis appears to be non-genetic in origin, but the exact etiology is currently unknown.[2] It is typically detected *in utero* in the second trimester of pregnancy by ultrasound. Infants with this defect are treated surgically to replace the bowel in the abdomen and close the defect. Improved surgical techniques have increased survival to over 90%.[2] However, these patients are still at risk of *in utero* mortality and significant postnatal morbidity.

One complication of fetal gastroschisis is an increased risk of *in utero* fetal demise (IUFD), or stillbirth, which is seven times higher in gastroschisis pregnancies compared to uncomplicated pregnancies. An IUFD incidence as high as 12.5% has been reported,[3] and prevalence of IUFD is 4.48 per 100 births compared with 0.62 per 100 births in the general population.[4] Currently, the cause of gastroschisis-related IUFD is unknown and there is no ability to predict which pregnancies are at risk of demise.

Babies that survive to delivery with gastroschisis may have significant life-long morbidity due to bowel damage. The etiology of bowel damage may be due to amniotic fluid exposure, which contains damaging cytokines and pro-inflammatory mediators, or mechanical constriction at the defect site. This damage can lead to bowel atresia, necrosis, perforation, edema, and peel formation, all of which may be associated with serious complications (See Figure 1). Much of the bowel damage appears to occur in later stages of pregnancy, and the degree of intestinal injury is thought to correlate with duration of amniotic fluid exposure.[5] This observation, in addition to the risk of demise, has led some to theorize that early delivery prior to term may be beneficial for babies with gastroschisis. However, currently there are no definitive data to support this.

Preterm birth has its own associated complications. The negative consequences of preterm delivery are well established. The most prevalent morbidities are pulmonary, including the need for respiratory assistance and transient tachypnea. Additional complications include intraventricular hemorrhage, sepsis, and the need for phototherapy. Preterm birth in infants with gastroschisis may negatively influence cognitive and motor development.[6] Increased hospital costs and length of stay are also associated with preterm birth.[7] Thus, the decision to induce labor early should not be taken lightly.

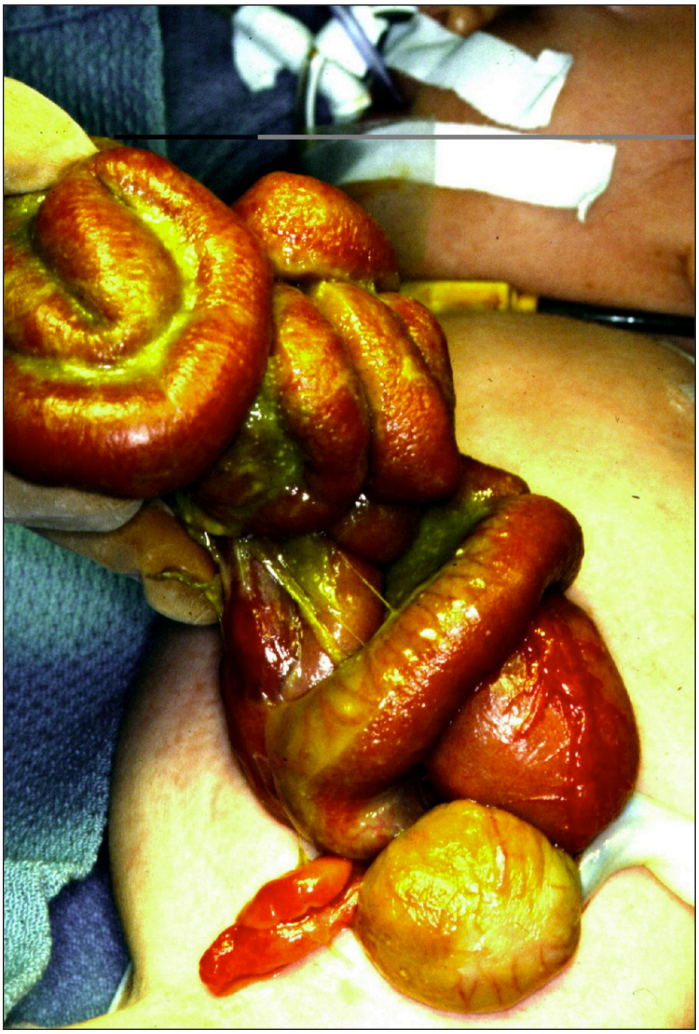

FIGURE 1: Gastroschisis with inflammatory bowel "peel" and externalized ovary and bladder.
Pediatric Surgery NaT (Not a Textbook). Gastroschisis. Saleem Islaam, Gerald Gollin, Shannon Koehler, Amy Wagner.

Previous studies have attempted to identify the optimal delivery timing in cases of gastroschisis. Investigators have studied outcomes related to delivery timing; these studies were largely retrospective, and the results were inconclusive. Some studies show evidence supporting improved outcomes in early delivery, whereas others show improved outcomes with term pregnancy.[8-9] Evidence from prospective trials is lacking. The only randomized prospective trial to investigate differences between delivery at term or late preterm in gastroschisis was

(GOOD) Study Pilot

underpowered.[10] This study randomized 42 patients into two groups: the spontaneous labor group and an elective delivery at 36 weeks gestation group. The trend indicated that there was no benefit to early delivery; however, when comparing the early delivery group with the spontaneous labor group, the former trended toward shorter time to full enteral feeding (30.5 vs. 37.5 days, respectively) and shorter hospital stays (47.5 days vs. 53 days, respectively). In 2013, a Cochrane Review on elective preterm birth for fetal gastroschisis was published,[11] and it only included the randomized prospective trial discussed above.[10] The *Cochrane Review* concluded that "there is a lack of published data in this area," and "further trials are needed."[11]

Given the contradicting results regarding the ideal delivery time for fetal gastroschisis, there is no foundation from which evidence-based guidelines can be built. Currently, the method of care is based entirely on the clinician's discretion and preference, and varies throughout the country. The increasing prevalence of gastroschisis cases, coupled with the uncertain care practices, make developing evidence-based treatment guidelines a critical priority.

We will conduct an international, multicenter, randomized prospective trial to evaluate the outcomes of inducing labor at 35 weeks compared with delivery at 38 weeks in cases of stable fetal gastroschisis. The trial will enroll 800 pregnant mothers from centers in the US and Canada, and investigate both maternal and infant outcomes. The trial is endorsed by the North American Fetal Therapy Network (NAFTNet). NAFTNet is an association of tertiary-care centers specializing in fetal surgery and complex fetal disorders.

We are grateful to have the support of the We Care Fund for the GOOD Study pilot. This funding was pivotal in allowing us to collaborate with centers across North America with a goal of enrolling 100 patients. Thanks to the generous grant support, we now have 18 centers who are participating in the trial. These pilot data are necessary to prove feasibility prior to applying for NIH funding. A program officer at the NICHD has already been identified who stated that our study is "meritorious and the specific aims are reasonable."

The proposed trial is the first large-scale, randomized trial investigating the optimal delivery time in fetal gastroschisis. Thanks to the We Care Grant, this trial will generate high-quality data about maternal and infant outcomes associated with delivery timing in cases of fetal gastroschisis. The results of this trial will form a strong foundation from which evidence-based clinical standards can be built, improving the lives of the thousands of babies born with gastroschisis each year and the mothers who carry them. •

FOR ADDITIONAL INFORMATION information on this topic, see references, please visit mcw.edu/surgery, or contact Dr. Wagner, 414-266-6561, awagner@chw.org.

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Renal Transplantation Using Solid Phase Immunoassays

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Organ transplantation is the preferred (and sometimes only) treatment option for many patients with a variety of end-stage organ diseases. In the United States, over 30,000 transplants were performed in 2015.[1] Historically, the primary means of assessing donor-recipient compatibility for transplantation has been by way of performing lymphocyte crossmatches. A crossmatch is performed in the laboratory by mixing recipient serum with donor T and B cell lymphocytes. A positive reaction (using reagents that can detect bound IgG antibody) is, in most cases (with the notable exception of the liver), considered a contraindication to proceeding with transplant.[2] Most histocompatibility laboratories currently perform a flow cytometry-based crossmatch (FCXM).The process of obtaining and transporting donor tissue or cells for crossmatching adds considerable time and expense to the overall process of transplantation.

Recent advances in solid phase immunoassays (SPI) have resulted in the ability to accurately identify HLA antibodies in the serum of potential transplant recipients, using synthetic microparticles, coated with purified HLA antigens.[3] The process of comparing an individual's known HLA antibody profile (as determined by SPI) with the tissue typing results from a potential donor is referred to as a "virtual crossmatch." The virtual crossmatch (VXM) has thus far been used primarily to predict the results of cell-based crossmatch assays (with the latter test presumed to be more clinically relevant). It has also been shown to increase access to transplantation for sensitized recipients, since a negative VXM is a strong predictor of a negative FCXM. A serious limitation of cell-based crossmatches, however, is a 10% false positive rate due to non-specific binding of IgG to lymphocyte cell surface receptors. Nonetheless, the FCXM is currently considered to be the gold standard for determining donor-recipient compatibility for transplantation.

Recently, we challenged the perceived superiority of cell-based crossmatches (over SPI), by reporting the outcomes for 508 consecutive renal transplant recipients who received their transplants at MCW-Froedtert (from 2005-2009). By protocol, recipients during this time period received a transplant if the VXM was negative for donor-specific HLA antibody (VXM-), regardless of the outcome of conventional flow cytometry crossmatches (FCXM).[5]Transplant outcomes (incidence of rejection episodes and graft survival) were analyzed using Kaplan-Meier and Cox Regression models, incorporating variables known to influence long-term outcomes for renal transplantation such as donor and recipient age, donor source (living vs. deceased), presence of diabetes, race, length of time on dialysis prior to transplant, cold ischemia time (for deceased donor transplants), degree of HLA sensitization and use of T cell-depleting agents for induction immunosuppression (such as thymoglobulin). Our analysis revealed that rejection episodes within the first year were similar between FCXM- and FCXM+ recipients, 12% and 13%. Equally important, long-term outcomes were equivalent for FCXM- and FCXM+ recipients. Figure 1 illustrates the graft outcomes for all 508 recipients and a subgroup of 118 sensitized recipients. Figure 2 shows outcomes for a subset of highly sensitized recipients. Sensitized recipients, by conventional wisdom, would be considered at high risk for rejection, if transplanted with a positive FCXM. The results of the multivariate analyses are summarized in Table 1. Flow cytometry crossmatch status (FCXM) was not an important variable for outcomes in any model tested (including both all-cause graft survival and death-censored graft survival). Our findings are consistent with the concept that a positive FCXM in recipients without detectable donor-specific HLA antibodies by SPI represents a "false positive" finding, which should not preclude transplantation.

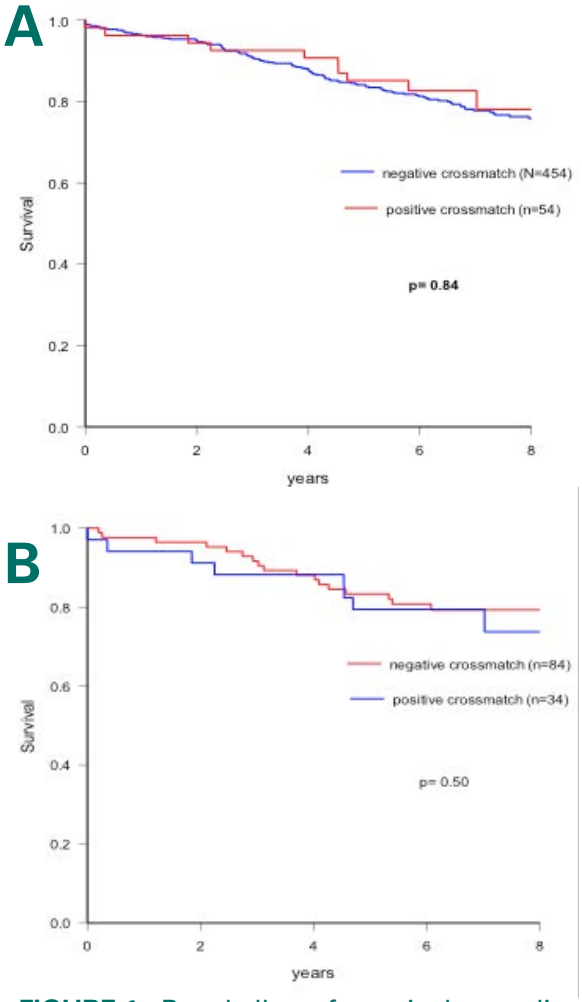

FIGURE 1. Renal allograft survival according to flow cytometric crossmatch (FCXM) result for all 508 recipients (A), and 118 sensitized recipients (B). All recipients were virtual crossmatch (VXM) negative.

to Determine Donor-Recipient Compatibility

As further validation of our outcomes data using this virtual crossmatch protocol, we examined the three year kidney allograft survival rates for our program, as reported by the Scientific Registry for Transplant Recipients (SRTR) during the five-year study period included in this study (2005-2009). The three-year actual graft survival rates were 91% (compared to an expected 86% using risk adjustment models, $p < 0.05$).

Our study is the first ever to examine long-term outcomes for kidney transplantation, when solid phase assays are used as the definitive test for assessing donor and recipient compatibility. The results have important implications in a number of areas. First, approximately 10% of potential kidney transplant recipients may be unnecessarily excluded from transplant when allocation decisions are made based on crossmatch information only. Second, in the case of paired kidney exchanges (which depend heavily on "preliminary results" using SPI), many potential chains break unnecessarily due to "failed crossmatches," which are because of false-positive results obtained using FCXM.

Another area of significance is in the management of imported deceased donor kidneys. Recent changes in UNOS policy for kidney allocation have increased regional and national sharing of kidneys with a "high kidney donor profile index" (formerly known as "expanded criteria") and for very highly sensitized recipients (> 99% PRA). As a result of these policies, 30% of the deceased donor kidney transplants at our center are now imported from outside our local area (compared to 10% historic rates). Use of the VXM as the definitive test of donor-recipient compatibility substantially changes how we manage these imported kidneys. At our center, for example, we are typically able to reduce cold ischemia time of the kidney by four to six hours by obtaining a current VXM prior to the kidney arrival.

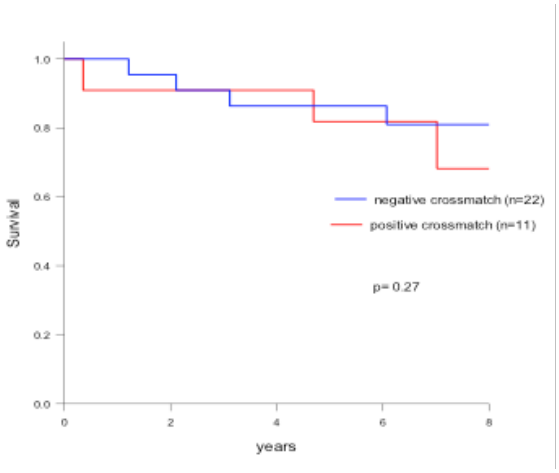

FIGURE 2. Renal allograft survival for highly sensitized recipients (panel reactive antibody, PRA > 80%), according to flow cytometric crossmatch (FCXM) result. All recipients were virtual crossmatch (VXM) negative.

TABLE 1. Multivariate Analysis of Risk factors Associated with Long Term Graft Survival (n = 508).

A. ALL CAUSE GRAFT SURVIVAL				
Risk Factor	**Hazard Ratio**	**95%CI-Lower[1]**	**95%CI-Upper**	**p value**
Diabetes: yes (vs. no)	2.04	1.41	2.97	<0.001
Deceased donor (vs. living donor)	1.99	1.26	3.15	0.003
AA race (vs. non-AA race)	1.43	0.97	2.11	0.07
Crossmatch positive (vs. negative)	1.25	0.67	2.35	0.49
B. DEATH CENSORED GRAFT SURVIVAL				
Risk Factor	**Hazard Ratio**	**95%CI-Lower**	**95%CI-Upper**	**p value**
Recipient age (years): > 60 (vs. < 60)	0.36	0.15	0.83	0.02
Donor age: < 50 (vs. ≥ 50)	0.54	0.31	0.94	0.03
Deceased donor (vs. living donor)	2.24	1.08	4.63	0.03
Crossmatch positive (vs. negative)	0.86	0.40	1.86	0.70

[1]95%CI, upper and lower 95% confidence intervals

In summary, we continue to use a protocol developed at MCW-Froedtert, which utilizes solid phase immunoassays as the definitive test to assess donor-recipient compatibility for kidney transplantation. Based on our recently published data from this study, we expect other kidney transplant centers to follow our lead and expand the use of this new technology in their own programs. We also anticipate that SPI will begin to play an increasingly important role in allocation of other solid organs such as heart, lung, pancreas and intestine. •

FOR ADDITIONAL INFORMATION on this topic, see references, please visit mcw.edu/surgery, or contact Dr. Johnson, 414-955-6930, cjohnson@mcw.edu.

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Impact of Adjuvant Therapy on Survival Following

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Pancreatic cancer (PC) is a major focus of research and treatment at MCW and one area of ongoing investigation is treatment sequencing. This is because, for patients who undergo upfront surgical resection, the median disease-free survival is only 6.9 months.[1] Therefore, multimodality care including systemic chemotherapy is recommended to optimally treat patients with localized PC. The survival benefit associated with the addition of systemic therapy following surgery has been well established. In the CONKO-001 trial, which randomized patients with resected PC to adjuvant gemcitabine versus observation, the median overall survival (OS) was 22.8 months with adjuvant therapy as compared to 20.2 months with observation.[1] Several subsequent studies have corroborated these findings and reproducibly reported that the median OS for patients who are able to successfully complete surgery and adjuvant therapy is 24 months.[2,3] However, the delivery of adjuvant therapy is unpredictable. Analysis of the Surveillance, Epidemiology and End Results (SEER) database has shown that approximately 50% of patients treated with upfront surgery do not receive the intended adjuvant therapy due to morbidity associated with surgery.[4]

Neoadjuvant therapy is an alternative treatment regimen for patients with localized PC, which ensures the delivery of systemic therapy. Early neoadjuvant clinical trials have established the feasibility of delivering systemic therapy in the neoadjuvant setting and furthermore, patients who are able to complete neoadjuvant therapy and surgery experience an improved OS as compared to a surgery-first approach.[5,6] In a phase II clinical trial performed at M. D. Anderson Cancer Center, patients with localized PC who received neoadjuvant gemcitabine-based chemoradiation and surgery had a median OS of 34 months.[5] No adjuvant therapy was given in this trial. Similarly, the MCW Pancreatic Cancer Program has reported a series of 69 patients with resectable PC who received neoadjuvant therapy. The median OS for patients who completed neoadjuvant therapy and surgery was 44.9 months.[7] Although practice guidelines recommend adjuvant therapy for all patients, the survival benefit of delivering adjuvant therapy after receipt of neoadjuvant therapy has not been well-described in the literature.

We recently evaluated the impact of adjuvant therapy on the survival of patients with localized PC who have completed neoadjuvant therapy and surgery. Our study cohort consisted of 217 consecutive patients, 110 (51%) with resectable and 107 (49%) with borderline resectable PC. All patients received neoadjuvant therapy prior to undergoing pancreatectomy with

Table 1: Patient Demographic and Clinicopathologic Characteristics.

Variable	Total (n=217)	No Adjuvant (n=87)	Adjuvant n=(130)	p-value
Age, median (IQR)	65 (13)	66 (14)	64 (12)	0.32
Male gender, n (%)	106 (49)	39 (45)	67 (52)	0.33
Charlson Comorbidity Index (CCI), median (IQR)	3 (2)	3 (2)	3 (1)	0.04
Clinical Stage, n (%)				<0.001
Resectable	110 (51)	28 (32)	82 (63)	
Borderline Resectable	107 (49)	59 (68)	48 (37)	
Neoadjuvant therapy, n (%)				<0.001
Chemotherapy	35 (16)	2 (2)	33 (25)	
Chemoradiation	74 (34)	24 (28)	50 (39)	
Both	108 (50)	61 (70)	47 (36)	
N Stage, n (%)				0.038
N0	134 (62)	61 (70)	73 (56)	
N1	83 (38)	26 (30)	57 (44)	
Postoperative CA19-9, n (%)*				0.71
Normal (≤ 35)	158 (75)	63 (76)	95 (74)	
Elevated (> 35)	54 (25)	20 (24)	34 (26)	

** Postoperative CA19-9 values were not available for 5 patients.*

Neoadjuvant Therapy for Localized Pancreatic Cancer

curative intent. The median OS for all 217 patients was 40 months, 45 months for patients who received adjuvant therapy and 34 months for patients who did not (p=0.15). However, nodal status and postoperative carbohydrate antigen 19-9 (CA19-9) level affected the survival benefit of delivering adjuvant therapy.

In our analysis, patients were categorized using the American Joint Committee on Cancer (AJCC) staging system for PC, N0 for node-negative disease and N1 for node-positive disease.[8] Of the 217 patients, 134 (62%) were N0 and 83 (38%) were N1. Of the 134 N0 patients, 73 (54%) received adjuvant therapy and 61 (46%) did not. Of the 83 N1 patients, 57 (69%) received adjuvant therapy and 26 (31%) did not. Among N0 patients (solid and dashed black lines), the median OS was 45 months and the receipt of adjuvant therapy did not significantly impact survival. However, among N1 patients, the median OS was 39 months with adjuvant therapy (solid grey line) as compared to 23 months without adjuvant therapy (dashed grey line) (p=0.05, Figure 1). This data suggests that patients with nodal metastases experience a greater benefit from adjuvant therapy than patients without nodal metastases. In an adjusted hazards model, the receipt of adjuvant therapy had a greater protective effect among N1 patients (HR: 0.40; 95%CI: 0.18-0.88) compared to N0 patients (HR: 0.72; 95%CI: 0.41-1.24).

CA19-9 is considered the most clinically valuable biomarkers among patients with PC, and has been correlated with survival.[9,10] Following pancreatectomy, CA19-9 levels were measured four to six weeks postoperatively and were classified as normal (≤ 35) or elevated (>35). Postoperative CA19-9 levels were available for 212 patients. Of the 212 patients, 158 (75%) had a normal postoperative CA19-9 and 54 (25%) were elevated. Of the 158 patients with normal postoperative CA19-9, 95 (60%) received adjuvant therapy and 63 (40%) did not. Of the 54 patients with elevated postoperative CA19-9, 34 (63%) received adjuvant therapy and 20 (37%) did not. The median OS for all 212 patients was 40 months, 46 months for the 158 patients with a normal postoperative CA19-9 and 20 months for the 54 patients with an

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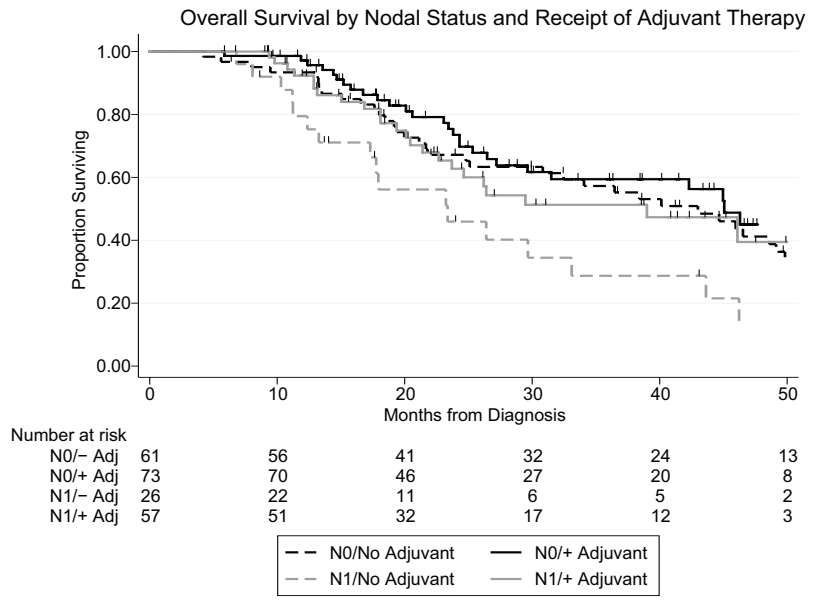

Figure 1: Impact of nodal status and adjuvant therapy on overall survival among patients with resectable and borderline resectable PC who completed all neoadjuvant therapy and surgery.

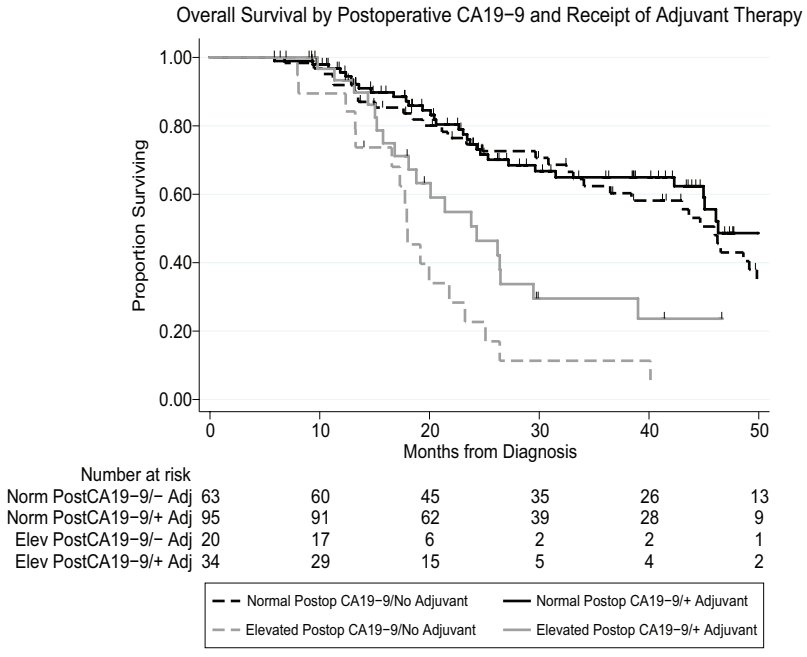

Figure 2: Impact of postoperative CA19-9 and adjuvant therapy on overall survival among patients with resectable and borderline resectable PC who completed all neoadjuvant therapy and surgery.

Pancreatic Cancer Therapies, continued from page 13.

elevated CA19-9 ($p<0.001$). The delivery of adjuvant therapy did not affect survival among patients with normal postoperative CA19-9 (solid and dashed black lines). However, among the 54 patients with elevated postoperative CA19-9, the median OS was 24 months with adjuvant therapy (solid grey line) as compared to 18 months without adjuvant therapy (dashed grey line) ($p=0.05$, Figure 2). In an adjusted hazards model, the receipt of adjuvant therapy had a greater protective effect among patients with elevated postoperative CA19-9 (HR: 0.48; 95%CI: 0.21-1.08), compared to patients with normal postoperative CA19-9 levels (HR: 0.84; 95%CI: 0.50-1.43).

In summary, nodal status and postoperative CA19-9 may affect the benefit of adjuvant therapy for patients who have previously received neoadjuvant therapy and surgery for PC. Although practice guidelines recommend adjuvant therapy for all patients with PC, our analysis suggests that patients with N1 disease and/or elevated postoperative CA19-9 may experience the greatest survival benefit. The benefit of adjuvant therapy following neoadjuvant therapy requires a prospective clinical trial to determine the outcome among patients with N0 disease and/or normal postoperative CA19-9. •

FOR ADDITIONAL INFORMATION on this topic, see references, please visit mcw.edu/surgery, or contact Dr. Tsai, 414-805-5084, stsai@mcw.edu.

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Utilization of the Nationwide Inpatient Sample for Abdominal Aortic Aneurysm Research: Big Data Leading the Way

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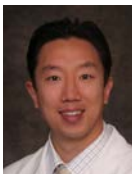

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A ruptured abdominal aortic aneurysm (AAA) is the thirteenth leading cause of death in the United States, with just over 11,000 cases reported between 2000 and 2010.[1] This averages to be about 1,000 cases annually, although most centers see only a small number of cases each year. This makes it difficult for any single center to report upon the true incidence of the disease or associate risk factors that impact outcomes; along with determining overall rates of complications, length of stay, survival, readmission, and cost of care (due to the fact that studies are simply not powered appropriately). A solution has been to combine data from multiple centers. This involves selection bias, as cases that occur at smaller community centers are missed. Other methods have been used to study relatively uncommon pathologies. These include meta-analyses, comprehensive reviews of the literature, and robust statistical extrapolation, although each of these methods is associated with limitations. Meta-analyses rely upon inclusion of studies that have a similar design, potentially missing cases that may occur at smaller centers and in rural populations. Reviews of the literature may include isolated case reports, but this represents only a subset of the overall number of cases. Statistical extrapolation is effective when the data are representative of the population, but has significant variance and rapid degradation of its sensitivity when based off a small subset of the actual number of cases.

A recent solution is the utilization of large administrative databases that have been used by major public health agencies for many years, as these data are nationwide. The databases include the Medicare Database by the Centers for Medicare and Medicaid Services (CMS), the National Surgical Quality Improvement Project (NSQIP) database sponsored by the American College of Surgeons, and the National Inpatient Sample (NIS), a part of the Healthcare Utilization Project (HCUP) and maintained by the Agency for Healthcare Research and Quality (AHRQ). The NIS is the largest all-payer inpatient database and includes a stratified, 20% random sample of all nonfederal inpatient hospital admissions throughout the United States.[1,2] The database is available from 1988 through 2013, and now includes data from 48 states around the country. When used with appropriate weighting, this discharge-level database accurately represents nearly 95% of all inpatient admissions in the United States.[1,2]

A variety of data points are available in this de-identified database. Patient demographics include age, gender, ethnicity, race, and insurance status. Household demographic data are also included. Disease-specific information includes a primary ICD-9 diagnosis code, and up to 24 additional diagnoses present at discharge. Up to 15 procedures that were completed during hospitalization are also included, again using ICD-9 codes. The time following admission that these procedures were completed is coded separately for each patient. Additional patient-specific healthcare information includes a variety of comorbidities such as congestive heart failure, diabetes, hypertension, end-stage renal failure, and many others; diagnosis-related groups (DRG), severity of illness and mortality scores; and overall groupings of the episode of care using DRG codes.[2] Details about the hospitalization are also included, such as transfer status, elective vs. emergency status, E codes used to identify emergency situations (such as trauma), and information about the hospital. Hospital teaching status, location, urban vs. rural site, information about nurse staff levels, and additional information about marketplace penetration are available. Physicians are de-identified, but tracking is possible between years as their numerical identifiers remain constant. Finally, charges are also given for each episode of care, and analytical tools exist to help convert this information into actual cost of care after adjusting for inflation.[2]

The scale of this database is enormous and researchers performing database analysis typically require investment in higher quality computer hardware and software to manage the magnitude of data. Our publication on AAA epidemiology used NIS data from 2000 to 2010 and included nearly 150,000,000 inpatient records, filled nearly 100 gigabytes of space, and required the use of special database and statistical software to properly identify patients and complete a statistical analysis.[1] A high-speed processor is required to manage these data in any reasonable time period, it was not uncommon for some of the database transformations to take several hours to complete.

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Abdominal Aortic Aneurysm Research, continued from page 15

The patients of interest are typically selected on the basis of ICD-9 diagnosis and procedure codes. While other databases sometimes use CPT codes to track procedures, this is a limitation of the NIS. A crosswalk between the CPT code and appropriate ICD-9 procedure code is also required. For example, if selecting patients who have an abdominal aortic aneurysm, five separate ICD-9 diagnosis codes could be used. Further selection of patients who underwent either open or endovascular repair requires the use of five separate ICD-9 procedure codes (Table 1).[1]

Once patients are properly selected, the data must be weighted to accurately reflect population-level data. Simple descriptive statistics can be generated on overall number of cases, averages calculated on patient age, ratios calculated on incidence in women and ethnic groups, and the overall incidence of comorbidities of interest calculated. Inpatient mortality can be calculated along with a median length of stay and median hospital charges (Table 2).[1] Prior to calculating actual dollar amounts, inflation must be taken into account using the Consumer Price Index.

Since the NIS is a population-level database, actual incidence and prevalence can be calculated for some diseases after taking into account weighting. The population of the United States can be determined from the U.S. Census Bureau, and the actual number of cases per 100,000 persons per year can be determined (Figure 1).[1] These data are particularly important when tracking trends in a certain disease or procedure over a period of time. Additional analysis on these trends can then be completed using more advanced statistical means.

TABLE 1: ICD-9 diagnosis and procedure codes used to select codes from the NIS.

ICD-9 code	Description
DIAGNOSIS CODES	
441.4	Abdominal aortic aneurysm without mention of rupture
441.9	Aortic aneurysm, not otherwise specified
441.3	Ruptured abdominal aortic aneurysm
441.5	Ruptured thoraco-abdominal aortic aneurysm, not otherwise specified
441.6	Ruptured thoraco-abdominal aortic aneurysm
PROCEDURE CODES	
38.34	Aorta resection and anastomosis
38.44	Replacement of abdominal aorta
38.64	Excision of aorta
39.52	Other repair of aneurysm
39.71	Endovascular abdominal aorta repair

ICD-9, International Classificaiton of Diseases, Ninth Revision; *NIS*, National Inpatient Sample.

Dua A, Kuy S, Lee CJ, Upchurch GR Jr, Desai SS. Epidemiology of aortic aneurysm repair in the United States from 2000 to 2010. *J Vasc Surg* 2014;59:1512-7.

TABLE 2: Demographics and outcomes for patients who underwent AAA repair in the NIS from 2000 to 2010.

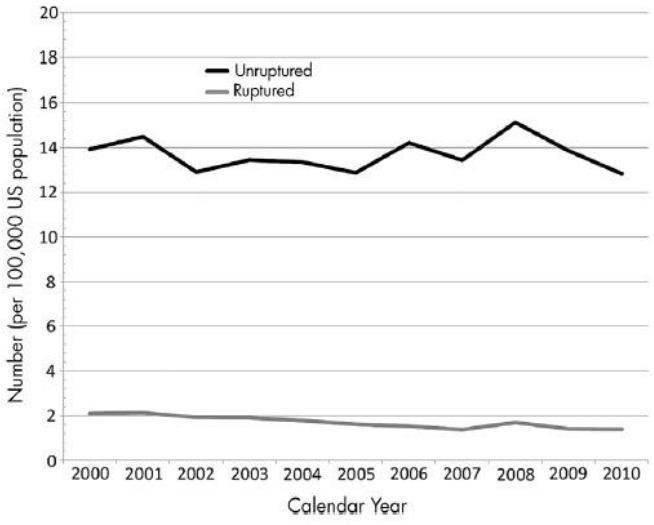
	ANEURYSM TYPE			
	Total	*Unruptured*	*Ruptured*	*P value*
Number	101,978	90,690	11,288	
Patient age in years ±SD	72.6 ± 8.7	72.5 ± 8.6	73.0 ± 9.3	<.001
Women, %	21	21	24	<.001
White, %	90	90	87	<.001
Comorbid conditions, %				
COPD	32	32	31	.177
DM	14	15	11	<.001
History of MI	11	12	5	<.001
In-hospital mortality rate	7	3.0	39	<.001
Median LOS (IQR), days	5 (2–8)	5 (2–8)	9 (3–17)	<.001
Median hospital charges (IQR)	$58,305 ($38,832–$90,508)	$56,537 ($38,178–$85,495)	$84,744 ($48,049–$158,226)	<.001

AAA, Abdominal aortic aneurysm; **COPD**, chronic obstructive pulmonary disease; **DM**, diabetes mellitus; **IQR**, interquartile range; **LOS**, length of stay; **MI**, myocardial infarction; **NIS**, National Inpatient Sample; **SD**, standard deviation.

Dua A, Kuy S, Lee CJ, Upchurch GR Jr, Desai SS. Epidemiology of aortic aneurysm repair in the United States from 2000 to 2010. *J Vasc Surg* 2014;59:1512-7.

In a retrospective study using the NIS, Cowan *et al*.[3] studied the epidemiology of AAAs in the United States between 1993 and 2003. This study showed that the numbers of patients undergoing elective AAA repair have remained relatively stable, despite the introduction of less invasive technology.[3] However, a higher percentage of patients underwent elective endovascular AAA repair compared to open repair due to decreased mortality.[2] In another retrospective study utilizing the NIS, Wainess *et al*[4] demonstrated that the repair of ruptured AAAs between 1988 and 2000 has not become safer but has decreased in incidence, which is likely due to earlier detection of AAA and reduction in risk factors that result in rupture.[4] These studies were important to outline trends in surgical practice for early detection and technique of elective repair of abdominal aortic aneurysms. Using the NIS, certain post-operative complications and their effect on mortality and hospital length of stay may also be evaluated. Eliason *et al*[5] was able to decipher that additional operations or secondary procedures following AAA repair resulted in worse inpatient mortality, especially when related to colon ischemia, respiratory failure and renal failure.[5]

FIGURE 1: Population estimates for unruptured (dark line, top) and ruptured (light line, bottom) abdominal aortic aneurysms in the United States from 2000 to 2010.

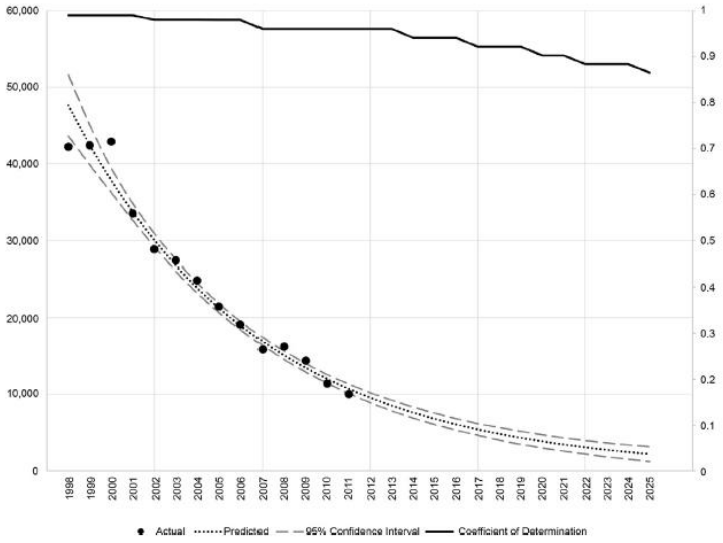


Dua A, Kuy S, Lee CJ, Upchurch GR Jr, Desai SS. Epidemiology of aortic aneurysm repair in the United States from 2000 to 2010. *J Vasc Surg* 2014;59:1512-7.

Our group took database research using the NIS a step further and determined the total number of open aneurysm repairs (OAR) completed for AAAs between 1998 and 2010 using the S-curve modified logistic regression function to forecast the number of open AAA repairs that would occur over the following 15-year period.[6] A subsequent deterministic sensitivity analysis was completed to highlight the accuracy of this forecast over the foreseeable future. It is noteworthy that this sensitivity analysis remained greater than 85% over a five-year forecasting period, a testament to the high quality data available within the NIS (Figure 2).[6] Incidentally, an S-curve function was used in this study as it best reflects the slow initial uptake of a new technology (EVAR), the rapid rise in use as the technology spreads, and the slow uptake as it reaches maximum penetration. Custom logistic regression functions may be more suitable for other models.

The data obtained from the NIS can be broken down by region (Table 3).[1] It can also be divided by whether the hospital is a nonfederal government-controlled entity, private non-profit, or private for-profit (Table 4).[7] Such analysis can be important when identifying disparities in care by region or hospital ownership.

FIGURE 2: Actual number of open abdominal aortic aneurysm (AAA) repairs (OAR) at the national level (black dots) compared with the predicted number of cases based off a modified S-curve regression model (dotted line). The 95% confidence intervals are given (dashed gray lines). The solid black line at the top is a modified correlation tornado chart showing the correlation of determination. This ranges from 0.99 in 1998 to 0.86 in 2025. The value drops below 0.90 after 2021. The horizontal axis represents the years out to 2025, the vertical axis on the left shows the number of open AAA cases weighted to reflect population-level estimates using the Nationwide Inpatient Sample (NIS), and the vertical axis on the right shows the values for correlation of determination. Values after 2011 are forecasted estimates based off the regression model.



Dua A, Kuy S, Lee CJ, Upchurch GR Jr, Desai SS. Epidemiology of aortic aneurysm repair in the United States from 2000 to 2010. *J Vasc Surg* 2014;59:1512-7.

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Abdominal Aortic Aneurysm Research, continued from page 17

Other variables that can be analyzed include teaching status and urban vs. rural location and demographics (Table 4).[7]

A separate analysis was completed using physician identifiers to determine the number of open and endovascular cases completed by doctor per year (Figure 3).[7] When plotting annual volume on the X-axis and mortality on the Y-axis, a logarithmic plot is created for some functions. When identifying outliers using control charts, the bottom 5% of all performers can be determined and a hypothesis generated about minimum performance standards. For example, mortality decreases substantially for patients undergoing open aneurysm repair when it is performed by a surgeon who has done at least five cases in a year as when reported by our group using the NIS.[7]

The power of the NIS database becomes particularly important when it is combined with data from other high-quality sources. For example, by determining hospital teaching status and case volume, we were able to determine the number of open AAA repairs being completed annually. We developed a logistic regression model to predict future cases, combined these data with the Accreditation Council for Graduate Medical Education (ACGME) resident case logs, and estimated the number of open aneurysm repairs being completed by trainees.[6] Our projection of the average surgery resident completing fewer than five aneurysm repairs by 2015 was later shown to be accurate in a subsequent publication.[6]

TABLE 3: Hospital bed size (small, medium, and large) as a function of location and teaching status as adapted from the National Inpatient Sample (NIS) Data Dictionary.

	HOSPITAL BED SIZE CATEGORIES		
Location and teaching status	Small, No.	Medium, No.	Large, No.
Northeast Region			
Rural	1-49	50-99	≥100
Urban, nonteaching	1-124	125-199	≥200
Urban, teaching	1-249	250-424	≥425
Midwest Region			
Rural	1-29	30-49	≥50
Urban, nonteaching	1-74	75-174	≥175
Urban, teaching	1-249	250-374	≥375
Southern Region			
Rural	1-39	40-74	≥75
Urban, nonteaching	1-99	100-199	≥200
Urban, teaching	1-249	250-449	≥450
Western Region			
Rural	1-24	25-44	≥45
Urban, nonteaching	1-99	100-174	≥175
Urban, teaching	1-199	200-324	≥325

Dua A, Furlough CL, Ray H, Sharma S, Upchurch GR, Desai SS. The effect of hospital factors on mortality rates after abdominal aortic aneurysm repair. *J Vasc Surg*. 2014 Dec;60(6):1446-51.

TABLE 4: Demographics and outcomes for patients who underwent repair for elective abdominal aortic aneurysm (AAA) from 1998 to 2011.

Hospital variables	Overall, %	OAR, %	EVAR, %	Elective admission, %	LOS, days	Costs, $	DRG mortality risk	Inpatient mortality, days
Control/ownership								
Government, nonfederal	13.5[a]	25.0[a]	75.0[a]	83.2[a]	2.0	28,972	1.8	2.0
Private, nonprofit	57.2[a]	22.4[a]	77.6[a]	86.0[a]	2.0	30,473	1.8	1.6
Private, for profit	29.3[a]	20.3[a]	79.7[a]	74.5[a]	2.0	28,081	1.8	2.0
Bed size								
Small	8.2[a]	21.7[a]	78.3[a]	83.4	2.0	30,477[a]	1.8	2.0
Medium	19.3[a]	21.2[a]	78.8[a]	83.7	2.0	27,925[a]	1.8	1.6
Large	72.5[a]	24.7[a]	75.3[a]	83.0	3.0	29,079[a]	1.8	1.9
Location								
Rural	6.2[a]	23.9	76.1	81.3[b]	2.0	30,593	1.7	1.7
Urban	93.8[a]	23.8	76.2	83.3[b]	2.0	28,867	1.8	1.8
Teaching Status								
Nonteaching	43.3[b]	22.4[a]	77.6[a]	82.5[b]	2.0	28,952	1.8	1.8
Teaching	56.7[b]	24.9[a]	75.1[a]	83.6[b]	3.0	28,945	1.8	1.8
Region								
Northeast	18.9[a]	21.2[a]	78.8[a]	83.3[a]	3.0	27,583[a]	1.8	1.8
Midwest	25.4[a]	26.6[a]	73.4[a]	84.9[a]	2.0	28,651[a]	1.8	1.8
South	39.0[a]	23.3[a]	76.7[a]	80.6[a]	2.0	27,740[a]	1.8	1.8
West	16.7[a]	23.9[a]	76.1[a]	85.3[a]	2.0	35,232[a]	1.9	1.9

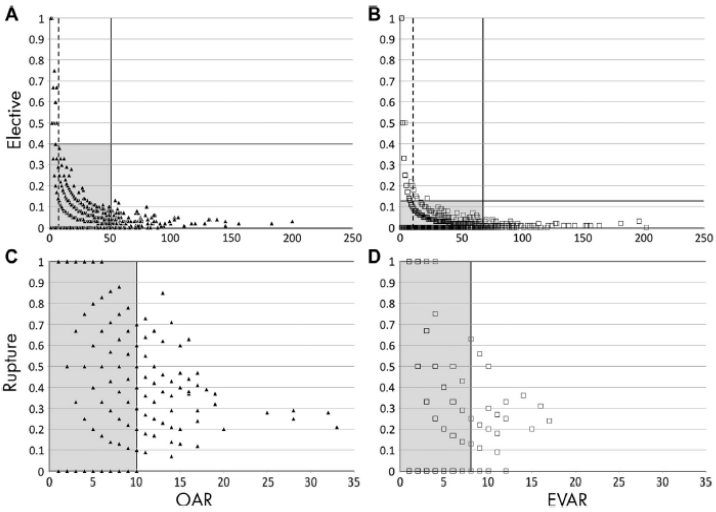
DRG, Diagnosis Related Group; **EVAR**, endovascular AAA repair, **LOS**, leng of stay; **OAR**, open AAA repair
a P< .001
b P< .05

Dua A, Furlough CL, Ray H, Sharma S, Upchurch GR, Desai SS. The effect of hospital factors on mortality rates after abdominal aortic aneurysm repair. *J Vasc Surg*. 2014 Dec;60(6):1446-51.

FIGURE 3: Open abdominal aortic aneurysm (AAA) repair (OAR) and endovascular AAA repair (EVAR) cases completed for unruptured and ruptured AAA for individual hospitals between 1998 and 2011.

A. OAR for unruptured AAA.
B. EVAR for unruptured AAA.
C. OAR for ruptured AAA.
D. EVAR for ruptured AAA.

Elective AAA repairs are located in the top row and ruptured AAA repairs in the bottom row. The first column demarcates OAR and the second column EVAR. The volume for each hospital is shown on the x-axis and inpatient mortality on the y-axis. Individual hospital volume and mortality data are presented by triangles for OAR and squares for EVAR. The shaded box indicates the ranges that include 95% of the hospitals by volume and by inpatient mortality. The limits of that box are extended as horizontal and vertical lines for each of the four groups. The single dashed vertical line for the elective AAA repairs is based off the threshold between low-volume and high-volume hospitals, as determined by trend analysis. For clarity, please note that the x-axes are different for elective vs. rupture cases.



Dua A, Furlough CL, Ray H, Sharma S, Upchurch GR, Desai SS. The effect of hospital factors on mortality rates after abdominal aortic aneurysm repair. *J Vasc Surg*. 2014 Dec;60(6):1446-51. doi: 10.1016/j.jvs.2014.08.111. Epub 2014 Oct 14.

Limitations of the National Inpatient Sample

Despite these advantages and publications that have made an impact on clinical care, there are significant limitations of the NIS. The data is coded by a research specialist, who may not have a substantial clinical background. These data may be coded on the basis of chart reviews, electronic medical record automation, or claims data submitted at the time of service. Defects in coding, incomplete data, and other variations can impact the results. While robust statistical analysis (and the use of missing values imputation) can help mitigate some of this, a proper evaluation of the data must be done to ensure that there is enough of a sample size to minimize the impact of erroneous or incomplete data.

Further, the NIS is a discharge-level database. We do not know the reason for admission, and this may be different than the discharge diagnosis for some patients. The database is also notable for the information that is not included. There is only limited information on past medical or surgical history, sparse data on family and social history, and no information on medications or allergies. There is no information about physical examination findings, laboratory values, or the results of imaging studies. The NIS is also limited by its lack of long-term follow-up data. Inpatient information is given, but it is not possible to track patients across the spectrum of care over a period of time. Some of these limitations can be remedied through the use of state-level databases, but the tradeoff is the difficulty with extrapolating this information for all patients.

Conclusion

Scarcity of certain diagnoses and procedures within single or even multi-institutional research datasets can limit the generalizability of conclusions. The NIS has over 150,000,000 records collected nationally over multiple years and therefore allows for the in-depth study of procedures, outcomes and diseases. It has been used extensively to study aortic disease and also been utilized to forecast the future of training in vascular surgery. The database is not without limitations and it does not readily allow for long-term follow-up or outcomes research. •

FOR ADDITIONAL INFORMATION on this topic, see references, visit mcw.edu/surgery or contact Dr. Lee, 414-805-9172, cjlee@mcw.edu.

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1. Dua A, Kuy S, Lee CJ, Upchurch GR Jr, Desai SS. Epidemiology of aortic aneurysm repair in the United States from 2000 to 2010. *J Vasc Surg*. 2014 Jun;59(6):1512-7. doi: 10.1016/j.jvs.2014.01.007. Epub 2014 Feb 20.
2. Nationwide Inpatient Sample. https://www.hcup-us.ahrq.gov/nisoverview.jsp. Accessed 10/11/2016.
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4. Wainess RM, Dimick JB, Cowan JA Jr, Henke PK, Stanley JC, Upchurch GR Jr. Epidemiology of surgically treated abdominal aortic aneurysms in the United States, 1988 to 2000.
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6. Dua A, Upchurch GR Jr, Lee JT, Eidt J, Desai SS. Predicted shortfall in open aneurysm experience for vascular surgery trainees. *J Vasc Surg*. 2014 Oct;60(4):945-9. doi: 10.1016/j.jvs.2014.04.057. Epub 2014 May 27.
7. Dua A, Furlough CL, Ray H, Sharma S, Upchurch GR, Desai SS. The effect of hospital factors on mortality rates after abdominal aortic aneurysm repair. *J Vasc Surg*. 2014 Dec;60(6):1446-51. doi: 10.1016/j.jvs.2014.08.111. Epub 2014 Oct 14.

Leading the Way

MEDICAL COLLEGE OF WISCONSIN

DEPARTMENT OF SURGERY
WELCOMES NEW FACULTY

We are pleased to welcome the following faculty to the Department of Surgery! Please refer to the cover of this issue for more information about these talented clinicians and scientists who are joining us.

Paul J. Pearson, MD, PhD

Chief of the Division of Adult Cardiothoracic Surgery, effective March 1.

Gwen Lomberk, PhD

Inaugural Chief of the Division of Research and Associate Professor of Surgery, effective July 1.

Marc A. de Moya, MD

Chief of the Division of Trauma/ Critical Care/Acute Care Surgery, effective June 26.

Raul A. Urrutia, MD

Professor of Surgery and Director of the Human and Molecular Genetics Center at the Medical College of Wisconsin, effective July 1.

DEPARTMENT OF SURGERY
EDUCATION IS OUR TOP PRIORITY

At the 2016 MCW Convocation Ceremony, the Department of Surgery was recognized by the educational excellence of its faculty.

Michael Malinowski, MD, was selected for the *Edward J. Lennon, MD, Endowed Clinical Teaching Award*. The MCW Society of Teaching Scholars (STS) presents this award to faculty members early in their career who have clearly "made a difference" in MCW's teaching programs. Dr. Malinowski also serves as an Associate Program Director and PGY1 Curriculum Director for the Department of Surgery.

Richard Steliga, MD, was selected for the *Marvin Wagner, MD, Clinical Preceptor Award*. The STS presents this award to volunteer clinical faculty who exhibit enthusiasm, selfless dedication, effective teaching and outstanding commitment to medical education. Dr. Steliga served as the site director at St. Joseph Hospital for the Surgery Clerkship until his retirement on May 31, 2016. Dr. Steliga was on the teaching faculty at St. Joseph's for 26 years. His dedication to the surgical residents of our department is legendary; Dr. Steliga is truly irreplaceable!

The Eighth Annual Medical College of Wisconsin Research Day was held on Wednesday, September 21, 2016. Our department was represented by eight poster presentations. **Andrew Kastenmeier, MD**, received the Outstanding Poster Award, in the "Junior Faculty Non-Basic Research" category, for his poster titled *Self-Directed Learning in the Surgery Clerkship through Individual Learning Plans*.

Timothy Ridolfi, MD, was also recognized as runner-up in the "Junior Faculty Non-Basic Research" category for his poster titled *Alvimopan Use Following Gastrointestinal Surgery is Associated with Decreased Length of Stay*.

DEPARTMENT OF SURGERY
AWARDS AND RECOGNITION

The Curriculum and Evaluation Committee (CEC) annually awards the MCW Outstanding Medical Student Teacher recognition pins. The CEC wishes to "recognize and affirm those individuals who, through their teaching excellence, advance student learning and provide added value to students' required medical training." Pins are awarded to faculty and residents for contributions in courses, clerkships, pathways, acting internships, or electives. The 2015-2016 Outstanding Medical Student Teacher Pin recipients from the Department of Surgery include the following individuals:

Full-Time Faculty
John Aiken, MD; Marshall Beckman, MD, MA; Kellie Brown, MD; Thomas Carver, MD; John Densmore, MD; T. Clark Gamblin, MD, MS, MBA; Matthew Goldblatt, MD; Johnny Hong, MD; Dave Lal, MD, MPH; C.J. Lee, MD; Brian Lewis, MD; Todd Neideen, MD; Philip Redlich, MD, PhD; Timothy Ridolfi, MD; and Travis Webb, MD, MPHE.

Volunteer Faculty
Anthony Nelson, MD; Kelli Pettit, MD; and Zane Prewitt, MD.

Residents
Chad Barnes, MD; Jacqueline Blank, MD; Munyaradzi Chimukangara, MD; Anahita Dua, MD, MS, MBA; Sarah Greenberg, MD, MPH; Kaleb Kohler, MD; Lisa McElroy, MD, MS; Robert McMillan, MD; John Miura, MD; and Tanner Spees, MD.

HISTORY CORNER

"The Times They Are A Changing," and The Milwaukee Seven

By Stuart D. Wilson, MD, Emeritus Professor, Department of Surgery

The Medical College of Wisconsin Department of Surgery is leading the way in training women for a career in surgery. The recent Nobel Laureate Bob Dylan's words from his 1964 song, "The Times They Are a Changing," were prophetic. The Department of Surgery General Surgery Residency program is approved by the Residency Review Committee for seven categorical resident positions (eight next year); this year we matched women in all seven positions.

During the Edwin Ellison era in the 1960's and the development of the Marquette (now MCW) integrated surgical residency programs, we had only men in our general surgery residency. Jan Turcotte, MD, was the first woman to finish our program in 1979. She went on to do a vascular surgery fellowship at the University of Chicago and then practiced surgery for 32 years in New York. Only 1-2% of American Board of Surgery diplomates were women before the 1980s. The number of women who have passed their board certifying exam has progressively increased nationally to 36% in 2015.

During the Robert Condon era (1978-1995), the number of women entering the general surgery residency program in Milwaukee began to noticeably change. Among the first to graduate were Terry Siegert, MD, Linda Sell, MD, and Mary Otterson, MD, MS. Dr. Condon recruited Mary Otterson in 1990 as the first full-time female faculty member in surgery, and then Julie Freischlag, MD, as the Chief of Surgery at the VA hospital. Dr. Freischlag went on to become the Halsted Professor and Chief of Surgery at Johns Hopkins Hospital and was recently named CEO of Wake Forest Baptist Medical Center, effective May 1. These faculty, and numerous female residents, paved the way as early role models and provided mentorship, creating an environment that has attracted the best and brightest women candidates to our program.

From left: Kayla Chapman, MD, Elizabeth Traudt, MD, Alexis Bowder, MD, Keona Childs, MD, Kathryn Haberman, MD, and K. Hope Wilkinson, MD.

Over the past 15 years, the number of women completing our general surgery residency program has increased over each five year period (2001-2005=26.6%, 2006-2010=32% and 2011-2015=61% in the Evans era).

Current analysis of the future surgical workforce needs for the United States predicts a shortage of general surgeons and surgeons in several other surgical specialties.[1] Surgery programs must continue to recruit and retain the best and brightest women. We continue to provide the best possible environment for all trainees in these challenging and ever-changing times. •

1. Sachdeva AK, *J Am Coll Surg.* 2011 Mar;212(3):320-6.

To refer a patient or request a transfer/consultation, please use the references below:

ADULT PATIENTS

All non-cancer requests
Referrals: 800-272-3666
Transfers/Consultations:
877-804-4700
mcw.edu/surgery

Clinical Cancer Center
Referrals: 866-680-0505
Transfers/Consultations:
877-804-4700

PEDIATRIC PATIENTS

Referrals/Transfers/
Consultations: 800-266-0366
Acute Care Surgery:
414-266-7858

THE MEDICAL COLLEGE OF WISCONSIN **DEPARTMENT OF SURGERY**

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Upcoming Events

MARCH 14–15: Justin Dimick, MD, Ellison Visiting Professor – Medical College of Wisconsin

APRIL 28: Acute Care Surgery Symposium – Miller Park, Milwaukee

MAY 9–10: Lena Napolitano, MD, Lunda Visiting Professor – Medical College of Wisconsin

MAY 16–17: Ross Milner, MD, Towne Visiting Professor – Medical College of Wisconsin

JUNE 16: Wayne A. I. Frederick, MD, MBA, President of Howard University, Eberbach Visiting Professor – Medical College of Wisconsin

JUNE 28: Michael La Quaglia, MD, Glicklich Visiting Professor – Medical College of Wisconsin

AUGUST 4: 2017 GI Symposium: Spotlight on Peritoneal Surface Malignancies and HIPEC – The American Club, Kohler

SEPTEMBER 29: Surgical Site Infection Summit – Crowne Plaza, Madison

OCTOBER 13: MCW Pancreatic Cancer Scientific and Translational Research Meeting – Location TBD

NEW FEATURE: *We now offer ABMS MOC Part 2 Self-Assessment credit for our Grand Rounds Lectures. Scan the QR code to proceed.*

Please contact Heidi Brittnacher (hbrittna@mcw.edu) for more information on any of these events.

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- Surgical Oncology
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Leading the Way is published three times yearly by The Medical College of Wisconsin – Department of Surgery, 9200 W. Wisconsin Ave., Milwaukee, WI 53226 ©2017

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