Bucknell UNIVERSITY GEISINGER

Bucknell **G**eisinger **R**esearch **I**nitiative

Enhancing and Expanding Relationships

November 28, 2012

Posters and Abstracts

Bucknell Geisinger Research Initiative

"Enhancing and Expanding Relationships"

A forum for Bucknell faculty and Geisinger physicians and researchers to share current and consider future research collaborations

Elaine Langone Center
Terrace Room
Bucknell University, Lewisburg
Wednesday, November 28, 2012

5:30 pm
Open for Poster Hanging

6:00 – 7:15 pm
Poster Session & Conversation
(Wine, Beer and Hors d'oeuvres)

7:15 pm
Remarks by

Michael A. Smyer, Ph.D.
Provost, Bucknell University

David H. Ledbetter, Ph.D.
Chief Scientific Officer, GHS

Short Progress Reports on
Currently Funded Projects

David Evans, PhD
Gregory Moore, MD, PhD

Eric Kennedy, PhD
Thomas Bowen, MD

Matthew Bailey, PhD
Priyantha Devapriya, PhD

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BUCKNELL UNIVERSITY POSTERS

Principal Investigator: Kathleen Bieryla[1], E.

Title: Quantifying the Forces and Position of an Endoscope

Co-investigators: D. Diehl[3], J. Shui[1], S. Talbot[1]

Department and Institution: Department of Mechanical Engineering, Bucknell University

Background: The forces resulting from endoscope motion in the body are important because a large force may cause perforation during a procedure. Currently, there is no way to attribute those forces to movement of the surgeon.

Aims: The goal of this project was to begin to quantify the forces and position of the endoscope using a simple model with the intention of expanding to a more accurate model.

Methods: A simplified Styrofoam model was created to be used with the Vicon motion analysis system as well as a six degree of freedom force sensor. The model consisted of a molded arc within the Styrofoam with an approximate radius of six inches. The force sensor was mounted underneath the model. A reflective marker was placed at the tip of the endoscope to track the position using the Vicon motion analysis system. Four trials of were collected of the endoscope moving through the model.

Results: As the endoscope traveled through the model, the forces oscillated creating multiple peak forces. The grouping of peak forces at specific areas of the path indicates that the force required to go through specific parts of the channel varies. It is hypothesized that the geometry of the path is the cause of the different peak types and is the subject of continued work.

Conclusions: The model proved to be effective in testing the forces and position of the endoscope. Future work will include incorporating the force sensor in a more realistic model. Additionally, surgeons will be used to determine how their movement affects the force inside the model.

Principal Investigator: Kathleen Bieryla

Title: Xbox Kinect Training May Improve Balance Measures in Older Adults

Department and Institution: Department of Mechanical Engineering, Bucknell University

Co-investigators: Eric Balaban

Background: Training using the Xbox Kinect may be a novel way to improve balance in older adults.

Aims: The purpose of this study is to investigate the feasibility of training using the Kinect to improve clinical measures of balance in older adults. It is hypothesized that older adults who train with the Kinect will increase their Berg Balance Scale (BBS) score and Functional Reach (FR).

Methods: Thirteen older adults (82.3 ± 5.1 years old) participated in the study. BBS and FR were completed before, one week, and one month after a three week training period. Six participants completed the training using the Kinect while seven subjects served as control and did not train. Three times each week, the training group was led through a custom routine that lasted approximately 30 minutes. The first 15 minutes was comprised of Your Shape: Fitness Evolved Zen sessions (Stream 1 and 2) followed by 15 minutes of games from Kinect Adventures. Clinical measures of balance before training were compared to one week and one month after training. An increase in BBS and FR would be considered an improvement in balance. Paired t-tests were conducted on the training and control group to determine if training influenced measures of balance.

Results: BBS scores significantly increased one week and one month after training when compared to before training for the experimental group ($p<0.05$). There was no significant change in BBS for the control group ($p>0.05$). FR was not significantly different from before training for either the control group or experimental group ($p>0.05$).

Conclusions: This pilot study provides some evidence that training using the Kinect can lead to improvements in some clinical measures of balance in older adults. A larger study is needed to confirm the efficacy of training using the Kinect as a method to improve balance. This training may be a fun, novel, and cost-effective way to improve balance in older adults.

Principal Investigator: Christine Buffinton, PhD

Title: **Stress and strain adaptation in load-dependent remodeling of the embryonic left ventricle**

Department and Institution: Department of Mechanical Engineering, Bucknell University
Co-investigators: Daniela Faas Ph.D., David Sedmera M.D., D.Sc.
Background: Altered pressure in the developing left ventricle (LV) results in altered morphology and tissue material properties. Mechanical stress and strain may play a role in the regulating process.
Aims: This study showed that confocal microscopy, three-dimensional reconstruction, and finite element analysis can provide a detailed model of stress and strain in the trabeculated embryonic heart. The method was used to test the hypothesis that end-diastolic strains are normalized after altered loading of the LV during the stages of trabecular compaction and chamber formation.
Methods: Stage-29 chick LVs subjected to pressure overload by conotruncal banding and underload by verapamil administration at stage 21 were reconstructed with full trabecular morphology from confocal images and analyzed with finite element techniques. Myocardial elastic modulus and intraventricular pressures from the three treatment groups, control, pressure-underloaded, and pressure-overloaded, were measured and incorporated in the models. High resolution ultrasound on hearts cultured ex ovo provided experimental verification of model results.
Results: The results show end-diastolic von Mises stress and strain averaging 50-82% higher on a volumetric basis in the trabecular tissue than in the compact wall. The volume-weighted-average stresses for the entire LV were 115, 64, and 147 Pa in control, underloaded, and overloaded models, while strains were 11, 7, and 4%; thus, neither was normalized in a volume-weighted sense. Localized epicardial strains at mid-longitudinal level were similar among the three groups and to strains measured from high-resolution ultrasound images. Sensitivity analysis showed changes in material properties are more significant than changes in geometry in the overloaded strain adaptation, although resulting stress was similar in both types of adaptation.
Conclusions: These results emphasize the importance of appropriate metrics and the role of trabecular tissue in evaluating the evolution of stress and strain in relation to pressure-induced adaptation.

Principal Investigator: Dan Cavanagh

Title: **The Development of Medical Technologies to Address Modern Healthcare Challenges**

Department and Institution: Department of Biomedical Engineering, Bucknell University

Co-investigators: J. Baish, J. Tranquillo, D. Ebenstein, E. Kennedy, K. Bieryla, W. King

Background: Modern engineering design methodologies and tools have been shown to be effective in the development of medical technologies to address relevant healthcare challenges. Recent advances in prototyping and fabrication technologies have accelerated the development process and permit rapid, iterative approaches to medical device design. For over six years, Bucknell engineers have worked productively with Geisinger clinicians and scientists on a wide range of projects aimed at developing medical devices to address important healthcare challenges.

Aims: The overall aim of this effort is to jointly leverage the clinical, scientific, and engineering expertise at Bucknell and Geisinger to devise novel solutions to a broad range of healthcare needs. Through the presentation of examples of recent collaborative medical device design projects that utilized the engineering design process and modern fabrication tools, we aim to identify and pursue solutions to new healthcare challenges.

Methods: Collaborative medical technology design projects will utilize the expertise of Bucknell engineering faculty, staff and students in conjunction with the healthcare expertise of Geisinger clinicians and scientists. Projects will involve numerous aspects of device design including, but not limited to, formal engineering design methodologies, rapid-prototyping and fabrication techniques, clinical needs, bench-top testing and evaluation, regulatory procedures, and/or market evaluations. Projects may be conducted as part of student design work, summer internship projects involving students and faculty, faculty research efforts, and/or student employment efforts.

Results: Past collaborative projects have resulted in the fabrication of physical prototypes designed to meet user's needs, required specifications and functions, and clinical requirements. In certain projects, efforts have been continued to develop and further test and evaluate subsequent prototypes. The broad range of clinical specialties involved have included orthopedics, surgery, emergency medicine, urology, neonatal intensive care, wound care, gastroenterology, cardiology and others.

Conclusions: Collaborative efforts between Geisinger clinicians and scientists and Bucknell engineering faculty, staff and students have the potential to develop useful solutions to current healthcare challenges.

Principal Investigator: Donna M. Ebenstein[1], C. Tristan Stayton[2]

Title: **Investigation of Material Properties of Red-Eared Slider Turtle Shell Bone Using Micro- and Nanoindentation**

Department and Institution: [1]Biomedical Engineering Department, [2]Biology Department, [3]Physics Department, Bucknell University

Co-investigators: Nicole Diamantides[1], Aylin Dincer[3]

Background: Turtle shells contain non-mineralized, fibrous sutures where the bony plates fuse together during shell formation. Little information is known about how the shell bone material properties vary within the shell. Knowledge of the variability in material properties in the shell would improve the accuracy of finite element models used to study turtle evolution.

Aims: The goal of this study was to use micro- and nanoindentation to investigate regional variations in bone properties with position in the shell and with distance from the suture.

Methods: Indentation involves pressing a small tip into a sample and monitoring the applied load and tip displacement to measure material properties such as elastic modulus (stiffness). Nanoindentation uses a smaller tip than microindentation, allowing measurements with higher spatial resolution. To investigate bone property variation within the plastron, indents were performed in 47 regions from a single plastron using nanoindentation. To investigate variation in bone properties near the suture, microindentation and nanoindentation were performed on bone specimens containing sutures, with indent position relative to the suture recorded.

Results: No trend was observed in material properties of bone with position in the plastron. In samples containing sutures, material properties remained constant in the bone for indents at least 1 mm from the suture, but were significantly different within 1 mm of the suture ($p<0.05$). The observed gradient in material properties within 1 mm of the suture may be due to a gradient in mineralization or because of the possible contribution of the suture under the bone.

Conclusions: These results demonstrate that there is no consistent trend in variation in material properties with position in the plastron, but there is variation in turtle bone properties near the suture that perhaps should be included in computational models of turtle shells. Future studies will focus on investigating the source of variation in the gradient region using chemical spectroscopy.

Conclusions: The present data suggest links between certain aspects of social cognition, OXTR SNPs, and visual face processing. Although on average, males and females may occupy different parts of a social cognition spectrum, they appear to be part of the same, continuous behavioral distribution with some of the differences being modulated by OXTR variants. Subsequent data collection integrating fMRI will also be presented.

Principal Investigator: Ken Field

Title: Farnesyltransferase Inhibitors in Cancer and Immunity

Department and Institution: Cell Biology/Biochemistry Program, Biology Department, Bucknell University
Co-investigators: Mike Hayes, Arielle Fisher, Jim McMichael, and Chelsea Dieck
Title: Farnesyltransferase Inhibitors in Cancer and Immunity
Background: Farnesyltransferase inhibitors (FTIs) are anti-cancer drugs that have been shown to induce apoptosis in cancer cells and are currently in clinical trials for advanced haematologic malignancies. Similar to statins, FTIs may also act as immunomodulators by preventing protein prenylation and affecting T cell subset differentiation and cytokine secretion.
Aims: We are testing whether FTIs synergize with certain components of the current Burkitt's lymphoma R-CHOP therapy. We also hope to better identify the effects of FTIs on the immune system and determine whether their effects on T cell differentiation and cytokine secretion may specifically modulate immune responses.
Methods: Human Burkitt's lymphoma cell lines are treated with FTIs and components of CHOP therapy for 48 hours *in vitro* and analyzed on a flow cytometer. To determine the effects of FTIs on the immune system, cytokine production is measured either in mice that have received skin allografts, or *in vitro* with cultured mouse T cells. *In vivo*, expression of cytokine genes are measured by real-time PCR. *In vitro*, cytokine production is measured by intracytoplasmic flow cytometry.
Results: FTIs activate the intrinsic pathway of apoptosis synergistically in combination with vincristine, a component of CHOP therapy. In mice undergoing an alloreactive immune response, we have found that FTI treatment blocks Th1 cell differentiation and interferon-g expression without affecting Th2 and Treg cells or cytokines. *In vitro*, we have similarly found that FTIs decrease interferon-g secretion from Th1 cells while IL-4 secretion from Th2 cells remains unaffected.
Conclusions: Evidence from human cell lines suggest that FTIs may be useful adjuncts to R-CHOP therapy for Burkitt's and, possibly, other non-Hodgkin's lymphomas. Further testing in primary cells from non-Hodgkin's lymphoma patients would be valuable. FTIs appear to be able to specifically modulate Th1 immune responses during an alloreactive immune response in mice. We speculate that these drugs may be clinically useful to modulate pathological Th1 immune responses without nonspecific immune suppression.

Principal Investigator: Judith Grisel

Title: b-Endorphin Influences Behavioral Responses to Ethanol and other Stressors in a Sex-Dependent Manner

Department and Institution: Department of Psychology, Bucknell University

Co-investigators:

Background: Endogenous opioids such as the peptide β-Endorphin (β-E) are synthesized and released in response to stress and alcohol (EtOH) through activation of the hypothalamic-pituitary-adrenal (HPA) axis. The opioid response in such cases is heritable and thought to serve a role in homeostatic functions as well as in rewarding and reinforcing properties of drugs of abuse such as alcohol. For example, increased release of β-E by acute EtOH administration may encourage the acquisition of alcohol drinking, but decreased synthesis and release of β-E with chronic use may be partly responsible for the increased anxiety that contributes to the maintenance of alcohol drinking.

Aims: We have been using *Pomc*^{tm1Low} transgenic mice to study the relationship between this peptide, stress and alcohol and hypothesize that those with low opioid tone may be less able to effectively cope with stressful stimuli as a result of insufficient attenuation of the stress response, and thus be more inclined to suffer from anxiety, self-administration of alcohol, and to develop alcoholism and depression.

Methods: We evaluated sensitivity to EtOH in several behavioral assays of anxiety, depression, and locomotor activation and sedation in adult male and female mice, with and without β-E. In addition we used a 2-bottle free choice limited access paradigm to evaluate oral self-administration of EtOH following stress exposure.

Results: We find an inverse relationship between β-E and stress/anxiety responses, but also that low b-endorphin leads to exaggerated effects of EtOH, including anxiolysis. In addition, many of the effects of EtOH that depend upon β-E are sex-dependent. For instance the sedative effects of EtOH are more profound in male mice lacking this peptide, while female transgenics are less sensitive than controls (C57BL/6J). Our data concur with the literature demonstrating that stress sensitivity is sexually dimorphic and females are be more sensitive to the effect of stress on EtOH sensitivity. This relationship appears to be moderated, at least in part, by β-E.

Conclusions: These data provide support for the contention that β-E plays an active role in coping behavior and may be implicated in the complex interplay of stress-related disorders including alcoholism.

Principal Investigator: Mark Haussmann

Title: Embryonic exposure to corticosterone modifies the juvenile stress response, oxidative stress and telomere length

Department and Institution: Department of Biology, Bucknell University

Co-investigators:

Background: Early embryonic exposure to maternal glucocorticoids can broadly impact physiology and behavior. The transfer of maternal glucocorticoids to offspring is likely to have both costs and benefits that are paid and collected over different developmental time periods. But, a recent link between elevated glucocorticoids and accelerated cellular aging in humans suggests that increased embryonic exposure to maternal glucocorticoids may also have long-term survival costs.

Aims: We manipulated yolk corticosterone (cort) in domestic chickens (*Gallus domesticus*) to examine the potential impacts of embryonic exposure to maternal stress on (i) the juvenile acute stress response and (ii) cellular aging processes including oxidative damage, antioxidant status, and telomere length.

Methods: Eggs were assigned to three groups balanced for mass: control (C, n = 15), low CORT (5 ng/ml CORT, n = 15), and high CORT (10 ng/ml CORT, n = 15). Upon hatch, chicks were weighed daily and at 25 days of age we measured activity of the HPA axis through a stress series. We also assessed oxidative damage to lipids and proteins, the status of the total antioxidant plasma barrier, and telomere length through the telomere restriction fragment assay.

Results: We report that juveniles exposed to experimentally increased cort *in ovo* had a protracted decline in cort during the recovery phase of the stress response. All birds, regardless of treatment group, shifted to oxidative stress during an acute stress response. In addition, embryonic exposure to cort resulted in higher levels of reactive oxygen metabolites and an over-representation of short telomeres compared with the control birds.

Conclusions: Individuals with higher levels of oxidative stress and shorter telomeres have the poorest survival prospects. Given this, long-term costs of glucocorticoid-induced phenotypes may include accelerated ageing and increased mortality.

Principal Investigator: Peter Judge

Title: Interpretation of social cues by brown capuchin monkeys (*Cebus apella*)

Department and Institution: Psychology Department and Animal Behavior Program, Bucknell University

Co-investigators: Jennifer Essler and Mattea Rossettie

Background: Apes are capable of reading the facial cues and informational gestures of conspecifics and humans to gain knowledge. Demonstrations of these same abilities in monkeys are either weak or equivocal.

Aims: We tested whether capuchin monkeys could acquire information from the cues of a conspecific. If one monkey, a "cueing monkey," was knowledgeable about the location of a reward, we predicted that an uninformed monkey, a "subject monkey," would use the behavioral signals of the cueing monkey (e.g., reaching) to infer the location of a reward.

Methods: The subject and a conspecific were placed into opposite ends of a testing chamber, where they could view each other. On a tray between the monkeys were two opaque containers, each with holes cut near the base on one side. The containers faced toward the cueing monkey so that only that monkey could see a reward placed inside by an experimenter. However, the subject monkey had learned that it could rotate the container when it was baited to obtain a reward. After the cueing monkey, but not the subject, witnessed the baiting of one of the two containers, the two containers were moved toward the subject monkey and we recorded whether the subject monkey selected the cup containing the reward.

Results: Of four monkeys that have completed training and testing, two subject monkeys selected the cup containing the reward significantly more often than expected in two consecutive 20-trial blocks of testing. Two monkeys did not perform significantly over chance after one hundred trials.

Conclusions: Two animals used the cueing monkey to guide their choices and successfully obtain rewards, whereas two others did not appear to apprehend the cueing monkey's signals. Results demonstrate that capuchin monkeys are capable of reading the attentional cues of a conspecific. Individual differences in the monkeys' ability to read social cues provide an assay of social awareness, which may provide avenues for translational research into the causes of autistic spectrum disorder.

Principal Investigator: Ben Marsh

Title: Uncovering cryptic governmental racial discrimination using GIS

Department and Institution: Geography and Environmental Studies, Bucknell University

Co-investigators: Allan Parnell & Ann Joyner, Cedar Grove Institute for Sustainable Communities

Background: Local governments have considerable power to provide benefits to residents within and outside of their boundaries. Local governments determine which areas are annexed into a municipality and which are excluded, local governments set land-use regulations and zoning, local governments select areas to receive infrastructure, and local governments identify areas to be "redeveloped." Through these powers, local governments can diminish or deny minority political standing in local affairs, limit access to public services, and reduce the value of minority property.

Aims: Identify and describe instances of 'cryptic discrimination' created by hidden, inequitable application of routine political geographical processes – zoning, annexation, etc.

Methods: GIS & demographic techniques; inclusion of environmental factors; quantitative analysis of access, disparate impact, discriminator outcomes. These methods are broadly applicable to community and environmental research.

Results: The work is primarily applied efforts to support legal, administrative, and community action activities. Numerous cases have been supported, usually successfully.

Conclusions: Racially-disparate application of local governments' power to shape local political geography creates barriers to equality that are difficult to discern on the ground, but which can be made visible though mapping of spatial data.

Principal Investigators: Gregory J. Moore, MD, PhD, David W. Evans, PhD

Title: **Social cognition and functional brain activity during face-processing tasks are modulated by oxytocin receptor variants**

Department and Institution: Program in Neuroscience, Bucknell University, Department of Radiology, Geisinger Health System

Co-investigators: SM Lazar, PT Orr, SM Myers, TD Challman, A Moreno De Luca, and David H. Ledbetter

Background: Oxytocin is a hormone that is believed to be associated with social behavior, such as pair bonding and social cognition in human and non-human mammals. Oxytocin has also been implicated in several neurodevelopmental and neuropsychiatric disorders, including autism spectrum disorders (ASD), and is believed to play a role in the social and social cognitive deficits that define the autism phenotype. Several Oxytocin receptor (OXTR) single nucleotide polymorphisms (SNPs) have been identified as autism risk factors, but their role in typical populations is largely uncharacterized.

Difficulty perceiving faces is also a deficit in ASD, and these deficits have been linked to social and social-cognitive problems in ASD. The N170 event-related potential (ERP) component is a cortical response to faces, occurring over temporo-cortical sites and is thought to be governed by the fusiform gyrus. Recent work has identified sex differences in the magnitude and hemispheric lateralization of the N170, but it is unknown how sex differences in the N170 ERP waveform relate to social cognition and OXTR variants in a typical population.

Aims: To examine the variation in and connection between measures of social cognition, face perception and to determine if these variations are modulated by OXTR gene SNPs. IN particular we examine several indices of social cognition, and our aim is to link the measures of social cognition to both face perception and OXTR variants. In so doing, we hope to map important genes, brain and behavior links in social cognition relevant to the study of autism and related disorders.

Methods: Forty-two undergraduates (18 males, 24 females) were given several measures of social cognition: the Social Attribution Task (SAT), Empathy Quotient (EQ), Systematizing Quotient (SQ), and emotional face response tasks. Subjects were subsequently exposed to images of human faces or houses while cortical brain activity was measured with a 32 channel EEG system. Subjects' saliva was collected and assayed for several OXTR SNPs.

Results: In males, the difference between the houses versus faces ERP amplitudes at electrode site P7 is associated with rs2268494 (R^2 =.21, p< .05) and scores on SQ/SAT (R^2= .24, p<.01). The difference at P8 is associated with rs2268494 (R^2= .29, p<.001) and rs237885 (R^2=.17, p < .05). In females using all predictors in the model, the only association that emerged was for P7 with SQ/SAT (R^2=.27, p=.01) and EQ/Emotion Recognition scores ($R^{2=}$.13, p<.01).

Conclusions: The present data suggest links between certain aspects of social cognition, OXTR

SNPs, and visual face processing. Although on average, males and females may occupy different parts of a social cognition spectrum, they appear to be part of the same, continuous behavioral distribution with some of the differences being modulated by OXTR variants. Subsequent data collection integrating fMRI will also be presented.

Principal Investigator: Kathleen C. Page

Title: Maternal and post-weaning high-fat diets contribute to depressive-like behavior and changes in hippocampal expression of genes mediating synaptic function

Department and Institution: Biology/Neuroscience, Bucknell University

Co-investigators: Elizabeth Jones, Endla Anday

Background: Recent studies have shown obesity is often accompanied by depression and that diet-induced obesity is correlated with leptin resistance. Moreover, leptin affects cognition and mood by disturbing cortical and hippocampal function. We have previously shown that adult male rats exposed to dietary saturated fat during gestation and after weaning have increased leptin levels and exhibit impaired spatial learning and memory.

Aims: We tested the hypothesis that pre-and postnatal exposure to excess saturated fat results in hippocampal dysfunction leading to depressive-like behavior and that this is associated with altered expression of genes mediating hippocampal synaptic function.

Methods: Dams were fed control or high fat diet (45% kcal saturated fat) prior to mating, pregnancy, and lactation. Male offspring from control and high fat-fed dams were weaned to control (CC or HFC) or to high-fat diet (CHF or HFF). At 150d the forced swim test was used to measure differences in time spent immobile. Animals were fasted overnight and sacrificed 24h after completion of behavioral testing. Serum leptin, insulin and corticosterone were measured by radioimmunoassay; RT-PCR was used to analyze hippocampal expression of genes mediating synaptic function.

Results: Hippocampal synaptophysin mRNA level was significantly reduced in offspring from HF dams, HFF,HFC (maternal diet effect, P=0.044) was susceptible to the modulating effects of the post-weaning diet (post-weaning diet effect, P=0.002). In contrast, synaptotagmin mRNA level was significantly elevated in offspring from HF-fed dams, HFC and HFF (maternal effect, P=0.007). Reductions in the ionotropic glutamate receptor, AMPAR1 (P=0.003), glial-derived neurotrophic factor, GDNF (P=0.034), microtubule-associated protein 2, MAP2 (P=0.011) and synaptosomal-associated protein, SNAP25 (P=0.011) were detected in HFF offspring compared to HFC offspring. Expression of glutamate receptor, AMPAR2, was not significantly different among the four groups. These changes in hippocampal gene expression correlated with depressive-like behavior detected using the forced swim test. Time spent immobile was significantly increased in animals fed a high-fat diet postweaning (P=0.014).

Conclusions: These data support that pre-and postnatal exposure to dietary saturated fat during critical periods of brain development has a complex and detrimental effect on hippocampal synaptic plasticity that may lead to affective disorders in adult life.

Principal Investigators: M. Shabahang[1], James Baish[2]

Title: Development of a Surgical Simulator for Open, Abdominal Training Procedures

Department and Institution: [1]Department of Surgery, Geisinger Health System, [2]Department of Biomedical Engineering, Bucknell University

Co-investigators: N. Woll[1], K. Bieryla[2], D. Cavanagh[2], D. Matteson[2], A. Moats[2], K. Shute[2]

Background: Residents are trained in surgical techniques by a combination of surgical skill simulators and clinical experience. Most surgical simulation focuses on laparoscopic surgery, but research suggests that there is a need for an open surgery trainer that has the versatility to simulate surgical techniques at various skill levels on lean or obese patients while remaining cost effective and intuitive to use.

Aims: The goal of this project was to develop an intuitive, modular, open surgical simulator for residents learning abdominal surgery skills on lean to obese patients.

Methods: The simulator was designed by Bucknell Engineering students and faculty under the advisement of Geisinger's director of general surgery and the coordinator of general surgery research and education. To meet the specifications, the surgical simulator was constructed with an aluminum frame and sliding polyethylene panels. The lid thickness can be selected to model adipose tissue of various thicknesses.

Results: Three training exercises were created: a bowel anastomosis, a common bile duct exploration, and a general knot tying exercise. These exercises were chosen because the skills necessary to complete the exercise are applicable to a wide array of procedures. Feedback from the surgical staff was used to verify the design. The final prototype was well received by residents; the dual layer bowel and tying exercise were found particularly useful. A more firm anchoring of the bowel within the pelvis was suggested to improve the usability.

Conclusions: The simulator provides an intuitive training mechanism for general surgery residents, and the modular design improves the usability of the simulator for residents of different skill levels. This project demonstrates a successful collaboration between Geisinger clinical staff and Bucknell engineering faculty and students to design medical devices.

Principal Investigator: George C. Shields

Title: Computational Study of an Anticancer Pharmacophore using Alpha-Fetoprotein-Derived Peptides

Department and Institution: Office of the Dean of Arts and Sciences; Department of Chemistry
Co-investigators:
Title: Computational Study of an Anticancer Pharmacophore using Alpha-Fetoprotein-Derived Peptides
Background: About 75% of breast cancers are estrogen-receptor positive (ER+) and are dependent upon estrogen (E2) for proliferation. Tamoxifen is the most widely used drug to treat these cancers, but its adverse side effects and the cancer's resistance to the drug have prompted the exploration of new drugs. Computational methods have been used to explore the use of alpha-fetoprotein-derived peptides (AFPeps) as potential drug candidates for the treatment of ER+ breast cancers. These AFPeps have been tested in uterine growth assays and breast cancer xenograft treatment assays in mice and were shown to be active in the inhibition of ER+ breast cancers.
Aims: Inexpensive computational methods have shown that the activity of the small AFPeps correlates with their ability to form a *beta*-turn motif. We employed more rigorous computational methods to conclusively determine if these peptides do form beta-turn conformations. We also wanted to develop an efficient computational protocol for determining the structure of small peptides.
Methods: For two tetrapeptides, TPVN and TOVN, we used inexpensive replica exchange molecular dynamics (REMD) simulations to sample 120 structures which are subsequently minimized using more reliable quantum chemical methods. The presence of a beta-turn motif in the most stable structures is used to evaluate predictions of simpler models and establish structure-activity relationships.
Results: The most stable structures do indeed adopt a beta-turn motif both in gas phase and solution. The agreement between simple and rigorous methods for determining the structures of TVPN and TOVN suggests that the correlation between the presence of beta-turn conformation and antibreast cancer activity holds true for larger peptides.
Conclusions: Small AFPeps which demonstrated anticancer activity in mice adopted beta-turn configurations in our simulations. Even though the mechanism of action is not known, our findings do provide a clear structure-activity relationship which can lead to the design of a drug based on this pharmacophore.

Principal Investigators: Ryan Snyder and Jim Maneval

Title: Unused Prescriptions – Destination and Fate Modeling

Department and Institution: Chemical Engineering, Bucknell University

Co-investigators:

Background: Active Pharmaceutical Ingredients (APIs) are the components in drug products used to treat and prevent disease. While a fraction of these chemicals are used, consumed or transformed by the body, a significant amount of an API either remains untaken or is not processed in the body and is excreted. Hence untaken or unprocessed APIs eventually end up as pollutants to land and water, or find their way into the hands of unintended users.

Aims: We propose a mathematical modeling framework, based on the concept of material balances, to determine the range of final destinations of unused APIs. The model can be used by professionals to assess how changes in behavior or regulation can affect the final destinations of the API.

Methods: The model is cast as a network of interacting units (nodes). The flow of an API through this network is computed by setting split probabilities at each node and then computing the flow of an API that ends in one of the terminals of the network (land, air or water reservoirs).

Results: Work to date has focused on developing the logic of the network so that it properly accounts for the potential routes an API may take between delivery from a pharmacy to final resting place. Drug and drug-use profiles, along with activities such as drug-abuse prevention or take-back programs and destruction technologies are incorporated by altering flows and split probabilities in Monte-Carlo simulation studies.

Conclusions: The development of a coherent model for assessing the flow of API materials is important for establishing a logical framework for policy decisions on drug disposal and control. By having a way to assess the effect of a regulatory or behavior change, more reasonable and effective approaches to the control of unused drugs are possible.

Principal Investigator: Robert A. Stockland, Jr.

Title: New Methodology for the Synthesis of Pharmacologically Active Molecules

Department and Institution: Chemistry, Bucknell University
Co-investigators:
Background: The development of new methodology for the synthesis of small molecules with enhanced bioactivity remains a current and challenging goal for the chemical community. Despite the intense interest in this area, many valuable functional group transformations remain underutilized in the synthesis of pharmacologically active molecules due to a range of synthetic problems. Thus, circumventing these problematic steps through the clever use of catalysts and additives will facilitate the synthesis of new organic architectures with enhanced activity.
Aims: Develop novel methodology for the synthesis of new SERMs and related small molecules through the design of unique approaches to chemical reactions.
Methods: Microwave Accelerated Organic Synthesis, NMR spectroscopy, determination of the SERM activity, and X-ray crystallography.
Results: In recent years we have developed the first example of a base-free Hirao cross-coupling reaction, the first successful Ulmann-type cross-coupling reaction using tetrahydrofurfuryl alcohol, and the successful synthesis of novel gold-derived SERMs (agonists).
Conclusions: Our research lab has successfully developed new methodology for the preparation of a range of new compounds including an intriguing class of SERMs. Current research is focused on developing new approaches for the synthesis of potentiators of therapeutic ionizing radiation.

Principal Investigator: Ruth Tincoff

Title: Infants' comprehension of words for action events and role of motor experience

Department and Institution: Psychology, Bucknell University

Co-investigators: Emily Blum, Becky Boucher, Robyn Roogow

Background: Recent research suggests that changes in motor abilities may have important influences on language development (Iverson, 2010). New motor abilities provide new opportunities for infants to explore their physical world, to engage with social partners, and might prompt more talk about actions (Smith et al., 2007, Karasik et al. 2008; Reid et al., 2010)

Aims: We hypothesize that differences in word comprehension ability might be related to infants' experiences with different kinds of motor actions. If motor experience influences vocabulary development, then infants might show better comprehension for actions with which they have more experience.

Methods: We tested for comprehension of two types of action events in a split-screen preferential looking paradigm: seated posture with manual actions, e.g., eat, and upright posture with gross motor actions, e.g., jump. The subjects were seventy-four infants (8.5-20.5 months old) from rural small towns in Central Pennsylvania. We gathered parent reports of motor development (Ages and Stages), vocabulary (MacArthur Bates Communicative Development Inventory), and parents' use of the target words. The summary of the survey data is in progress. Infants were assigned to a Younger or Older subject group based on the Ages and Stages standard that independent walking is typically developed by 15 months of age. Then, infants were assigned to either the "seated-manual" action condition or the "upright-gross motor" action condition. Looking times were scored frame by frame from digital video recordings.

Results: Preliminary results show that only infants in the Older Group-Seated Actions showed evidence of looking longer at the video that matched the word being presented.

Conclusions: These results might indicate that comprehending action events is related to an infants' degree of motor experience. Alternatively, there might be task demands that interfered with the comprehension abilities for the infants in the other conditions.

Principal Investigator: Brandon M. Vogel

Title: Development of a Nanoparticle Platform for Targeted Controlled Drug Delivery

Department and Institution: Chemical Engineering, Bucknell University

Co-investigators: Alyssa Becker, Quinn Blanco, Adam Walsh, Doug Vogus and Zach Oberholtzer

Background: In 2008, the National Academy of Engineering established a series of engineering grand challenges for the 21st century categorized into the areas of Energy and Environment, Health, Security, and Learning and Computation. A grand challenge for healthcare is to engineer better medicines by improving patient compliance, reducing cost, improving safety, and targeting therapies to specific sites of the body. The use of nanoparticles as drug delivery systems for targeted drug delivery has appropriately garnered much attention over the past five years. Many of these systems are composed of degradable polymer nanoparticles with biological ligands that can target specific cell receptors, such as folic acid receptors. By using a degradable polymer, the nanoparticle can deliver its payload once it reaches the desired location. Targeting diseased cells and tissues can spare healthy tissue from receiving the therapy. However, the targeting concept relies on many assumptions: the nanoparticles have the correct biological ligands and stability, the nanoparticles will not be removed through the reticuloendothelial or immune system, the polymer physics and chemistry of the polymer erosion process are well understood and controlled, the therapy remains active and stable in the degradable polymer during storage and throughout release. While several targeted nanoparticle systems exist in the literature, many of these systems suffer from difficult and low yielding production methods, inefficient and tedious methods to couple the biological ligands to the surface of the nanoparticle.

Aims: The aim of this work is to develop a robust platform to produce multi-gram scale core-shell polymer nanoparticles capable of encapsulating and controllably releasing therapeutics, remaining stable *in vivo* and having simple coupling chemistry to enable decorating the surface of the nanoparticle shell with biological targeting ligands to target specific tissues.

Methods: We have developed a platform to continuously produce polymer nanoparticles in the size range of 200 to 300 nm in diameter using an impinging jet mixer. We use the mixer to generate a surfactant stabilized oil in water emulsion of polymer droplets in water. The polymer nanoparticles are isolated through centrifugation. In a second step, we can add inorganic shells to the polymer nanoparticles. During the shelling process we can control the surface chemistry of the shell to make the particles more stable in aqueous environments or biological fluids, and add targeting ligands.

Results: We will show the size and in some cases shape of the nanoparticles can be controlled by controlling the nature of the emulsion used to produce the polymer nanoparticles. The emulsion properties are dictated by knowledge of the water, solvent polymer phase behavior can be used to identify processing conditions to produce nanoparticles. Additionally, we will show that surfactant choice during processing of both the nanoparticle cores and shells has a large influence on the final particle morphology and stability. Finally, we show that we have

added shells to the polymer cores by selectively reacting a fluorescent dye onto the surface of our polymer core-shell nanoparticles and imagining the particles with a fluorescent microscope.
Conclusions: We have developed a scalable and robust core-shell nanoparticle platform for targeted delivery of therapeutics.

Principal Investigator: Sinisa Vukelic

Title: Novel Use of Raman Spectroscopy for Identification of Cancer Biomarkers

Department and Institution: Mechanical Engineering, Bucknell University
Background: This project describes the development of a new diagnostic tool for automated diagnosis of prostate cancer based on Raman spectroscopy. Prostate cancer is the most common cancer among American men and the second leading cause of cancer-related death. One out of six men is diagnosed with prostate cancer during their lifetime. Therefore this disease represents a significant burden on the society.
Aims: The proposed technology takes a radically different approach to the use of Raman spectroscopy through eliminating reliance on statistics. Current strategies in the field utilize statistical methods to analyze overly complex Raman signals without appreciating the underlying biology. The diagnostic method described here focuses on the molecular analysis of fatty acid synthase, an enzyme overexpressed in cancer cells, and increased RNA/DNA synthesis to distinguish between normal and malignant tissue.
Methods: Based on such molecular differences, Raman spectroscopy is used to produce a comparative molecular fingerprint of normal and malignant prostate tissue. Biologically relevant Raman bands representing significant diagnostic biomarkers are identified. A mathematical model that describes the Raman signals is developed. From the model quantitative changes in biomarker expression will be extracted and utilized as diagnostic and prognostic tools.
Results: Biologically relevant Raman bands representing significant diagnostic biomarkers are identified. A mathematical model that describes the Raman signals is developed. From the model quantitative changes in biomarker expression are extracted and utilized as diagnostic and prognostic tools. In the short term this technology has potential to transform the field of prostate cancer by reducing costs, while at the same time reducing patient anxiety due to the speed of the assay. In the medium term this assay could become a prognostic tool for distinguishing slow growing versus aggressive prostate cancers, which have significantly different treatment and prognostic outcomes.
Conclusions: The research efforts to produce an automated cancer diagnostic method have been very intensive in the past few years. The current efforts in the field mostly rely on statistical analysis of the Raman signal from the tissue or image processing and give approximately 20 to 30 percent false negative results, which is unacceptable for diagnosis. The premise behind the work proposed here is to unambiguously identify biomarkers that differentiate normal from malignant tissue based on its chemical composition. Looking beyond prostate cancer, the proposed technology has the potential to be expanded into a versatile and robust analytical platform able to deliver diagnoses for a broad range of cancers, and in the future this technology could monitor tissue responses to treatments such as small molecule drugs.

Principal Investigator: Amy Wolaver

Title: The Impact of Community Health Centers on Patient-Mix, Healthcare Use & Outcomes for AMI Patients

Department and Institution: Bucknell Institute for Public Policy, Bucknell University
Co-Investigators:
Background: The literature on community health centers (CHCs) shows that they reduce total health care costs and reduce hospitalizations for ambulatory care sensitive conditions. Less is known about the potential impact of CHCs on intensity of healthcare use for patients who are hospitalized.
Aims: To determine whether better access to primary care proxied by CHC access changes the average mortality risk of admitted patients, improves inpatient outcomes measured by mortality, and lowers intensity of healthcare use measured by length of stay and total charges for acute myocardial infarction (AMI) patients.
Methods: Using inpatient discharge data for Pennsylvania from 2009 multivariate regression analysis is used to examine the impact of number of CHCs per 10,000 persons in a zip code on in-hospital mortality, mortality risk at admission, length of stay and total charges for white and black patients with a primary diagnosis of AMI. Regressions include controls patient demographics and neighborhood characteristics.
Results: Better access to care from higher CHC access has no statistically significant estimated effect on inpatient mortality and patient risk-factors at admission for AMI patients. For each additional CHC per 10,000 persons in the zip code, the estimated length of stay for AMI patients drops by approximately 2% (relative to sample average of 4.8 days) and a drop of approximately $2600 in total charges.
Conclusions: Community health centers are associated with less intensive healthcare use for inpatient AMI patients, but do not seem to alter the patient-mix or mortality probability. The expansion of CHCs under healthcare reform has the potential to reduce overall healthcare spending.

Principal Investigator: Richard Zaccone

Title: A Mobile App for Gastric Bypass Surgery Patients

Department and Institution: Computer Science Department, Bucknell University

Co-investigators: Christopher Still, Craig Wood

Background: Patients who are considering gastric bypass surgery and patients who have had the surgery need to know how much weight loss they should expect. Doctors have not had tools that will help them with this task. Our software fills that gap.

Aims: We set out to develop an iPhone app that would help patients who are considering gastric bypass surgery and patients who have already had the surgery. Previously, explaining how much weight loss a patient should expect involved some guess work. Our app will give patients a clear idea of how much weight loss they can expect over the next several years.

Methods: We used a statistical model developed at Geisinger using information gathered from previous gastric bypass surgeries. The model takes into account the patient's age, height, weight and uses that information to compare the patient to others who have had the surgery.

Results: We produced an iPhone and iPad app that informs gastric bypass patients about how much weight loss they can expect. Patients enter their weight weekly and then email the results to their doctor. The doctor uses this information to monitor the patient's progress.

Conclusions: Christopher Still has been using the app with his patients at Geisinger. The patients find the app easy to use and they find the information it provides useful. Patients using online blogs have responded positively also.

BUCKNELL UNIVERSITY ABSTRACTS

Principal Investigator: James W. Baish

Title: Computational Models of Transport Processes in Clinical Processes

Department and Institution: Biomedical Engineering, Bucknell University

Background: Physical laws such as the conservation of mass, momentum and energy have long been known to govern all living and nonliving systems, but the complexity of living systems has generally limited our ability to make useful predictions. Recent advances in the speed and capability of computer models have opened new avenues of investigation. Computer models are rapidly becoming a third form of experimentation in the life sciences that complement the traditional in vivo and in vitro approaches.

Aims: We will demonstrate examples of computer models in several anatomical domains that elucidate processes that inform the planning and execution of clinical procedures. Specifically, we will show results from studies of urine flow in the partially obstructed ureter, freezing of tissue during cryoablation, movement of interstitial fluid in solid tumors and concentrations of a drug near an injection point.

Methods: The commercial package COMSOL® has been used to develop computer models of a variety of processes that involve the movement of fluids, heat or chemicals in the body. Based on the finite element method, COMSOL® offers a flexible modeling environment where objects of complex shapes can be created with computer-based drawing tools or by importing them from medical images.

Results: Our models predict physical variables such as pressure, flow rate, temperature, cooling and heating rates and concentrations. The real power of the models is achieved when the numerical models are used to perform parametric studies, i.e. numerical experiments that control all variables in the system except one that may be arbitrarily manipulated. Powerful graphical representations of the results with animations and 3-D graphics are possible.

Conclusions: Computer models can form a useful adjunct to clinical and bench top experiments providing insights that are not otherwise readily obtained.

Principal Investigator: Christine Buffinton Ph.D.

Title: Effect of Calcification Properties on Stress in Models of Atherosclerotic Plaque

Department and Institution: Department of Mechanical Engineering, Bucknell University

Co-investigators: Donna M. Ebenstein Ph.D.

Background: The main constituents of atherosclerotic material include fibrous tissue, fatty deposits, and thrombus. Calcifications often occur in more advanced lesions. The effect of calcifications on arterial wall stress have been largely ignored, in part because the material properties of the calcified areas were taken equal to fibrous plaque, and in part because they were assumed to have a stabilizing influence. Recent nanoindentation measurements suggest that their stiffness is actually similar to bone.

Aims: This work examined the sensitivity of wall stress in atherosclerotic models to the elastic modulus of calcified inclusions.

Methods: Arterial models containing normal arterial tissue, fibrous plaque, and macrocalcifications were created in the COMSOL multiphysics simulation software and assigned material properties from literature. The modulus of calcified plaque varied from 2.3 MPa to 10 GPa. Stress and strain for a lumen pressure of 18.7 kPa were calculated for 60 models: three variations in four geometric parameter groupings for five different calcified plaque moduli. Three geometries contained an arc-shaped calcification varying in distance from the lumen, arc length, and thickness; one contained a circular calcification of varying diameter.

Results: Stress at the junction of fibrous plaque and calcified plaque increased with increasing calcification modulus. In the arc-shaped calcification geometries, maximum von Mises (VM) stress occurred at the inner junction of fibrous plaque and calcification. Geometry was a large modifier of the stress. With a 10 GPa calcification modulus, the stress concentration increased from 3.5 to 16 as distance from lumen increased, and from 3.5 to 6 as arch length increased. Increasing calcification thickness had less effect, with stress concentrations of 3 to 4, and all increases in VM stress were small for circular geometries (maximum 1.4).

Conclusions: This study indicates the importance of obtaining accurate mechanical properties and geometries for models of atherosclerotic arteries and aneurysms. Macrocalcifications, instead of providing a stabilizing influence on the plaque, may predispose to rupture at the interface between fibrous plaque and calcified plaque. The interfacial properties between the calcified and non-calcified regions are particularly important and should be characterized in actual tissue samples.

Principal Investigator: Donna M. Ebenstein[1]

Title: Facilitating Nanoindentation Analysis of Compliant Biomaterials Using a Surfactant

Department and Institution: [1]Biomedical Engineering Department, [2]Chemical Engineering Department, Bucknell University

Co-investigators: Julie C. Kohn[2]

Background: Nanoindentation is often used for biomaterials characterization due to its ability to measure mechanical properties with microscale spatial resolution. One challenge when testing compliant, hydrated biomaterials is tip-sample adhesion, which leads to inaccurate modulus values when using traditional analysis methods. One method to extract accurate modulus values in the presence of adhesion is to analyze nanoindentation data using equations based on the Johnson-Kendall-Roberts (JKR) adhesion model. However, this analysis is not implemented in commercial software and is difficult to automate.

Aims: The primary goal of this project was to investigate the use of surfactants to eliminate adhesion and facilitate accurate modulus measurement in hydrated, compliant biomaterials using standard software analysis.

Methods: Polydimethyl siloxane (PDMS) elastomers and poly(ethelene glycol) (PEG) hydrogels with a range of modulus values were tested. The surfactant investigated in this study was Opti-Free Express contact lens solution (OFX). Two hydration conditions were tested for each sample: dry and OFX for PDMS and water and OFX for PEG. Nanoindentation data were analyzed using the standard software in the absence of adhesion and the JKR method in the presence of adhesion.

Results: Polymer samples tested in air exhibited high adhesion forces between the tip and the sample. Using OFX surfactant eliminated adhesion, allowing analysis of the data using the standard software. Adding OFX also facilitated surface detection in liquids, likely due to reducing the capillary forces on the indenter shaft. Moduli measured under different hydration conditions and using different analysis methods were consistent within 7% for both materials. Moduli of PEG hydrogels measured immediately after submersion in OFX and after 24 hours in OFX were not significantly different ($p<0.05$).

Conclusions: This study demonstrates that surfactants can be used to minimize adhesion when testing compliant samples without changing the properties of hydrogel samples, allowing reliable modulus measurement using the indenter software. In addition, the use of a surfactant facilitates surface detection and automated data collection processes.

Principal Investigator: Sinisa Vukelic

Title: Investigation of the Morphology of the Features Generated via Femtosecond Lasers in the Interior of a Bovine Cornea Sections

Department and Institution: Mechanical Engineering, Bucknell University

Co-investigators:

Background: Non-linear absorption, a unique property of the ultrafast laser, enables treatment of the interior of transparent dielectrics without affecting its outside surface. Proper use of optical and laser parameters provides control over different processing mechanisms, namely, confined microexplosion or thermal accumulation. Former has been utilized for keratomileusis flap formation during intraLASE LASIK surgeries and latter has potential for use in photorefractive keratectomy (PRK). Although already deployed in surgical practice, mechanisms of bubble formation in intraLASE procedures and void size prediction are not fully understood.

Aims: It is proposed to investigate feature morphology and laser-tissue interaction of cornea subject to femtosecond laser pulses for laser assisted corneal surgery. Two main aspects are to be considered, first understanding of the underlying physics behind of the bubble formation; second prospects of corneal thinning in a single-step process and thus eliminating the need for the flap formation and subsequent use of excimer lasers.

Methods: It is to be determined how to control formation of bubbles generated by femtosecond laser pulses. The relationship between laser and parameters determining delivery of the pulse onto the target material is not understood and yet it likely plays significant role in bubble formation. Further material removal rate is at the moment based on purely empirical evidence. Investigating such relationships will provide better insight to the underlying mechanisms and enable development of predictive capabilities for the proposed processes. Sections of the bovine cornea will be utilized to study cavity bubble formation and its properties. To enable this fundamental research, corneas form fresh bovine eyes will be sliced to 150 um thickness with microkeratomes. Influence of the numerical aperture (NA) and optical aberrations in beam delivery system in conjunction with varying laser pulse energy on size and shape of the voids will be studied at this stage. The experiments will be conducted using both the oscillator (low pulse energy and high repetition rate) and chirped amplified (high pulse energy and low repetition rate) systems with a number of objective lenses ranging from objectives with relatively low NA (~0.6) to the ones providing very tight focus (NA>1) objectives to generate voids. The experiments will take three stages: (a) laser focused in the interior of a bovine cornea section to investigate mechanism of a single cavity formation and interaction between adjacent cavities (Fig. XXa). The simplicity facilitates morphology, mechanical properties and structural investigation; (b) flap formation on a fresh bovine eye to study application of the findings in stage (a) as a simulation of surgical settings.

Results: Morphology of the femtosecond laser induced voids generated by the microexplosion mechanism is highly dependent on the characteristics of the beam delivery system. Size of the focal volume into which the laser energy is focused is a function of the numerical aperture (NA)

of an objective. The lower NA is responsible for generation of voids with high aspect ratio, but makes the focal volume looser and thus more difficult for the micro-explosions to occur. Thus higher pulse energies are needed for voids to form. This is usually the case in currently available systems. One the other hand NA above 1.0 provides tight focus and concentrates laser pulse energy into a small focal volume further enabling formation of nanoscale features using pulse energy in orders of nano-Jules. This mode is appealing due to considerably smaller affected region and very low pulse energies, which has potential to significantly reduce tissue necrosis after the procedure. Further, the hypothesis is in line with the previous studies, which correlate higher repetition rate with lower level of inflammation, as the oscillators have repetition rate in order of tens of MHz.

Conclusions: Preliminary studies have shown potential in controlling feature size and shape in transparent dielectrics subject to femtosecond laser pulses. However, the deep relationship between optical and laser parameters and its influence on the patient outcome is not well understood. The described study aims resolve this issue. It is known that that the focal volume is related to the numerical aperture of the focusing lens. However, how to link them to the feature morphology that is bubble geometry in flap formation is unclear and prediction capability needs to be developed.

GEISINGER HEALTH SYSTEM POSTERS

Principal Investigator: Glenn H. Bock, MD

Title: The Use of Large Clinical Dataset Analyses to Improve Prevention and Screening: The Case of Child-Onset Hypertension

Department and Institution: Pediatric Nephrology, Geisinger Health System

Co-investigators: Sam Kao MS, Nancy Ososkie RN, Joseph Leader BA, Barbara Leauber PA-C, Jonathan Bock BA, Ryan Colonie BS

Background: Electronic health records and data warehouses enable analyses of effectiveness and strength-of-evidence of clinical management paradigms. Despite evidence that childhood-onset hypertension (HTN) contributes to adult cardiovascular mortality, the condition is commonly unrecognized, leading to lost opportunities for primary prevention and timely intervention.

Aims: Evaluate BP screening and clinical management of HTN in children in Geisinger's primary care practices to determine:

- adherence to current BP screening guidelines
- accuracy and timeliness of HTN recognition and evaluation
- factors impacting (positively or negatively) on HTN identification
- opportunities to investigate treatment effectiveness and outcomes using electronic management paradigms.

Methods:

Subjects: Aged 3-17 years;Setting: Peds, Med-Peds, FP primary care office visits (OV)
Time: 2002-2010;Data Source: Geisinger data warehouse using SQL.;Data Set: • Provider specialty • Age, gender, BMI%ile • BP%ile
• Visit year • Lab and imaging tests • Subspecialty consultation
• HTN on Problem List (PL)
BP groups: • Normal • PreHTN • HTN
BMI groups: • Normal • Overweight (OW) • Obese (OB)
Earliest abnormal BP = HTN "onset age". Significance is $p < .01$ unless otherwise indicated.
Results: From 2002-2010 101,652 children had 264,869 routine OV. BP was recorded at 93% of OV. BP was significantly less likely with younger age, OV in earlier years, and both Med-Peds and FP compared to Peds. A BP group was determined in 67,455 pt (66%); HTN group 6,166 (9%). OB was more frequent in HTN (33.6%) vs controls (14.6%). OB prevalence was significantly lower at younger HTN "onset" age, and at no age was > 46%. HTN EHR PL entries were infrequent; <6% in Stage 2 HTN pts. PL entry was significantly associated with adherence to current guidelines for laboratory studies, imaging, and subspecialty consultation. A HTN PL entry was more likely in OB pts vs normal or OW and with increasing age (both $p<.001$).

Conclusions: Screening BP was frequent during routine OV but most HTN children were unrecognized. Despite infrequent HTN PL entry, its potential role in driving medical care warrants exploration. Older and OB HTN children were more frequently recognized; the youngest and less OB HTN patients may be at particular risk. An EHR-embedded algorithm will soon provide uniform and timely intervention for children with HTN. The resultant data also will allow critical analyses of current clinical guidelines.

Principal Investigator: Thomas D. Challman, MD

Title: The Childhood Routines Inventory in Children with Autism Spectrum Disorders

Department and Institution: Neurodevelopmental Pediatrics, Geisinger Health System

Co-investigators: DW Evans, SM Myers, S Lazar, PT Orr, A Moreno De Luca, DH Ledbetter

Background: The study of restricted, repetitive behavior (RRB) in autism spectrum disorders (ASD) has been largely neglected relative to the research on other features associated with ASD.

Aims: To examine the similarities and differences in RRB in children with neurodevelopmental disorders by exploring the factor structure of the Childhood Routines Inventory (CRI) and comparing the CRI factors across various clinical subgroups.

Methods: Over 1000 consecutive patients seen at a neurodevelopmental disorders clinic received the CRI by mail. Caregivers of three-hundred seventeen children completed the CRI. Children were classified into three diagnostic groups: those with ASD, those with intellectual disability or global developmental delay (ID/DD) but no ASD, and those with another neurodevelopmental disorder (ND) without ASD or ID/DD. We conducted a principal components analysis of the CRI.

Results: Consistent with earlier work with the CRI, Just Right and Repetitive Behaviors factors emerged. A third factor was also retrieved – Sensory Sensitivities, with the 3 factors accounting for a total of 58% of variance. ANOVAs compared the three clinical subgroups on each of the three CRI factors. Groups differed on all three weighted factor scores: Just Right ($F(2, 309)=4.56$, $p=.01$; Repetitive Behavior ($F(2, 309)=9.81$, $p< .0001$ and Sensory Sensitivities ($F(2,309)=10.02$, $p< .0001$. Post hoc tests revealed that the ASD group engaged in more Just Right, Repetitive Behavior and had more Sensory Sensitivities than both the ID/DD and ND groups.

Conclusions: Our findings suggest that the structure of the CRI varies depending on the clinical status of the population. In children with neurodevelopmental disorders, a third factor (Sensory Sensitivities) emerges that has not appeared in factor analysis with typical populations. The CRI, unlike other measures of RRB, results in a range of scores and distribution that facilitates the exploration of RRB in a variety of clinical populations.

Principal Investigator: F. Daniel (Dan) Davis, Ph.D.

Title: Bioethics, Geisinger, and Bucknell: Imagine the Possibilities

Department and Institution: Bioethics, Geisinger Health System
Co-investigators: Ideas and proposals from potential collaborators and co-investigators are sought and welcome.
Background: Bioethics is a multidisciplinary field encompassing both theoretical and empirical modes of inquiry. With the recruitment of a new bioethics director and the anticipated recruitment of additional core staff, Geisinger has launched a new initiative in the field.
Aims: The aims of the new initiative include advancing patient care through clinical ethics education and consultation, improving the ethical dimensions of quality care, and stimulating and carrying out research in empirical as well as theoretical bioethics. Examples of proposed projects include a study of parental attitudes toward genomic sequencing in newborns (using qualitative and quantitative methods) and a study investigating the outcomes of early, structured provider-family communication in advanced chronic illness (using quantitative methods).
Methods: Research in bioethics can be conducted through the use of any one or more of a wide range of methods, depending on the aims and hypotheses. Ethnographic methods, qualitative methods (including focus groups and interviews), quantitative surveys, conceptual analyses—all of these and more have been used to illuminate one or more of the amazing diversity of questions with which bioethics is concerned. Bucknell faculty working in a range of disciplines—from philosophy and history to sociology, psychology, and economics—are encouraged to imagine the possibilities for fruitful collaborations in bioethics with Geisinger.
Results: The results should be scholarship that contributes to one or more goals, including improving the quality of patient care; identifying and understanding patient or familial attitudes toward participation in research or health care; enhancing provider-patient communication; and advancing bioethics education for the public as well as for physicians, nurses, and biomedical scientists.
Conclusions: If you have an idea or proposal for research in bioethics, please contact Dan Davis, Ph.D., director of Bioethics, Geisinger Health System, Weis Center for Research, 100 North Academy Avenue, Danville, PA, 17822, (570) 214-7340 or ddavis1@geisinger.edu.

Principal Investigator: William DiFilippo, MD; Thomas Scott, DO

Title: Symplicity HTN-2: Europe, Australia, and New Zealand

Department and Institution: Nephrology. Geisinger Health System
Co-investigators: William DiFilippo, MD; Susan Kilbride, MS; Jeffrey Ruhl, MS
Background: Renal sympathetic nerve activation plays an important role in the pathogenesis of essential hypertension(HTN). Selective ablation of the sympathetic nerves through the renal arteries can substantially reduce blood pressure(BP) in patients for resistant HTN. The duration of antihypertensive effect and long-term safety of renal denervation (RDN) requires further follow up.
Aims: To demonstrate that catheter-based RDN is a safe and effective treatment for resistant HTN.
Methods: Subjects who meet all criteria after the screening period will undergo a renal artery angiogram to evaluate renal artery anatomy. Only subjects with eligible renal artery anatomy will be randomized. Eligible subjects will be randomized at a 1:1 ratio to a treatment or control group.
Results: Analysis of the data at 6, 12, and 18 months post procedure demonstrated a reduction of mean systolicBP(SBP) and diastolic BP(DBP). (P-value <0.01)6M: -28mmHg SBP, -10mmHg DBP 12M: -26mmHg SBP, -10mmHg DBP 18M: -31mmHg SBP, -12mmHG DBP Renal function measures were unchanged post procedure. (P-value <0.01) 6M: eGFR (mL/min/1.73m²) -1.61 ± 12.14 12M: eGFR (mL/min/1.73m²) -2.78 ± 11.95 No further data collected Pulse pressure and heart rate also decreased significantly. (P-value <0.01) Pulse Pressure(mmHg) 6M: -18.0 ± 18.5 12M: -16.4 ± 19.6 18M: -18.9 ± 20.7 Heart Rate(BPM) 6M: -3.9 ± 11.8 12M: -5.6 ± 10.8 18M: -3.8 ± 11.9
Conclusions: RDN appears to safely and effectively reduce BP in subjects with treatment resistant HTN. There were no significant changes in renal function measurements through 12 months of follow up.There was a significant decrease in systolic/diastolic pressures, pulse pressure, and heart rate following treatment with the Symplicity renal denervation system. Symplicity HTN-3 is actively enrolling patients throughout North America

Principal Investigators: Priyantha Devapriya, PhD; Ronald Dravenstott

Title: An Inpatient Bed Demand Prediction Tool for Surgical Smoothing – A Monte Carlo Simulation

Department and Institution: Innovation Analytics and Operations Research, Geisinger Health System

Co-investigators: David Franklin, MD, Ruth Nolan, Priyantha Devapriya, PhD

Background: The inpatient bed demand for elective surgeries is significant and predictable. For a health system with high inpatient bed occupancy, bed planning and staff planning are critical to maintain smooth operations. Currently a daily bed huddle, along with other interactions, allows hospital staff to identify potential bed crunches. High-census situations are identified by estimating discharges and arrivals and determining if there is a problem. These days are typically identified the morning of, or the day prior to, a high-census situation.

Aims: To develop a decision support tool to predict the future surgical and medical inpatient bed demand to determine if a high-census situation exists in the near future. To predict the number of occupied beds, and issue a warning to suggest taking measures to mitigate the impact of a potential high census situation.

Methods: A Monte Carlo Simulation model was developed to forecast the 14-day bed demand. Empirical probability distributions were constructed for inpatient length of stay and patient flow between care levels based on the previous 6 months of GMC EHR data. The model is connected to the GMC EHR to feed the current state information including Emergency Department midnight holds, PACU midnight holds, recent medical and surgical inpatient arrivals, and inpatient census.

Results: During a 52-day test period the model correctly predicted the occupancy level 60% (31 of 52) of the time and predicted the high-census days 60% (3 of 5) of the time. A false warning was issued 6% (3 of 52) of the time. The tool is currently used by GMC surgical scheduling staff.

Conclusions: The Monte Carlo Simulation model successfully predicted future bed demand. The purpose of the tool is to identify future high-census situations, and those were predicted during the test period. By using the decision support tool, hospital staff could be notified of 60% of the high-census situations encountered during the test period.

Principal Investigator: Porat Erlich, PhD, MPH

Title: Personalized Regimens in Surveillance Endoscopy (PRSuE)

Department and Institution: Center for Health Research, Geisinger Health System
Co-investigators: Michael Komar, MD; Kimberley Fairley, DO; Jinhong Li, MD.
Background: Colonic polyps detected on screening examination are a strong risk factor for future cancer. Individuals with such findings require follow-up consisting of sequential colonoscopies known as post-polypectomy surveillance. Current practice guidelines recommend stratifying surveillance intensity according to individual risk, predicted from baseline risk factor variables. Acceptance of personalized surveillance as per guidelines by healthcare systems is limited due to safety concerns, conflated with technical barriers.
Aims: The overarching aim of this study is to assess safety and effectiveness and facilitate implementation of the stratification guidelines.
Methods: Subjects were included if they had a minimum record length of one year between 01/01/2003 and 03/31/2011, were seen at least once by a GHS primary care provider within that period, were 50 years old or older and were asymptomatic for CRC and without prior colonoscopies or colonic findings on the date of cohort entry. Data were retrieved from GHS's data warehouse. Colonoscopy indication was ascertained from operative notes. Multivariate logistic regression was used to estimate the relative odds of developing colorectal malignancy as a function of previous colonic findings adjusting for background variables.
Results: The cohort included 110,452 primary care patients with a mean record length of 5.2 years excluding look-back. There were 23,995 prevention colonoscopies performed on cohort subjects including 15,528 (65%) screening and 8472 (35%) surveillance colonoscopies. The percentage of surveillance colonoscopies from among prevention colonoscopies increased by 90% from 26.5% in 2004 (888 of 3357) to 50.3% in 2010 (1755 of 3489). The resection yield for colorectal malignancy in surveillance colonoscopy was 1.1%, 2.3-fold higher than the comparable yield in screening colonoscopy. Subjects with benign findings at screening had 6.8-fold higher odds for developing colorectal malignancies compared to subjects without such findings, adjusting for age, sex, BMI and family history of cancer.
Conclusions: Surveillance is necessary for risk mitigation in patients with a history of previous colonic findings. To control a secular increase in surveillance work, the intensity of surveillance may be personalized based on risk as per guidelines, however, further research will be needed to assess the safety and effectiveness of this practice and facilitate its implementation

Principal Investigator: Jove Graham, PhD

Title: Decreasing long term complications following hip fracture using a Medical Home concept

Department and Institution: Geisinger Center for Health Research; Department of Orthopaedics, Geisinger Health System

Co-investigators: Thomas R. Bowen, MD; Kent A. Strohecker, MS: Kaan Irgit, MD; Wade R. Smith, MD

Background: Hip fracture (HF) patients experience high morbidity/mortality in the first postoperative year after hospital discharge. Post-discharge care management using a Patient-Centered Medical Home (MH) model attempts to reduce such complications by using nurse care managers to coordinate the transition from hospital to home and subsequent care.

Aims: This study compared 6 and 12 month outcomes between two prospective cohorts of HF patients, with and without post-discharge MH management.

Methods: A prospective, matched cohort of patients (n=194) surgically treated for HF from 2010-2011 at two hospitals, half of whom received MH care, was studied. Patients were not randomized but received MH only if their primary physician's office was participating in the program. MH patients were matched (1:1) to patients who did not receive MH, on the basis of surgery date (±90 days), sex, age, major comorbidities, prior hospitalizations and ED visits. Mortality rates, hospitalizations, ED visits, and prescriptions per patient were compared between the two cohorts at 6 and 12 months. Patients surviving at 12 months completed a quality-of-life (EQ-5D) and pain/function questionnaire (Harris Hip Score) via telephone. Statistical analysis was performed using log-rank survival analysis and Poisson regression (expressed as odds ratios, OR) with $p<0.05$ considered significant.

Results: At 6 months post-operatively, patients receiving MH post-discharge management had a significantly lower mortality rate than patients receiving standard care (11 vs. 26% respectively, $p<0.01$). At 12 months, a difference persisted (23 vs. 30%, $p=0.12$) but was no longer statistically significant. All-cause hospitalizations, ED visits and prescription orders per patient were similar at 6 months ($p=0.69$-0.91) and 12 months ($p=0.16$-0.83). Similarly, the mean EQ-5D QOL scores were similar between the two groups (0.73 vs. 0.77, $p=0.38$), and the MH patients had a slightly improved mean HHS pain/function score (70.4 vs. 67.4) but were not statistically significantly different ($p=0.47$).

Conclusions: Our study demonstrates the addition of post-discharge primary care from a MH program was successful in significantly reducing mortality in the 6 months following HF. It is important to note that the main benefits were seen in the first six months, so there may be an optimal, short-term period during which MH care should be focused.

Principal Investigators: Brian Irving, PhD, George Argyropolous

Title: AgRP Deficient Female Mice have Elevated Body Weight and Hypothalamic Mitochondrial Oxidative Capacity

Department and Institution: Obesity Institute and Weis Center of Research, Geisinger Health System

Co-investigators: Steve Roesch, Crystal Kane, Amanda Styer

Background: The central orexigenic agouti-related protein (AgRP) increases food intake when ubiquitously over expressed. Unexpectedly, AgRP deficiency also produces elevated food intake in female, but not male AgRP (-/-) mice. Moreover, the female AgRP (-/-) tend to be heavier than their wild type (WT) littermates.

Aims: To determine whether differences in mitochondrial respiratory capacity and control couldcontribute to the propensity of the female AgRP (-/-) mice to gain more weight compared to their WT littermates.

Methods: High-resolution respirometry was utilized to perform multiple substrate-inhibitor titration (SUIT) protocol designed to assess mitochondrial respiratory capacity and control in (mechanically and/or chemically) permeabilized hypothalamus, liver, skeletal muscle, and white adipose tissue acquired from 180 d old female AgRP (-/-) mice and their WT littermates. Results: Female AgRP(-/-) mice had higher state-3 respiration (63+2 vs 47+3 pmol/s/mg, p=0.036) and higher maximally uncoupled respiration (66+3 vs 53+4 pmol/s/mg, p=0.045) than their WT littermates. However, there were no significant differences between groups for the respiratory control ratios in the hypothalamus. There were no significant differences between groups for the O2 fluxes or respiratory control ratios in the liver, white adipose tissue, or gastrocnemius muscle.

Conclusions: Similar to the present results, obese Zucker rats were reported to have enhanced mitochondrial oxidative capacity in the hypothalamus. In conclusion, AgRP deficiency in female mice results in elevations in hypothalamic mitochondrial oxidative capacity, likely contributing to their increased food intake and body weight.

Principal Investigator: David J. Kolessar, MD
Title: Geriatric Hip Fracture Program (GHFP)

Department and Institution: Dept of Orthopaedics, Geisinger Health System
Co-investigators: Anthony J. Balsamo, MD; Michele Gingo, BS, RN; Robert Emery, PA-C; Alex Piczon, PA-C; Walter Koss, PA-C; Steven Milewski, PA-C
Background: Geriatric hip fractures (HF) pose a significant public health concern. In the United States, the population 65 years and older is the fastest growing segment of society. This group is at the highest risk for osteoporosis and HF. Coordinated efforts between orthopaedic surgeons and geriatricians have produced better outcomes as well as cost savings.
Aims: Compare patient outcomes with and without a coordinated care effort in the treatment of acute HF.
Methods: A 24-month consecutive period compared patient outcomes with and without a coordinated care effort in the treatment of acute HF's at a single institution. Interdisciplinary team members collaborated to develop evidence based and consensus protocols to standardize the care of geriatric HF patients. Standardized admission, preoperative and postoperative order sets were created and installed into the electronic medical record. Study population consisted of patients 65 years and older with an acute HF treated surgically over 24 consecutive months. The control group consisted of HF treated operatively during the 12 month period (08/01/2009 to 07/31/2010) just preceding the implementation of the GHFP. Primary metrics evaluated included the Geometric 'Actual' mean length of stay (LOS), 30-day readmission rate, and discharge disposition. The Geometric 'Actual' LOS is used by the Centers for Medicare and Medicaid (CMS) to calculate LOS, charges and cost.
Results: The Geometric 'Actual' mean LOS demonstrated a 14% improvement with the control group at 5.1 days vs. the GHFP group at 4.4 days. The reduction in readmission rate was remarkable. A 28% reduction in readmission rate (13.3% to 9.5%) comparing the two groups before and after implementation of the GHFP was demonstrated. Discharge disposition patterns changed. Specifically, the percentage of patients discharged to an acute inpatient rehabilitation facility increased from 28.3% to 47.6% (19.3% increase), with the expectation of going home following their acute rehabilitation. This reallocation of patients resulted from a reduction of transfers to skilled nursing facilities (59.2% control group vs. 39.7% GHFP group).
Conclusions: Geriatric Hip Fracture Programs offer patients more efficient care without loss of quality. An interdisciplinary team approach may help prevent future fragility fractures and many of the iatrogenic sequelae associated with immobility. Coordinated programs are needed to handle the anticipated increase in fragility fractures, in a quality, cost containing manner. Implementing a standardized interdisciplinary team approach to geriatric HF improved the ability to meet or exceed some commonly used healthcare quality measures. Improvements in LOS and readmission rate had an actual savings of 156 hospital bed days in one year. Discharge disposition reallocated patients from skilled nursing care facilities to acute inpatient rehabilitation centers with the expectation of patients returning to their home environment. The increasing aging demographic will consume a larger proportion of healthcare resources treating osteoporotic fractures in the coming years. The ability to deliver cost-effective, quality healthcare will be critical to the future economic viability of healthcare systems.

Principal Investigators: Gerard Tromp, Helena Kuivaniemi and David J. Carey for the Geisinger eGenomic Medicine (GeM) Project

Title: Merging Genomic Data for Research in the Electronic Medical Records and Genomics Network Lessons learned in eMERGE

Department and Institution: The Sigfried and Janet Weis Center for Research, Geisinger Health System

Co-investigators: Marylyn D. Ritchie, Shefali Setia, Gretta Armstrong, Loren Armstrong, Yuki Bradford,Dana C. Crawford, David R. Crosslin, Mariza de Andrade, Kim Doheny, M. Geoff Hayes, Gail P. Jarvik,Iftikhar Kullo, Rongling Li, Cathy A. McCarty, Daniel Mirel, Lana Olson, Shaun Purcell, Elizabeth Pugh, V.Lotay, Omri Gottesman, Jonathan L. Haines

Background: Biobanks linked to electronic health records (EHR) is an emerging area of research fordissecting the architecture of complex traits. Electronic phenotyping algorithms are deployed in largeEHR systems to "ascertain" samples for analysis. The eMERGE network, an NHGRI funded initiative,consists of nine sites, each with DNA databanks linked to EHRs.

Aims: The aims were to develop a pipeline for merging data from different genotyping arrays based on imputation to maximize sample size and power.

Methods: Over 42,000 samples were genotyped using one of the available Affymetrix or Illumina genome-wide genotyping arrays. These data were imputed using BEAGLE and October, 2011 release of 1000 Genomes cosmopolitan reference panel.

Results: Because of the computational complexity, a distributed imputation pipeline was implemented. In this scheme, the genome was divided by SNPs into 30,000 marker "SNPlets" with 700 markers of overlap on each side, resulting in 510 SNPlets. This parallelized pipeline resulted in over 556 billion SNPs (more than 13 million per individual) based on hundreds of thousands of CPU hours.

Conclusions: The dataset generated consists of genome-wide SNPs on thousands of individuals all linked to EHR systems where numerous phenotypes can be explored. The lessons learned by this group of investigators will be valuable for the genomics community also dealing with the combining of largescale genomic datasets.

Principal Investigator: Fan Lin MD, PhD

Title: The Evaluation of Hepatocyte Nuclear Factors 1B (HNF-1B) Expression for Potential Application in Tumor Diagnosis

Department and Institution: Laboratory Medicine and Pathology, Geisinger Health System

Co-investigators: Meng Xianmin MD, PhD; Haiyan Liu MD, PhD

Background: HNF-1B, a transcription factor, is normally expressed in liver, kidney and gastrointestinal tract. Studies reported 82% of ovarian clear cell carcinoma (CCCA) and 100% of bladder and urethral CCCA express HNF-1B. However, the expression of HNF-1B in other tumors has not been well documented.

Aims: In the current study, we immunohistochemically investigated the expression of HNF-1B in a large series of carcinomas (CA) from various organs, to explore the potential utility of HNF-1B in tumor diagnosis.

Methods: A total 1120 cases of CA from 14 different organs were selected, and constructed for tissue microarray (TMA) blocks. Immunohistochemical evaluation of HNF-1B (Sigma, Lot No. HPA2083) expression using a single immunostaining system (Ventana) was performed on the TMA sections. The staining pattern was recorded as negative (<5% of tumor cells stained), 1+ (5-25%), 2+ (26-50%), 3+ (51- 75%), or 4+ (>75%).

Results: Majority of the thyroid CA (95%, 80 of 84 cases) and prostatic adenocarcinoma (ADC) (97%, 94 of 97 cases) were negative for HNF-1B. In contrast, 94% (51 of 54 cases) of lung ADC, 91% (106 of 117 cases) of renal carcinoma (RCC), and 88% (38 of 43 cases) of urothelial CA expressed HNF-1B. In endometrial ADC, the expression of HNF-1B decreased with higher tumor; grade while the reverse was true for breast CA.

Conclusions: Our data suggest the potential diagnostic utility of HNF-1B in differentiating thyroid CA from lung ADC when working on a TTF-1 positive tumor. It may be diagnostically useful in the interpretation of small biopsies to differentiate prostatic ADC from renal or bladder CA. These data highlight the diagnostic utility of CA IX in 1) differentiating CRCC from other renal tumors, such as chromophobe RCC and oncocytoma; 2) distinguishing low grade CRCC from normal renal tubules, which can be challenging in small tissue biopsies or fine needle aspirations; 3) separating cholangiocarcinoma from HCC, which may have treatment implications; and 4) identifying metastatic CRCC from other metastases such as seminoma, prostate adenocarcinoma, papillary and follicular thyroid carcinomas, and breast carcinoma. In conclusion, cellular specimens with adequate cell block material are more likely to generate definitive diagnosis and IHC stains are helpful in confirming the presence of malignant lesions. Likewise, familiarity with evaluating biliary brush cytology and improved endoscopic brushings are also key factors. This new approach will help improve diagnostic sensitivity, and ultimately the accuracy in evaluating biliary brush cytology.

Principal Investigator: Tooraj Mirshahi,PhD

Title: Role of MC4R and Its Variants in Weight Loss After Roux-en-Y Gastric Bypass Surgery

Department and Institution: 1Weis Center for Research, Geisinger Health System and 2Department of Internal Medicine, The University of Texas Southwestern Medical Center

Co-investigators: U. L. Mirshahi, Ph.D.1, J. F. Zechner, B.S.2, C. H. Still, D.O.1, V. Aguirre, M.D., Ph.D.2

Background: Factors that influence long-term weight loss after Roux-en-Y gastric bypass surgery (RYGB) are poorly defined. The melanocortin 4 receptor (MC4R) plays important roles in regulating energy homeostasis, satiety and glucose metabolism.

Aims: Rare variants of the *MC4R* comprise the most prevalent monogenetic obesity disorder, while two common *MC4R* alleles, *I251L* and *V103I,* are negatively associated with obesity. We examined the role of *MC4R* variants in long-term weight loss after RYGB in a cohort of 1433 extremely obese patients during a 48-month period before and after surgery.

Methods:

Results: We found 80 patients with rare and common variants of *MC4R* in the RYGB cohort. Amongthese, 26 patients carry the *I251L* variant, 36 patients carry the *V103I* variant, and 18 patients carry rarevariants. Overall, *I251L* allele carriers lost 9% more weight (~9 kg) compared to the non-carriers,continued rapid weight loss longer, regained less weight, and had lower pre-surgery HOMA-IR values.Weight loss was not different among patients having the *V103I* allele, any rare variant, or the referenceallele. We also examined the effectiveness of RYGB on weight loss in diet induced obese mice (DIO)compared to weight matched *Mc4r(-/-)* and *Mc4r(+/-)* mice. Remarkably, *Mc4r(-/-)* mice failed to lose significant weight after surgery compared to sham operated littermates. However, DIO mice and *Mc4r(+/-)* mice had similar weight loss after surgery.

Conclusions: The human and mouse data support the notion that MC4R is *necessary* for weight loss after surgery, while a single copy is *sufficient*. Finally, carrying a copy of the *I251L* allele improves weight loss outcomes.

Principal Investigator: Anne Moon, MD PhD

Title: Models of Congenital Heart Disease for Clinical and Translational Research

Department and Institution: Weis Center for Research, Geisinger Health System

Co-investigators: Randall Prather PhD, National Swine Resource and Research Center, University of Missouri

Background:
More than 2% of infants are born with congenital heart defects (CHDs) resulting in mortality greater than all pediatric cancers combined. To provide effective genetic testing, preventative strategies, and better treatment, we must understand the fundamental mechanisms of heart development and how they are affected by environmental and genetic factors.
Survival of children with CHDs has become possible by the efforts of pioneering physicians and scientists. Pediatric cardiothoracic surgeons and related subspecialists undergo extensive training however this is currently accomplished by apprenticeship on human patients. These patients are infants with complex CHDs of very small hearts, delicate physiology, and multiple organ system dysfunction. We hypothesize that present limitations in training and drug testing cause higher morbidity and mortality than would occur if accurate animal models of CHD were used for training and developing new drugs and devices specifically for these patients.

Aims:
1) Determine how altered Fibroblast Growth Factor (FGF) signaling causes lethal CHDs.
2) Determine how mutations in TBX3 cause ulnar-mammary syndrome, CHDs and arrhythmias in humans.
3) Develop anatomically and physiologically correct models of CHD.

Methods:
We study gene-targeted mice with altered FGF8 and Tbx3 gene function in specific cells of the developing embryo. We are developing both teratogenic and genetic models of CHD in swine which closely replicate human anatomy and physiology.

Results:
We are discovering the precise cellular and molecular events that depend on FGF8 and Tbx3 function at different times and locations in the embryo during heart development. We have found that FGF8 is absolutely required for development of the outflow tract of the heart. Tbx3 is not only required for formation and function of the heart's electrical conduction system, but for normal cardiac function in adults. We are collaborating with the National Swine Resource and Research Center to create swine CHD models.

Conclusions:
Information garnered through basic scientific investigation is driving the development of better CHD models to improve physician training and drug and device development without risking health of vulnerable human CHD patients.

Principal Investigator: Janet Robishaw, PhD

Title: What do congenital heart defects and statins have in common?

Department and Institution: Weis Center for Research, Geisinger Health System
Co-investigators: Anne Moon, MD
Background: Statins are considered Category X teratogenic drugs. As these drugs are increasingly prescribed orinadvertently used by women of child-bearing age, there have been conflicting reports regarding theincidence of head/heart defects in their offspring. In addition to inhibiting cholesterol synthesis, statins block post-translational modifications of the G-protein γ subunits that regulate numerous biological processes. In *Drosophila*, statin treatment produces cardiac defects that can be phenocopied by genetic ablation of the G-protein γ subunit in flies. Whether a related G-protein γ subunit is required for normal cardiogenesis in mammals is not clear.
Aims: The overall goal was to assess the functional consequences of genetic ablation of *Gng5* encoding the Gprotein γ5 subtype in mice.
Methods: A mouse model was created and extensively analyzed from the developmental to the molecular level.
Results: Homozygous disruption of *Gng5* produces severe cardiac defects that are incompatible with survival.Although mutant embryos have an overtly normal linear heart tube at embryonic day (e)8.5, subsequent looping of the heart tube and formation of the outflow tract are notably absent in mutants by e9.5. Since this phenotype is associated with a reduced number of cardiac progenitors, the results point to a likely role for the G-protein γ5 protein in maintaining the proliferative capacity of this cell population that provides the additional cells needed for formation of the outflow tract.
Conclusions: Identifying a novel player involved in the formation of the outflow tract will be important for preventing congenital heart disorders that will only come from a better understanding of the mechanism(s) underlying the normal process. In on-going studies, we will determine whether this cardiac defect can be recapitulated in mice treated with statins. If validated, these findings will help inform the decision to prescribe statins to women of child-bearing age. There were no significant changes in renal function measurements through 12 months of follow up. There was a significant decrease in systolic/diastolic pressures, pulse pressure, and heart rate following treatment with the Symplicity renal denervation system. Symplicity HTN-3 is actively enrolling patients throughout North America.

Principal Investigator: Brian Schwartz, MD, MS

Title: Crop field exposure and the risk of methicillin resistant *Staphylococcus aureus* (MRSA) infection in Pennsylvania, USA

Department and Institution: Johns Hopkins Bloomberg School of Public Health, Center for Health Research, Geisinger Health System
Co-investigators: Joan Casey, MA, Frank C. Curriero, PhD, MA, Walter F. Stewart, PhD, MPH
Background: Over the past decade in the United States, the incidence of community-associated methicillin-resistant *Staphylococcus aureus* (CA-MRSA) infection has increased and its epidemiology has changed. Recently, contact with livestock and agriculture have been identified as risk factors for MRSA colonization. Few studies exist that examine the association between agricultural exposure and MRSA infection in humans.
Aims: To first estimate individual-level exposure to pig and dairy/veal manure-applied crop fields and then to use a case-control analysis to estimate risk of MRSA infection in groups with differing levels of exposure.
Methods: To investigate this association we used electronic health record data on over 400,000 primary care patients of the Geisinger Health System, which provides primary care services from 41 community practice clinics and 4 hospitals in over 31 counties in northeastern Pennsylvania, an area with many concentrated animal feeding operations (CAFOs) and concentrated animal operations (CAOs). In Pennsylvania the state oversees permitting of both CAFOs and CAOs in the form of nutrient management plans (NMPs). NMPs detail information about the farm including location, the number and type of animal, manure produced on site, as well as quantity, season and destination (at the township-level) of exported manure. Exported manure is generally spread on crop fields, which represents a potential source of exposure to MRSA bacteria for members of nearby communities. Geographic information systems (GIS) were used to create three exposure metrics of manure application to crop fields (manure CAFOs and CAOs).
Results: We identified 1,713 CA, 1,521 healthcare-associated (HA) MRSA cases and 3,336 frequency-matched controls from 2005 to 2010. The fourth quartile of each crop field manure exposure metric was positively associated with CA-MRSA (OR = 1.2 [1.0–1.5]; 1.3 [1.1–1.6]; 1.2 [1.0–1.4], respectively); there was evidence of a stronger association in townships (OR = 1.5 [1.1 – 1.8]).
Conclusions: Crop field manure exposure may be a risk factor for CA-MRSA. decreased risk (OR=0.97), as was type 2 diabetes (OR=0.45), and myelogenous neoplasms (OR=0.66). The diagnosis of benign neoplasms was significantly inversely associated with AAA (OR=0.59), which is a novel finding. Systolic blood pressure (OR=1.03), cerebrovascular disease (OR=1.32), kidney disease (OR=1.40), peripheral artery disease (OR=3.56), pulmonary disease (OR=1.42) and coronary stenosis (OR=2.14) were all significantly associated with an increased isk of AAA.

Conclusions: This study demonstrated that Geisinger EMR data can be used to assess risk factors and identify new associations. The regression coefficients from these analyses will be incorporated into future genomic analysis to identify variants associated with AAA risk. These findings could serve to enhance the current AAA screening guidelines to more efficiently target patients and increase screening utilization.

Principal Investigator: Azadeh Stark, PhD

Title: Using the Electronic Health Record and the National Cancer Institute's Breast Cancer Risk Assessment Macro to Identify Women at Increased Risk for Breast Cancer

Department and Institution: 1)Clinical Innovation, Geisinger Health System, Danville, PA
2)Center for Health Research, Geisinger Health System, Danville, PA
3)Cancer Service Line, Geisinger Health System, Danville, PA

Co-investigators: Amanda Bengier, BS1, Jonathan Darer, MD1, Azadeh Stark, PhD2, Victor G. Vogel, MD2

Background/Aims: Women at increased risk for breast cancer (BC) are eligible to take selective estrogen receptor modulators (SERMs) to reduce their risk; Food and Drug Administration (FDA) approval of tamoxifen or raloxifene for BC risk reduction and American Society of Clinical Oncology guidelines for the use of SERMs recommend the two drugs for any woman over the age of 35 years with a 5-year risk of 1.67% or greater but identifying those women can be challenging. The National Cancer Institute (NCI) has developed an open source Breast Cancer Risk Assessment Macro (BrCa RAM) that can be run using SAS software. By leveraging Geisinger Health System (GHS) Electronic Health Record (EpicCare), the Department of Radiology's software (RIS-IC), and Pathology's software (CoPath) we were able to calculate 5-year and lifetime risk of developing invasive BC.

Methods: BrCa RAM calculates risk based on patient age, number of biopsies, did a biopsy ever display atypical hyperplasia (Yes/No), age at menarche, age at first live birth, number of first degree relatives with breast cancer, and patient race. We were able to extract and format these elements from EpicCare, RIS-IC, and CoPath. Demographic information was obtained from EpicCare, pathology information from the CoPath, and personal history from RIS-IC.

Results: We found 91,692 women between the ages of 35-90 in the RIS-IC database who have ever received a screening mammogram. We identified 9,021 patients with a calculated 5-year breast cancer risk 2 and the mean age was 59.7 years. The number of patients by 5-year risk score category were: 2-2.5% (n=3,551); 2.5%-3% (n= 1,946); 3%+ (n=3,524).

Conclusions: The BrCa RAM is a powerful tool that enabled GHS to calculate breast cancer risk for our entire population. Using this macro we were able to identify patients for prophylactic SERM treatment which can potentially prevent or delay a woman's risk of developing BC.

Principal Investigator: **Steven R. Steinhubl, MD**

Title: Prevalence of Framingham Heart Failure (HF) Signs and Symptoms in a Primary Care Population One Year Prior to the Diagnosis of HF and Matched Controls Identified by Text Mining Longitudinal Electronic Health Records (EHR)

Department and Institution: Center for Health Research and Division of Cardiology, Geisinger Health Systemand the TJ Watson Research Center, IBM

Co-investigators: Rajakrishnan Vijayakrishnan, MD, Roy J. Byrd, PhD (ABD), Jimeng Sun,PhD, Brent Williams,PhD, Zahra Daar,MS, Shahram Ebadollahi, PhD, Walter F. Stewart, PhD, MPH

Background: HF is a complex syndrome with multiple pathophysiological manifestations that frequently overlap those of other diseases, making early diagnosis challenging. Tools that allow for the automated detection of patients in the early stages of HF would allow for preventive actions.

Aims: We sought to study a text mining algorithm constructed with specific grammars for automatically extracting Framingham HF criteria from physician notes.

Methods: We extracted complete EHR data from 6355 incident HF patients and 26,052 group matched controls from Geisinger Clinic primary care practices. Incident cases occurred between 2003-2010. Text mining software was validated for detection of positive and negative affirmation of Framingham HF major and minor diagnostic criteria. The software was then applied to all EHR text files (e.g., progress notes) on cases in the year before HF diagnosis and a comparable index date for controls.

Results: Major criteria for HF were identified in 52.43% of cases and 24.59% of controls. Minor criteria were identified in 88.39% and 49.69%, respectively. There was substantial variability in the prevalence of the individual criteria in cases and controls. Rales, dyspnea on exertion and ankle edema were documented most commonly in HF cases, but were also common in the control population.

Conclusions: Sophisticated text mining techniques allow for the early identification of HF signs and symptoms prior to formal diagnosis although overlap exists with control patients. Refinement of diagnostic criteria through text mining techniques to identify clustering of positive and negative affirmations of current criteria plus the development of novel HF criteria that reflect modern practice may improve discrimination.

Principal Investigator: Nikos Tapinos

Title: Lymphoid cell kinase (Lck) is a crucial early mediator of Schwann cell migration, sorting, and myelination

Department and Institution: Molecular Neuroscience Lab, Weis Center for Research, Geisinger Health System
Co-investigators: Jennifer Ness-Myers
Background: Myelination in the peripheral nervous system requires complex signaling events between Schwann cells (SCs), axons, and the basal lamina. The signaling pathways involved in the myelination in the peripheral nervous system are not fully understood. Lymphoid cell kinase (Lck), a non-receptor tyrosine kinase Src family member, regulates proliferation in M. leprae-infected Schwann cells through a PKC /Lck dependent signaling pathway.
Aims: We investigated the effect of Lck in laminin-induced signaling in SCs and its role in migration, lamellipodia formation, and myelination in the PNS.
Methods: LCK KO mice, SC monocultures, SC/DRG co-cultures and Lck-specific inhibitors were used to identify Lck actions through protein interaction analysis, identification of signaling pathway activation, migration assays, and electron microscopy.
Results: Phosphorylation of the Lck active site can be detected after 10 min of laminin treatment of rat SCs and in SCs seeded on a laminin substrate for 4 hours. Downregulation of beta1-integrin with siRNA inhibits laminin-induced activation of Lck in SCs. Small molecule inhibitors of Lck significantly inhibit paxillin phosphorylation and Rac-GTP levels in SC monocultures on laminin and in RSC-DRG co-cultures. Inhibition of LCK significantly reduces the number and rate of radial lamellipodia formation by SCs plated on a laminin substrate. In vitro myelin studies of RSC-DRG co-cultures treated with LCK inhibitors and analysis of DRG explants from normal and LCK KO mice show a reduction in myelin formation and internode length. Schwann cell migration on axons is decreased by Lck inhibitors and in LCK KO Schwann cells. LCK KO mice show a delay in myelination and defects in nonmyelinating SCs and also exhibit a delay in demyelination following sciatic nerve axotomy.
Conclusions: These data suggest that Lck is a critical component of laminin signaling in Schwann cells and affects migration, sorting, and myelination of the peripheral nervous system.

Principal Investigator: Marc S. Williams, MD

Title: Cost-Effectiveness of Interleukin 28B Genotype-Guided Protease Inhibitor Therapy in Treatment-Naïve Patients with Hepatitis C Virus Genotypes 2 or 3

Department and Institution: Weis Center for Research, Department of Gastroenterology, and the Center for Health Research; Geisinger Health System

Co-investigators: Jonathan A. Bock, BA; Kimberly J. Fairley, MS, DO; Robert E. Smith, MD; Daniel D. Maeng, PhD; James M. Pitcavage, MSPH; Nicholas A. Inverso, MD

Background: The addition of protease inhibitors to standard of care (SOC) dramatically increases treatment response in Hepatitis C Virus (HCV) genotype 1 patients. Moreover, Interleukin 28B (IL28B) genotyping helps predict responsiveness for these patients. However, the economic implications of incorporating IL28B genotyping in HCV genotype 2/3 infected patients are unknown.

Aims: This study used a treatment algorithm that included IL28B genotype-guided therapy to examine the short and long-term cost-effectiveness of utilizing these single-nucleotide polymorphisms in treatment-naïve HCV genotype 2/3 infected patients.

Methods: A treatment algorithm was constructed to reflect a therapy regimen for treatment-naïve patients with HCV genotype 2/3 infection using pegylated-interferon, ribavirin, and telaprevir. To examine the role of the IL28B gene in affecting costs and health outcomes, a decision tree was derived from the treatment algorithm in order to populate a predictive cost model for therapy using our treatment algorithm.

Results: Expected short-term costs of therapy following our algorithm were $21,648.92 and $47,972.84 for the CC and TT genotypes at rs12979860, respectively, and $47,972.84 and $21,648.92 for patients with the CT genotype at rs12979860 and the TG/GG and TT genotypes at rs8099917, respectively. Predicted costs among patients undergoing SOC therapy were $20,758.92. Sustained virologic response (SVR) rates for genotypes 2/3 were predicted to occur in 82.2% (8,220 of 10,000) of patients overall—88.83% (8,883 of 10,000) and 65.91% (6,591 of 10,000) for the CC and TT genotypes at rs12979860 and 81.01% (8,101 of 10,000) overall for patients with the CT genotype at rs12979860 [72.08% (7,208 of 10,000) and 86.78% (8,678 of 10,000) for the TG/GG and TT genotypes at rs8099917]. Markov modeling predicted a 27.29 quality-adjusted life-expectancy (QALE) after following our treatment algorithm while adding $7,766.51 in long-term costs. The model predicted only a 26.65 QALE after SOC therapy (while adding $9,599.05 in long-term costs).

Conclusions: Although short-term treatment costs of an IL28B genotype-guided approach exceed those of SOC for treatment-naïve HCV genotype 2/3 infected patients, Markov modeling suggests that lower long-term costs and improved health outcomes may be achieved by the proposed algorithm and provides a dominant cost-effective strategy for treating this population of HCV infected patients.

Principal Investigator: Kenneth Wood, MD

Title: Inpatient flow Analysis of Geisinger Medical Center

Department and Institution: Innovation Analytics & Operations Research, Geisinger Health System
Co-investigators: Dr. Matt Bailey, Christopher Stromblad, Dr. Priya Devapriya, Dr. John Bulger
Background: Inpatient flow is an issue of national significance. The excess demand for inpatient beds is intensified by a mismatch between the time of day patients are discharged and the time a bed is required for admission. The IHI has been promoting a flow management approach called RTDC that seeks to develop a daily plan to expedite the discharge of specific number of patients to meet that day's bed demand.
Aims: A detailed discrete event simulation model will be developed to evaluate several operational and patient care metrics to guide system changes and improvements. Areas of study include: evaluating bed capacity and budgeting impacts; quantifying the relationship between discharge improvement and overall flow metrics; quantifying the impact of reducing length of stay; and analytically test the IHI's hypothesis that discharging even a small number of patients earlier will have a disproportionate impact on system flow metrics.
Methods: The model relies upon a thorough analysis of patient flow and the complex process of patient placement. To generate empirical probability distributions and non-homogeneous Poisson arrival processes within the model required an extensive amount of data analysis. We required distributions for source-dependent length of stays for all care levels, inpatient flows in all directions, and daily discharge. Results: • Decision support was provided to add 30 rooms at GMC to minimize admission wait times and to align with strategic opportunity. • Low impact of early discharge initiatives was proved and the project was abandoned. • The model assisted the budgeting process • The first academic paper is being finalized for submission to a peer reviewed journal
Conclusions: The model was successfully populated with GMC EHR and provided decision support to evaluate the impact of discharge improvement initiatives, quantify the optimal bed mix, and evaluate bed capacity investment decisions. The model is being generalized to GWV and will be used to evaluate various inpatient flow healthcare policy issues in the future.

Principal Investigator: Xiaowei Yan, PhD

Title: Polymorphisms in Chronic Inflammation Mediated Pathway Genes Associated with Risk of Postmenopausal Breast Cancer (PMBC)

Department and Institution: Center for Health Research, Geisinger Health System

Co-investigators: Azadeh Stark, Xin Chu, Ryane Colonie, Jessica Webster, Ling Li, Jeffery Prichard, Victor Vogel and James Evans (Geisinger Health System)
Jill Barnholtz-Sloan, Case-Western Reserve University

Background: PMBC most likely arises from combinations of less penetrant SNPs of common genes in combination with environmental and lifestyle risk factors. Adiposity at 21.3% has the largest population attributable risk (PAR) for PMBC of all other factors. Studies suggest that SNPs in the FTO gene and other genes, i.e. estrogen receptor (ERS1), prostaglandinendoperoxide synthase 2 (COX-2), ghrelin-obestatin ligand for growth hormone secretagouge receptor (GHRL), growth hormone secretagouge receptor (GHSR), interleukine 6 (IL6), mitogenactivated protein kinase (MAP3K1), may increase risk of PMBC.

Aims: To report on the association between the complex of SNPs of genes and the risk of postmenopausal breast cancer.

Methods: Cases and control matched by age and date of blood donation were identified from the MyCode cohort. Demographic, pathology and clinical data were retrieved. The SNP genotyping was performed on a Life Technologies TaqMan OpenArray Genotyping System and analyzed using the Life Technologies TaqMan Genotyper Software. Each SNP was tested individually adjusting for known breast cancer risk factors. Multiple-SNP nonepistatic analysis was performed to fit multiple SNPs simultaneously with adjustment for other common clinical factors.

Results: Cases (N=159) and controls (N=829) had a mean age of 65 years (± 9) and 64 years (± 9), respectively. A higher proportion of cases (26.5%) were diagnosed with metabolic syndrome (p=0.0003) and had reported family history of breast cancer (p=0.001). Risk of PMBC increased for homozygotes for the A allele of rs689470 (PTGS2 gene)(OR= 3.38; 95% CI=1.09-10.51, p=0.03), and the minor allele C of rs889312 (MAP3K1gene) (OR=1.98; 95% CI=1.08-3.63, p=0.03); while, we observed lower risk for homozygotes for the G allele of rs2383529 (OR= 0.32; 95% CI=0.11-0.92, p=0.03), C alleles of rs3020314 (ESR1 gene) (OR= 0.51; 95% CI=0.26-0.98; p=0.04) and A allele of rs7801617 (IL6 gene) (OR=0.13; 95% CI=0.03-0.55, p= 0.006).

Conclusions: Our preliminary findings concur with previous reports suggesting SNPs of 2 genes, MAP3K1 and PTGS2 are associated with the risk of PMBC independent other factors. MAP3K1 gene acts in the MAPK-signaling pathway and is responsible for regulation of transcription of estrogen receptor; while, PTGS2 is an inflammatory mediator that up-regulates aromatase expression and subsequently local synthesis of estrogen in the breast.

GEISINGER HEALTH SYSTEM ABSTRACTS

Principal Investigator: Thomas R. Bowen, MD

Title: Outcome of Hemiarthroplasty in Stable (AO/OTA 31B1) Femoral Neck Fractures

Department and Institution: Department of Orthopaedics, Geisinger Health System
Co-investigators: Kaan Irgit, MD; Raveesh Richard, MD; Andrew Cornelius, MD; Cassondra Andreychik; Daniel S. Horwitz, MD
Background: Treatment of femoral neck fracture varies according to the fracture patterns and patient's age. Although most orthopaedic surgeons are in favor of internal fixation for the management of nondisplaced femoral neck fractures, some surgeons believe reconstruction rather than fixation of these fractures in the elderly population leads to weight bearing and results in less mortality. Significant morbidity/mortality rates after femoral neck fractures have been documented, it is important for an orthopaedic surgeon to know which technique has lower mortality and complication rates.
Aims: To evaluate the mortality, reoperation and complication rate after surgical treatment of nondisplaced femoral neck fractures.
Methods: We retrospectively compared the complication and reoperation rates between two groups which matched in age, gender, BMI and ASA scores. Followup was a minimum of 24 months and all patients were at minimum 60 years old. The primary outcomes were complications of surgery and the need for revision surgery. Secondary outcome was the cost of the primary surgery.
Results: The mean age of the 98 patients in the osteosynthesis group was 82 (range,60-104) and 80(range,60-90) in the 38 patients treated with hemiarthroplasty. Mean follow up was 44 ± 1.4 (range,24- 92 months). Overall complication and reoperation rates were similar in both groups, however infection was significantly higher in the hemiarthroplasty group. Mortality rates 1 year after the surgery were significantly higher in the osteosynthesis group. Intraoperative blood loss and length of stay were significantly lower in the osteosynthesis group. The hemiarthroplasty group had a much higher cost compared with the osteosynthesis group.
Conclusions: Hemiarthroplasty has no benefit in decreasing complications and reoperations for stable femoral neck fractures in the elderly. The cost of surgery and infection rates are higher with hemiarthroplasty as compared to osteosynthesis for these stable fracture patterns.

Principal Investigator: **Matthew Butler, MD**

Title: **Renal Dysfunction in Ovarian Cancer**

Department and Institution: Center for Health Research, Department of Internal Medicine, Division of Medicine, Gesinger Health System
Department of Medicine, NYU Langone Medical Center

Co-investigators: Azadeh Stark, PhD, Rhadika Gogoi, MD, H. Lester Kirchner PhD, Joseph B. Leader BA, and Franco M Muggia, MD

Background:
Epithelial ovarian cancer (EOC) is the 5th leading cause of cancer death among women. Over the past two-decades, the overall survival of women diagnosed with EOC has improved because of earlier diagnosis, improvement in surgical intervention and systemic and intra-peritoneal chemotherapy. Research has been focused on the therapeutic potential of agents that inhibits of DNA repair by targeting the base-excision repair pathway mediated by poly ribose polymerase (e.g. PARP). The potential clinical impact of PARP inhibitors can be significant in terms of improving survival. However, PARP inhibitors have considerable side effects, i.e. compromised renal function, which can have significant impact on quality of life and curtail the opportunity of participating in clinical trials and to benefit from neo-adjuvant therapies.

Aims:
1. To estimate the rate of compromised renal function among EOC patient
2. To compare this rate adjusted for dose, duration and the composition of chemotherapeutic cocktail and other confounding factors.

Methods:
We have assembled a historical cohort of women diagnosed with EOC, 1/1/2000 and 12/31/2011, using the electronic medical records. Demographic, clinical, surgical and chemotherapeutic data will be extracted. We will employ time-dependent longitudinal statistical techniques.

Results:
Contribution of each patient will be evaluated in terms of person-year, because of the time dependency of renal function. Effects of chemotherapy on the renal function, the end point, will be measured and will be compared.

Conclusions:
Findings from this pilot project will permit us to develop a larger, multi-center, research to evaluate the potential utility of serum-based biomarkers for renal function in EOC patients, before administration of chemotherapy. Ultimately, we would like to identify women who are at a greater risk for renal compromise and therefore, minimize the potential harm of chemotherapeutic agents through administration of the most effective and yet least toxic cocktail.

Principal Investigator: Gerard J. Cush, MD

Title: Calcaneal Fixation: Extensile Lateral vs. Sinus Tarsi Approach – Early Outcome Evaluation

Department and Institution: Department of Orthopaedics, Geisinger Medical Center

Co-Investigators: Kaan Irgit, MD; Blake E. Moore, MD; Steven Lillmars, DO; James C. Widmaier, MD

Background:
Operative treatment of calcaneus fractures can be challenging due to the cancellous bone matrix, the thin soft tissue envelope, and high rate of postoperative infection. The extensile lateral (ELA) incision is the most commonly used approach for the operative treatment of displaced intraarticular calcaneus fractures (DIACF). Wound healing is a major concern with the ELA.

Aims:
Compare radiographic outcomes and wound healing complications with sinus tarsi approach (LSTI) and ELA in Sanders type 2 and 3 DIACFs.

Methods:
We retrospectively reviewed the electronic medical records of 60 patients (64 DIACFs) with Sanders type 2 and 3 DIACFs treated operatively either with LSTI or ELA to evaluate the complications and radiographic outcomes. Fractures treated non-operatively, Sanders type 4, tongue type, and open fractures, patients < 18 years of age, previous calcaneal injury and having less than 12 month follow up were excluded. Radiographic outcomes were assessed by measuring angles of Gissane and Bohler and calcaneal height on preoperative and postoperative x-rays.

Results:
Each group had 32 fractures. Groups were matched in female to male ratio, age, BMI, injury mechanism, fracture classification distribution, average time between injury to surgery, and graft utilization. The operation time in minutes was 139.0±12.7 and 82.2±4.8 and the mean hospital length of stay in days was 2.11± 1.12 (range, 1-6) and 1.35±0.12 (range, 1-3), respectively in the ELA and LTSI groups. Twelve fractures in the ELA group developed wound complications (37.5%). The LTSI group had no wound complications. There was only one (3.1%) re-operation in the LSTI group, whereas in the ELA group 9 patients (28.1%) had reoperations. A significant radiographic correction in Bohler's angle, Gissane angle and calcaneus height was achieved with both approaches.

Conclusion:
LSTI can satisfactorily reduce and fix Sanders type 2 and 3 intraarticular fractures with significant low wound healing problems. Further prospective comparative studies are necessary to determine long term functional outcome and progression of subtalar arthrosis. treatment with the Symplicity renal denervation system. Symplicity HTN-3 is actively enrolling patients throughout North America.

Principal Investigator: **Ronald Dravenstott ; Priyantha Devapriya, PhD**
Title: **Improving ED Patient Flow at Geisinger Wyoming Valley Using Discrete Event Simulation**

Department and Institution: Clinical Innovations – Operations Research, Geisinger Health System
Co-investigators: Priyantha Devapriya, PhD, Ronald Strony, MD et al
Background: The GWV ED is a level 2 trauma center serving high volumes of patients seeking emergent care. Currently the GWV ED is facing capacity constraints and undesirable Door to Doc times. Discrete event simulation has been applied to numerous industries to identify bottlenecks and predict performance of a system based on running what-if scenarios. This technique has recently been applied to the healthcare industry and EDs.
Aims: • To test the impact of future flow-related performance improvement projects before implementation in the actual ED. • To predict how the ED wait times and bed utilization will react to varying conditions including changes in population acuity and ED volume • To create a framework for other ED models.
Methods: A Discrete-Event simulation model was developed. The layout of the model was based on AutoCAD drawings of the ED, ensuring accurate walking distances and paths. Empirical probability distributions were created using data from the GWV EHR for patient arrivals, treatment times, and ED departure destinations. The model was centered on patient flow through the system and utilization of resources.
Results: The model has been verified and validated for FY 2011 and FY 2012. The arrivals to the model match the actual arrivals to the GWV ED. The time that the patients spend in a bed in the model match the time in the GWV ED.
Conclusions: Modeling an Emergency Department is a complex undertaking. Though extensive data exists in the EHR, more data is required for a detailed staff resource analysis. Because of this discrepancy, the focus of this model has been on patient flow and bed utilization rather than staff utilization. A scenario investigating the boarding time, the amount of time a patient remains in an ED bed after being admitted to the hospital, as a bottleneck is pending. excluding look-back. There were 23,995 prevention colonoscopies performed on cohort subjects including 15,528 (65%) screening and 8472 (35%) surveillance colonoscopies. The percentage of surveillance colonoscopies from among prevention colonoscopies increased by 90% from 26.5% in 2004 (888 of 3357) to 50.3% in 2010 (1755 of 3489). The resection yield for colorectal malignancy in surveillance colonoscopy was 1.1%, 2.3-fold higher than the comparable yield in screening colonoscopy. Subjects with benign findings at screening had 6.8-fold higher odds for developing colorectal malignancies compared to subjects without such findings, adjusting for age, sex, BMI and family history of cancer.

Conclusions: Surveillance is necessary for risk mitigation in patients with a history of previous colonic findings. To control a secular increase in surveillance work, the intensity of surveillance may be personalized based on risk as per guidelines, however, further research will be needed to assess the safety and effectiveness of this practice and facilitate its implementation.

Principal Investigator: Daniel Feldmann, MD

Title: Single vs. Two-Tunnel Technique During Open Treatment of Acromioclavicular (AC) Joint Disruption

Department and Institution: Department of Orthopaedics, Geisinger Health System
Co-investigators: Jove Graham, PhD; Glen Feltham, MD; Kent Strohecker, MS
Background: Coracoclavicular (CC) ligament reconstruction with semitendinosus tendon (ST) grafts has become more popular and has achieved relatively good results; however optimal reconstruction technique, single-tunnel or two-tunnel, still remains controversial.
Aims: To compare the clinical and radiographic data of allogenous ST grafting with single- or two-tunnel reconstruction techniques of the AC Joint.
Methods: The outcomes of 21 consecutive patients who underwent anatomical reduction and ST grafting for AC joint separation were reviewed retrospectively. Patients were divided into two groups: single-tunnel group (n=11) and two-tunnel group (n=10). All patients were evaluated clinically and radiographically using a modified UCLA rating scale.
Results: The majority of the separations (18 of 21) were Rockwood type V, with one each in type III, IV and VI categories. The overall mean follow-up time was 16 months, and at the time of the latest follow-up, the overall mean UCLA rating score was 14.1 (range 8-20). The percentage of good-to-excellent outcomes was significantly higher for patients with the two tunnel technique than for those with the one-tunnel technique (70% vs. 18%, respectively, p=0.03). Within the single-tunnel group, there was no statistically significant difference in percentage of good-to-excellent outcomes between patients with vs. without tightrope augmentation (17% vs. 20%, p>0.99). Similarly, within the two-tunnel group, there was no significant difference in the percentage of good-to-excellent outcomes between the graft only and augment groups (67% vs. 75%, p>0.99).
Conclusions: Anatomical reduction of the AC joint and reconstruction CC ligaments are crucial for optimal joint stability and function. Two-tunnel CC reconstruction with an allogenous ST graft provides statistically significantly better radiographic and clinical results compared to the single-tunnel reconstruction technique. Additionally, tight-rope augmentation does not appear to provide improved clinical or radiographic outcomes, to handle the anticipated increase in fragility fractures, in a quality, cost containing manner. Implementing a standardized interdisciplinary team approach to geriatric HF improved the ability to meet or exceed some commonly used healthcare quality measures. Improvements in LOS and readmission rate had an actual savings of 156 hospital bed days in one year. Discharge disposition reallocated patients from skilled nursing care facilities to acute inpatient rehabilitation centers with the expectation of patients returning to their home environment. The increasing aging demographic will consume a larger proportion of healthcare resources treating osteoporotic fractures in the coming years. The ability to deliver cost-effective, quality healthcare will be critical to the future economic viability of healthcare systems.

Principal Investigators: Gerard Tromp and Helena Kuivaniemi

Title: MicroRNA Expression Signature in Human Abdominal Aortic Aneurysms

Department and Institution: The Sigfried and Janet Weis Center for Research, Geisinger Health System

Co-investigators: Matthew C Pahl, Kimberly Derr, James R Elmore, Charles M Schworer, Irene Hinterseher, David P Franklin, John L Gray, David J Carey

Background: Abdominal Aortic Aneurysm (AAA) is a disorder with a growing significance in developed countries due to aging demographics and undetermined biological mechanisms. miRNAs are small noncoding RNAs that generally act as post-transcriptional regulators of gene expression. Recently they have been implicated in several cardiovascular disorders and may provide a mechanism for the differential expression of genes identified in previous genomic studies of AAA.

Aims: We investigated the possibility that microRNAs (miRNA) play a role in human AAA. Methods: To determine differences in miRNA levels between AAA (n = 5) and control (n = 5) infrarenal aortic tissues, a microarray study was carried out. Results were adjusted using Benjamini-Hochberg correction (adjusted $p < 0.05$). Real-time quantitative RT-PCR (qRT-PCR) assays with an independent set of 36 AAA and seven control tissues were used for validation. Potential gene targets were retrieved from miRNA target prediction databases Pictar, TargetScan, and MiRTarget2. Networks from the target gene set were generated and examined using the network analysis programs, CytoScape® and Ingenuity Pathway Core Analysis®.

Results: A microarray study identified eight miRNAs with significantly different expression levels between AAA and controls (adjusted $p < 0.05$). Real-time qRT-PCR assays validated the findings for five of the eight miRNAs. A total of 222 predicted miRNA target genes known to be differentially expressed in AAA based on a prior mRNA microarray study were identified. Bioinformatic analyses revealed that several target genes are involved in apoptosis and activation of T cells.

Conclusions: A genome-wide approach revealed several differentially expressed microRNAs in human AAA tissue suggesting that miRNAs play a role in AAA pathogenesis. Analysis of the predicted miRNA targets revealed several genes involved in the apoptosis of smooth muscle cells.

Principal Investigator: Haiyan Liu MD, PhD

Title: Analysis of the atypia of undetermined significance/follicular lesion of undetermined significant (AUS/FLUS) category – experience from 1,366 thyroid fine needle aspiration biopsy (FNA) cases

Department and Institution: Laboratory Medicine and Pathology, Geisinger Health System

Co-investigators: Xianmin Meng MD, PhD; Fan Lin MD, PhD

Background: The Bethesda System for Reporting Thyroid Cytopathology (BSRTC) introduced the AUS/FLUS category in 2007. Limited studies reported follow-up of this category based on repeat FNA or surgical resections.

Aims: In the current study, we retrospectively reviewed a large series of consecutive cases of thyroid FNA to identify AUS/FLUS cases with available follow-up thyroidectomies, generating a follow-up data for this new category and its clinical significance.

Methods: One-hundred-eleven cases of AUS/FLUS were identified from 1,366 consecutive cases ofthyroid FNA at GMC since 2010 (when BSRTC was implemented). Fifty-three of 111 cases had follow-upthyroidectomy, and were further subcategorized into 1) atypical follicular cells with papillary carcinomafeatures (AFC-PTC); 2) follicular (includes Hürthle cell) lesions (FL); and 3) atypia, not otherwise specified (Atyp. NOS). The follow-up surgical diagnoses were analyzed.

Results: Among the 111(8.1%, 111 of 1366) AUS/FLUS cases, 53 cases had follow-up thyroidectomy. The FNA and surgical correlation of those 53 cases is evaluated. Thirty-five of 53 (66%) cases were benign, including nodular goiter (NG) (26%, 14 of 53), thyroiditis (25%, 13 of 53), and follicular adenoma (FA) (15%, 8 of 53). Eighteen of 53 (34%) cases were malignant, mainly PTC (78%, 14 of 18), including 2 incidental papillary microcarcinomas.

Conclusions: Our data are compatible with the reported literature using the BSRTC system on thyroid FNA, with a lower rate in non-diagnostic and suspicious categories. Correct diagnosis of thyroiditis, which usually shows lymphoid cells and focal nuclear atypia, will further reduce the rate of AUS/FLUS and unnecessary thyroidectomies.

Principal Investigator: Haiyan Liu

Title: Immunohistochemical Evaluation of Carbonic Anhydrase IX (CA IX) Expression in Tumors and Normal Tissues

Department and Institution: Department of Pathology, Geisinger Health System
Co-investigators: Adelina Luong-Player and Fan Lin
Background: Carbonic anhydrase IX (CA IX) is a membrane isoenzyme and regulator of cellular homeostasis and proliferation, and ultimately tumor progression. Studies have shown that it is often overexpressed in clear cell renal cell carcinoma (CRCC), with a reported diagnostic sensitivity of 85-100%. However, the data on its reactivity to other tissue types and tumors are inconsistent due to differences in antibodies, staining conditions, and staining platforms.
Aims: In this study, we examined the diagnostic utility of CA IX in various types of tumors and nonneoplastic tissues using Ventana staining system.
Methods: Immunohistochemical (IHC) evaluation of the expression of CA IX (Cell Marque, mouse monoclonal antibody, clone MRQ-54) was performed on a total of 1,238 cases of carcinomas (1,167) and normal tissues (71) from various organs on tissue microarray (TMA) sections and 18 cholangiocarcinomas on routine sections. The staining intensity (scale of 1 to 4, in increasing order) and distribution were recorded.
Results: Immunostaining results showed overexpression of CA IX in 90% (36/40) of low grade CRCC and 86% (32/37) of high grade CRCC. In addition, 90% (26/29) of cholangiocarcinomas were positive with diffuse staining (3+ or 4+) in 70% of cases. In contrast, only 3 of 17 (18%) of HCC were focally (1+) and weakly positive. No staining or focal weak staining was seen in ChRCC, oncocytomas, seminomas, breast CA, thyroid CA, and prostate CA. Amongst the normal tissue counterparts, all normal renal tubules (N=20) showed no staining except one case with focal weak staining.
Conclusions: These data highlight the diagnostic utility of CA IX in 1) differentiating CRCC from other renal tumors, such as chromophobe RCC and oncocytoma; 2) distinguishing low grade CRCC from normal renal tubules, which can be challenging in small tissue biopsies or fine needle aspirations; 3) separating cholangiocarcinoma from HCC, which may have treatment implications; and 4) identifying metastatic CRCC from other metastases such as seminoma, prostate adenocarcinoma, papillary and follicular thyroid carcinomas, and breast carcinoma

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Principal Investigator: Haiyan Liu

Title: Parameters Impacting the Diagnostic Sensitivity of Biliary Brush Cytology

Department and Institution: Departments of Pathology and Gastroenterology, Geisinger Health System

Co-investigators: Adelina Luong-Player, David Diehl, Fan Lin

Background: Adequate evaluation of biliary brush cytology is extremely important in the screening of pancreaticobiliary malignancies. Although biliary brushing is a standard screening method used in many institutions, the diagnostic sensitivity has been low nationwide, with an estimate of 30%. Specimens diagnosed as "Suspicious" or "Malignant" are more helpful for clinicians and provide better guidance for patient management compared to those diagnosed as "Atypical."

Aims: This study examines factors that affect the diagnostic sensitivity of biliary brush cytology.

Methods: Biliary duct brushings (N=536) from 2003 to mid 2012 were reviewed. Cases were classified according to four diagnostic categories: "Benign", "Atypical", "Suspicious", and "Malignant." Each diagnostic category was then compared to corresponding biopsy or resection specimens, if available, for correlation. The degree of cellularity, availability of cell block material, and usage of immunohistochemical (IHC) stains was also assessed.

Results: When compared to surgical specimens with tissue-proven malignancy, an average of 35% (8/23) of biliary brushings from 2003-2006 were diagnosed as "Suspicious" or "Malignant" in contrast to 47% (29/62) between 2007 and mid 2012. In general, the availability of diagnostic cell block material has increased over the years and suboptimal specimens have shown an overall decline with time. There is also an increasing trend in the use of immunohistochemical (IHC) stains; most were contributory to the final diagnosis.

Conclusions: In conclusion, cellular specimens with adequate cell block material are more likely to generate definitive diagnosis and IHC stains are helpful in confirming the presence of malignant lesions. Likewise, familiarity with evaluating biliary brush cytology and improved endoscopic brushings are also key factors. This new approach will help improve diagnostic sensitivity, and ultimately the accuracy in evaluating biliary brush cytology.

Principal Investigator: Tooraj Mirshahi, PhD

Title: A Conserved Mechanism for Gating in Ionotropic Glutamate Receptors

Department and Institution: Weis Center for Research, Geisinger Health System
Co-investigators: Bryn S,. Moore, Uyenlinh Mirshahi, Tonya L. Ebersole
Background: Opening of ionotropic glutamate receptor (iGluR) channels controls excitatory neurotransmission that is critical to central nervous system function.
Aims: The crystallographic structure of GluA2, the prototypical iGluR, reveals a receptor channel with a clamshell-like ligand-binding domain (LBD) that closes in the presence of glutamate2. Closure of the LBD opens a channel gate on the pore lining α-helix3. How this LBD closure leads to gate opening remains unclear.
Methods: **Results:** We show that a pivoted bending mechanism in the most conserved region of the channel pore is responsible for gating. We found that a highly conserved pore facing alanine at position 621, two turns of the helix below the gate, serves as a pivot. Substituting A621 to the smaller more flexible glycine resulted in a non-desensitizing channel with significant agonist-independent basal activity and ~ 36-fold increase in glutamate potency without changes in expression or binding. In addition, the partial agonist kainate acted as a full agonist and the antagonist CNQX acted as a partial agonist on GluA2(A621G). In contrast, introducing flexibility by a glycine substitution above the channel gate reduced activity and glutamate potency.
Conclusions: Closure of the LBD opens the channel by pulling apart the pore helix around a pivot at a small amino acid below the gate. Our data show a common mechanism for gating among glutamate receptors and potassium channels and suggest that an evolutionarily conserved mechanism may control gating in otherwise distinct ion channels. found that FGF8 is absolutely required for development of the outflow tract of the heart. Tbx3 is not only required for formation and function of the heart's electrical conduction system, but for normal cardiac function in adults. We are collaborating with the National Swine Resource and Research Center to create swine CHD models. **Conclusions:** Information garnered through basic scientific investigation is driving the development of better CHD models to improve physician training and drug and device development without risking health of vulnerable human CHD patients.

Principal Investigator: **Scott M. Myers**

Title: **Incomplete penetrance versus variable expressivity in del 16p11.2: analysis of cognitive performance and social functioning as quantitative rather than dichotomous measures**

Department and Institution: Neurodevelopmental Pediatrics, Geisinger Health System

Co-investigators: A Moreno-De-Luca, TD Challman, DW Evans, PT Orr, RP Goin-Kochel, E Hanson, R Bernier, L Green Snyder, JE Spiro, WK Chung, JN Constantino, DH Ledbetter.

Background: The recurrent ~600 kb 16p11.2 deletion is a common pathogenic copy number variant (CNV) among individuals with neurodevelopmental disorders. Initially identified in patients with autism and/or intellectual disability (ID), this CNV has also been found in apparently-unaffected controls, which has been interpreted as evidence of incomplete penetrance.

Aims: To evaluate whether there is incomplete penetrance by examining the impact on social functioning, autism features, and cognition in probands relative to familial controls.

Methods: We studied 30 probands with *de novo* del 16p11.2 from the Simons Variation in Individuals Project and their non-carrier parents (n=58) and siblings (n=19). Autism status was determined using the ADI-R and ADOS. Full-scale IQ (FSIQ) and Social Responsiveness Scale (SRS) scores, which are continuously distributed and highly heritable, were used evaluate cognition and social behavior.

Results: Only 32% (9/28) of probands met ADI-R/ADOS criteria for autism. Mean SRS T-scores were 72 in probands, 47 in parents, and 45 in siblings (higher scores reflect more severe social impairment). Analysis of mean SRS scores revealed a 2.6 SD deleterious shift in probands relative to controls ($p=3.28\times10\text{-}19$). Mean FSIQ scores were 83 in probands, 110 in parents, and 107 in siblings. Only 16.6% (5/30) of probands fit diagnostic criteria for ID (FSIQ<70). However, mean FSIQ was 1.8 SD lower in probands compared to controls ($p=1.72\times10\text{-}17$).

Conclusions: By comparing probands to non-carrier relatives using quantitative traits (IQ and SRS scores) rather than dichotomous diagnoses, we showed that del 16p11.2 has a significant deleterious impact on social behavior and cognition. These data are more consistent with variable expressivity related to genetic/family background than incomplete penetrance.

Principal Investigator: Janet Robishaw, PhD

Title: Modeling the Genetic Basis of Human Epilepsy

Department and Institution: Weis Center for Research, Geisinger Health System
Co-investigators: Tooraj Mirshahi, PhD
Background: Epilepsy affects ~1% of the population. However, no effective medical treatments exist for 30% ofpatients and none of these drugs prevent or reverse the epileptogenic process itself. Thus, there is a critical need to better understand the genetic basis of this disease.
Aims: Impaired inhibitory neurotransmission by gamma-aminobutyric acid receptors (GABAB) is commonly observed in epileptic patients, but whether this is a cause or a consequence of the disease remains an enigma. By introducing this human genetic lesion into mice, we were able to: 1) assess causality; 2) identify modifier genes that exacerbate the seizure phenotype; and 3) establish the utility of this mouse model as a therapeutic testing platform.
Methods: A gene targeting strategy was used to create an animal model mirroring a human genetic lesion. Subsequently, neurological, behavioral, electrophysiological, biochemical, and molecular analyses of these mice were performed.
Results: Mice with a GABAB defect show no overt seizure phenotype. However, by crossing these mice onto different genetic backgrounds, additional genes were identified that interact with the GABAB defect to produce a spontaneous seizure phenotype associated with high mortality. Finally, by administering a ketogenic diet to these mice, the potential utility of this model as a therapeutic testing platform was confirmed.
Conclusions: Mouse models recapitulating human genetic lesions provide a powerful means for understanding the genetic bases of diseases. Analysis of our mouse model of human epilepsy suggests that manipulating the output of the GABAB network may be a more efficacious therapeutic strategy than targeting the combinatorial genetic changes that appear to be unique to each patient as revealed by our RNA Seq analyses. From a clinical perspective, it is particularly intriguing that impairment of the GABAB network has been associated with epileptic disorders, whereas gain-of-function mutations within this same network have been linked to an autism phenotype with epileptic features. Collectively, these data indicate that strict control of the GABAB network is important for normal neurological function.

Principal Investigator: Paul Roda, DO

Title: Serial observations of a cohort carrying the JAK2V617F mutation in a low allele burden

Department and Institution: Geisinger – Hazleton Cancer Center, Geisinger Health System
Co-investigators: Ferrari A, Mesa R, Tang W, Emanuel R, Hoffman R, Cordovado SK, Irvin-Barnwell, EA
Background: After the development of highly sensitive assays for JAK2V617F, several groups described the prevalence of the mutation in non-diseased cohorts. However, the outcome of these cohorts is not well described, and it is unknown whether they progress to clinical disease, lose the JAK2V617F cell line, or remain asymptomatic.
Aims: The objective of this study is to follow JAK2V617F positive normal individuals, characterize progression of allele burden and disease, and identify changes in the quality of life (QOL) of these patients.
Methods: In 2009, the Agency for Toxic Substances and Disease Registry screened 1,170 residents of Northeast Pennsylvania for the JAK2V617F mutation. Eleven residents were positive for the mutation, including 2 found to have a myeloproliferative neoplasm (MPN). Seven residents positive for the JAK2V617F mutation agreed to be part of the study. Participants were examined biannually and asked about medical events and symptoms seen in the MPNs. The physical examination included evaluation of spleen size and assessment of the integument for erythromelalgia and digital infarction. QOL and MPN symptoms were assessed using the MPN-SAF questionnaire. Blood from participants was evaluated for JAK2V617F allele burden.
Results: The average allele burden was 0.16%, 0.19%, 0.12%, 0.17%, and 0.26% at the baseline visit, and office visits 1, 2, 3, and 4, respectively. To date no individual has developed symptoms or physical findings indicative of a MPN. The QOL of these patients has remained stable, and is more favorable than the QOL previously reported in patients with PV.
Conclusions: This study is the first to prospectively evaluate changes in health and allele burden in healthy JAK2V617F positive individuals. To date none has developed an MPN or experienced a significant change in their allele burden (p-value = 0.09). Further serial observations will ascertain the natural history of healthy individuals with low JAK2V617F allele burdens. There were no significant changes in renal function measurements through 12 months of follow up. There was a significant decrease in systolic/diastolic pressures, pulse pressure, and heart rate following treatment with the Symplicity renal denervation system. Symplicity HTN-3 is actively enrolling patients throughout North America.

Principal Investigator: Brian Schwartz, MD, MS

Title: **A Multilevel Analysis of the Burden of Coal Abandoned Mine Lands and Severity and Progression of Diabetes Using Hemoglobin A1c.**

Department and Institution: Johns Hopkins Bloomberg School of Public Health and Center for Health Research, Geisinger Health System

Co-investigators: Ann Y. Liu, PhD, Frank C. Curriero, PhD, MA, Thomas A. Glass, PhD, MA Walter F. Stewart, PhD, MPH

Background: Coal abandoned mine lands (AMLs) are a consequence of a long history of natural resource extraction and are prevalent across Pennsylvania, making them an excellent example of chronic environmental contamination (CEC) that could influence health through contextual impacts. Communities with high AML burden are associated with greater socioeconomic deprivation, which has been linked to adverse individual health outcomes such as kidney and cardiovascular diseases. Diabetes is of particular interest because it is a common, costly, and chronic progressive disease often assessed by measuring levels of a well-validated clinical management biomarker, hemoglobin A1c (HbA1c), with several behavioral risk factors that can be influenced by the built and social environments. CEC in communities could shape individual health by modifying health-related behaviors and stress pathways. These hypotheses suggest that a chronic disease such as type 2 diabetes would be a very appropriate evaluation of the individual health impacts of community CEC.

Aims: We aimed to evaluate cross-sectional and longitudinal contextual associations between the burden of AMLs in communities and individual type 2 diabetes using HbA1c as a biomarker.

Methods: Community burden of AML, represented by 10 metrics created from data in the Reclaimed Abandoned Mine Land Inventory System, was assessed in relation to individual HbA1c levels in a multilevel analysis of over 28,000 diabetic primary care patients of the Geisinger Clinic. Both cross-sectional and longitudinal evaluations of associations were assessed.

Results: In adjusted models, 5 AML measures were associated ($p < 0.05$), and 3 additional were borderline associated ($0.05 \leq p \leq 0.10$), with higher HbA1c levels or change in HbA1c levels over time.

Conclusions: This study provides the first empirical evidence of adverse impacts of chronic environmental contamination in communities on an important chronic disease. These findings can direct the use of AML reclamation funds to more explicitly address the stated goal of improving public health.

Principal Investigator: Diane T. Smelser, PhD

Title: Electronic Medical Records as a Source for Identification of Risk Factors for Abdominal Aortic Aneurysm in Preparation for the eMERGE Phase II Network

Department and Institution: Weis Center for Research, Geisinger Health System

Co-investigators: Gerard Tromp, James R. Elmore, Helena Kuivaniemi, David P. Franklin, and David J. Carey

Background: The Geisinger Health System (GHS) maintains an extensive electronic medical record (EMR) system containing an abundance of phenotypic information with great potential for retrospective research studies, such as identifying disease risk factors. As part of the eMERGE Phase II Network, GHS will be leveraging this data source for clinical risk factors to combine with genomic data to determine those at risk for abdominal aortic aneurysm (AAA). We assessed the feasibility of utilizing our EMR to obtain phenotypes that are significantly associated with AAA.

Aims: Methods: GHS is the main health provider serving a highly stable population in central and northeastern Pennsylvania. Clinical and diagnostic data from January 2004 to December 2009 were extracted from the Geisinger EMR. The study population consisted of cases diagnosed with AAA (*n*=964) and controls without AAA from the Geisinger MyCode® biobanking repository (*n*=14,555). The de-identified dataset was cleaned and formatted for research purposes. Data were analyzed unmatched, then matched on the confounders of sex, age, body mass index and smoking status. Matching was performed randomly, by propensity score and group-frequency procedures. Bootstrap replication procedures (with and without replacement and weighting) confirmed the reproducibility of the results.

Results: We replicated the direction and magnitude of common risk factors published in traditional epidemiologic AAA studies. We present the most conservative estimates from the bootstrap analyses in our results. Diastolic blood pressure was significantly associated with a decreased risk (OR=0.97), as was type 2 diabetes (OR=0.45), and myelogenous neoplasms (OR=0.66). The diagnosis of benign neoplasms was significantly inversely associated with AAA (OR=0.59), which is a novel finding. Systolic blood pressure (OR=1.03), cerebrovascular disease (OR=1.32), kidney disease (OR=1.40), peripheral artery disease (OR=3.56), pulmonary disease (OR=1.42) and coronary stenosis (OR=2.14) were all significantly associated with an increased risk of AAA.

Conclusions: This study demonstrated that Geisinger EMR data can be used to assess risk factors and identify new associations. The regression coefficients from these analyses will be incorporated into future genomic analysis to identify variants associated with AAA risk. These findings could serve to enhance the current AAA screening guidelines to more efficiently target patients and increase screening utilization.

Principal Investigator: **Azadeh Stark, PhD**

Title: Expression of ALDH1 as a marker of mammary stem cells in benign and malignant breast lesions of Ghanian women.

Department and Institution: Center for Health Research, Geisinger Health System

Co-investigators: Schwartz T, Pang J, Kleer CG, Martin I, Toy K, Wicha M, and Newman LA (University of Michigan Comprehensive Cancer Center, Ann Arbor, MI). Awuah B, Quayson S, Kingman S, Abantanga F, Jiagge E, Oppong JK, Osei-Bonsu E, Adjei E, (Anoyke Kumasi, Ghana) Yan X (Center for Health Research, Geisinger Health System). Chitale D, (Henry Ford Health System, Detroit, MI)

Background: Genomic research has unraveled the molecular subtypes of breast cancer (BC). About 15-20% of invasive BC is "triple-negative" (TNBC) – defined as absence of hormone receptors and HER2 over-expression. TNBC has more aggressive pathophysiology and the effectiveness of current chemotherapeutic options is sporadic at best. Risk of TNBC varies by racial/ethnic heritage; TNBC accounts for about 15% of invasive BC in White-American women compared to 25% in African American women, and 75% in women of West African descent. Since women with TNBC have a worse prognosis than those with other subtypes, these differences likely contribute to the observed racial/ethnic disparity in BC treatment. Animal models suggest that the more pathophysiology aggressive nature of TNBC may be attributed to the mammary stem cell features. Little is known about expression of the mammary stem cell marker aldehyde dehydrogenase 1 (ALDH1) in African women. Novel data are reported regarding ALDH1 expression in benign and cancerous breast tissue of Ghanaian women.

Aims: To report ER, PR, HER2 and ALDH1 expression in benign and cancerous breast tissue of Ghanaian women.

Methods: Formalin-fixed, paraffin-embedded specimens were transported from the Komfo Anoyke Teaching Hospital in Kumasi, Ghana to the University of Michigan for centralized histopathology study. Expression of ER, PR, HER2, and ALDH1 was assessed by immunohistochemistry. ALDH1 staining was further characterized by its presence in stromal versus epithelial and/or tumor components of tissue.

Results: A total 69 women, diagnosed with benign conditions of the breast (BBD) with mean age of 24 (± 8.4) years, and 104 women with breast cancer with mean age of 49 (± 13.4) years contributed to this study. The proportion of women with BBD expressing stromal ALDH1 (n=40, 58%) was statistically significantly higher than those with cancer (n=44, 42.3%) (P= .043). Among women with cancer, those with TNBC had the highest prevalence of ALDH1 expression, either in stroma or in epithelial cells. More than 2-fold higher likelihood (OR=2.38, 95% CI 1.03-5.52, P=.042) of expression of ALDH1 in the TNBC subtype relative to all subtypes combined was observed.

Conclusions: ALDH1 expression was higher in the stromal components of benign compared with cancerous lesions. Of the four subtypes of breast cancer, expression of ALDH1 was the highest in TNBC.

Principal Investigator: Azadeh Stark, PhD

Title: Routine sub-classification of mammographic suspicious lesions potentially can reduce the harm of unnecessary breast biopsy.

Department and Institution: Center for Health Research, Geisinger Health System

Co-investigators: Naimei Tang, Felix Fernandez-Madrid (Karmanos Comprehensive Cancer Institute and Department of Internal Medicine, School of Medicine, Wayne State University. Dan Chitale, Department of Pathology, Henry Ford Health System, Detroit, MI
Xiaowei Yan, Center for Health Research, Geisinger Health System

Background: Presently, women diagnosed with mammographic suspicious lesions (BIRADS™ 4) are recommended to undergo breast biopsy for pathologic evaluation. About 80% of these women are diagnosed with benign conditions of the breast of no clinical significance. The annual economic cost of these unnecessary biopsies has been estimated at $3.5 billion and the psychological impact on women and their families is large and negative and there are possible complications due to scarring. Concerns about negative breast biopsies have been expressed in terms of over-diagnosis and interventions that can be disfiguring and expensive. We report findings from a sequential case series study of women diagnosed with BIRADS™ 4.

Aims: To report on the pathologic outcome of breast biopsies in women diagnosed with BIRADS™ 4 by age and by other risk factors used in Gail model.

Methods: So far we have identified a total of 1,447 cases from the radiology database which was then linked to electronic health records to download data on pathology outcome, clinical and demographic risk factors for breast cancer. We used multivariate logistic regression to estimate the risk of malignancy within 4A and 4B sub-classifications. Statistical analyses were conducted using SAS package (v 9.2).

Results: Mammograms of 268 (18.5%) were sub-classified as 4A, 112 (7.7%) as 4B, 75 (5.2%) as 4C and 992(68.5%) were not sub-classified. Malignancies were diagnosed in 6.7% (n=18) of women with 4A, 25% (n=28) with 4B, and 80.0% (n=56) with 4C. While, 18.2% (n=183) of women without sub-classifications were diagnosed with malignancies. Among women with 4A or 4B sub-classifications, the likelihood for malignancy increased significantly for women ≥ 55 years (OR=7.5, 95% CI 2.09-27.02, P=0.02), but no significant association was detected for the younger age group (P> 0.56).

Conclusions: Given the harm of biopsy and the wide difference in the prevalence of malignancy, routine sub-classification of BIRADS™ 4 is recommended, especially for women ≥ 55 years. Our findings further confirm that many of breast biopsies can be avoided; however, unless a method that is less invasive but has the same level of validity and reliability as breast biopsy is developed, the present diagnostic guidelines and practices most likely will remain unchanged.

Principal Investigator: Christopher Stromblad; Priyantha Devapriya
Title: Outpatient Clinic Provider Scheduling for Pediatric Gastroenterology

Department and Institution: Innovation Analytics & Operations Research, Geisinger Health System
Co-investigators: Dr. Michael Ryan, Gloria Gerrity, Dr. Priyantha Devapriya, Gina Kapelewski, Lindsey Bussom
Background: Scheduling clinic and procedure time for each provider involves a series of detailed constraints. Currently the scheduling of outpatient clinics is performed manually with a goal in mind of reducing the number of cancelled clinic visits and procedures. The patient demand is assumed to be static across time and location and is estimated yearly. The impact of the provider scheduling decisions is not measured or evaluated. There is no tool available that allows a detailed comparison between operational or strategic decisions regarding the scheduling of providers to clinic locations of a given service line.
Aims: A decision support tool is developed to streamline, automate and optimize the provider scheduling process incorporating patient demand • To simplify and reduce the non-value added provider scheduling time • To make the scheduling process less people dependent • To ensure the outlined scheduling constraints are satisfied while increasing patient access and reducing patient wait time for an appointment • To enhance the agility of the schedule to handle changes including urgent requirements and cancelations
Methods: A mixed-integer program (MIP) was developed allowing for all hard constraints to be satisfied while searching for an optimal provider schedule. The MIP was modeled using AIMMS software. Graphical user interfaces were developed to allow leadership and operations managers to run what-if scenarios.
Results: The research project is still in progress though a set of metrics have been defined and identified as targets for this project, including measures around the patient demand. The hypothesis is that applying this tool to both operational and strategic decisions will allow the capacity of a service line in terms of physicians and clinics by location to match the patient demand.
Conclusions: The need for this tool has been expressed by Geisinger and once the pilot study of applying this tool in one service line has proved useful, there is a desire to expand this across multiple service lines.

Principal Investigator: Christopher Stromblad
Title: Modeling Time-Dependent Patient Arrivals in Hospital Simulation Models

Department and Institution: Innovation Analytics & Operations Research, Geisinger Health System

Co-investigators: Dr. Priyantha Devapriya

Background: Simulation has been an increasingly applied modeling and decision support tool in the healthcare industry during the past couple of decades. Used appropriately it can be helpful in identifying bottlenecks that may appear in a stressed system and capturing performance metrics when trying out suggested policy changes or varying the number of available resources. The arrival process is an important part of the system for any simulation modeler, especially since the actual arrival rates of patients often are highly dependent on the time of day. Therefore it is important to include this dependency when creating a valid simulation model of healthcare systems.

Aims:

• To develop algorithms that would provide Poisson distributed time-dependent interarrival times based on historical data, for discrete event simulation purposes.

• To prove the applicability of the proposed algorithms by illustrating the risk of ignoring the inherent time-dependency of patient arrivals in terms of the impact of simulation results.

Methods: Two algorithms were developed to generate Poisson distributed time-dependent inter-arrival times and compared in terms of the quality of the output, computational complexity and memory requirements. An experiment highlighting the necessity of timedependent inter-arrival times in simulation modeling was conducted using a randomly generated dataset. In the experiment a discrete-event simulation model of a generic hospital was created, and the proposed algorithms were used as the arrival processes and compared to a homogeneous Poisson arrival process.

Results: The wait times caused by time-dependent arrivals are captured in the proposed algorithms and would be significantly underestimated if a homogeneous Poisson distribution was applied. The research was published in a peer reviewed conference proceeding.

Conclusions: The proposed algorithms for generating inter-arrival times were proved to be a useful way of incorporating time-dependency in patient arrivals for computer simulation purposes. They have both been used at Geisinger Health System for several of the computer simulations created including Inpatient Flow Simulation and ED Flow Simulation.

Principal Investigator: Nikos Tapinos, PhD

Title: Role of nuclear ErbB3 in controlling Schwann cell myelination

Department and Institution: Molecular Neuroscience Laboratory, Geisinger Health System
Co-investigators: Amanda Skiles, Eng H. Yap, Andras Fiser
Background: The interaction between ErbB receptors (ErbB2 and ErbB3) on the surface of Schwann cells and neuronal Neuregulin-1 (NRG1) constitutes the pivotal signal that controls Schwann cell development, association with axons, and myelination.
Aims: We have recently described the presence of nuc-ErbB3 in Schwann cells and its role as a transcriptional regulator. We wanted to determine the role of nuc-ErbB3 expression on myelination in an *in vitro* Schwann cell DRG axon co-culture model.
Methods: We utilized TF-TF arrays, genome-wide ChIP-chip arrays, knockin mouse generation, and electron microscopy to analyze nuc-ErbB3 role in Schwann cells.
Results: The mice express normal levels of the full-length ErbB3 receptor and the ErbB3 associated protein Pa2G4. Using a TF-TF array we show that nuc-ErbB3 interacts with several transcription factors in the nuclei of Schwann cells to form multi-protein complexes. In addition, computational analysis of a genome-wide ChIP-chip array reveals a specific DNA binding motif for nuc-ErbB3. Finally, we generated a knockin mouse, which carries a mutation at the NLS motif of nuc-ErbB3 so it lacks nuc-ErbB3 expression in the nucleus.
Conclusions: Electron microscopy of the sciatic nerves reveals that the nuc-ErbB3 knockin mice exhibit a demyelinating neuropathy, which implies a central role of nuc-ErbB3 during myelination and for the maintenance of myelin architecture in the PNS.

Principal Investigator: Nikolaos Tapinos, PhD

Title: Novel in vitro culture models to study migration of glioblastoma multiforme

Department and Institution: Molecular Neuroscience Lab, Weis Center for Research, Geisinger Health System

Co-investigators: Kristin Snyder, Jennifer Ness-Myers, John Zepecki, Atom Sarkar

Background: Glioblastoma multiforme (GBM) is the most aggressive form of primary brain tumors, accounting for 78% of all central nervous system malignancies. The disturbing migratory nature of GBM renders advances in surgical resection, chemotherapy, and radiation ineffective.

Aims: Here, we present two new in vitro approaches to study GBM cell migration by using: 1) dorsal root ganglion neurons (DRG) from rat embryos in Campenot chambers, a compartmented culture system, as described by Campenot and Martin (2001) and 2) electrospun fibermats coated with poly-D-lysine/laminin.

Methods: DRG neurons are co-cultured with oligodendrocytes from newborn rats to form compact myelin tracks. Human cancer stem cells derived from primary GBMs are placed on the various culture systems for quantification by live cell imaging. The electrospun fibers represent an alternative to the DRG co-culture system that is easier to obtain and allows quantification of various mechanical properties like fiber diameter and rigidity and how these factors influence GBM cell migration.

Results: In the compartmented systems, individual stem cells from the neurospheres partially differentiate and migrate away from the central mass and along axons, interacting with both non-myelinated and myelinated nerve fibers. A small number of GBM stem cells also exhibit mesenchymal migration, a characteristic of invading GBM cells.

Conclusions: Both models allow for treatment with selective migratory inhibitors, reducing the need for laborious in vivo experiments and unreliable migration assays in early GBM drug discovery. Therefore, the use of compartmented cultures and electrospun fibermats may be an effective approach to quantify both GBM/neuronal cell interactions and differences in cell motility with drug treatments.

Principal Investigator: Xiaowei Yan, PhD

Title: Sensible use of ICD-9 diagnosis of observational data in breast and endometrial cancer research

Department and Institution: Center for Health Research, Geisinger Health System

Co-investigators: Ryan Colonie, Jeffery Prichard, Radhika Gogi and Azadeh Stark, Geisinger Health System, Weng Feng, University of Tennessee in Memphis.

Background: Utilization of administrative data (such as EHR data) in population-based research is resource advantageous, despite its potential limitations. Few studies have fully assessed the validity and efficiency of EHR- retrieved data. We developed ICD-9 based algorithms and operational processes to evaluate applicability of EHR-derived cancer data.

Aims: To develop ICD-9 algorithms and operational process to evaluate applicability of HER derived cancer data.

Methods: We retrieved data between 01/01/2002-12/30/2011 from 4 different EHR sources and developed 3 ICD9-based diagnostic algorithms [1+, 2+ and 5+]. Women were classified into breast or endometrial cancers or benign breast conditions (BBC). One trained abstractor manually reviewed medical records and recorded data into a structured database. Every 10 observations were selected and reviewed. Basic descriptive statistical analyses were conducted; observations with questionable values were flagged for re-evaluation. The final dataset was considered the "gold standard" and used to validate the algorithms and to assess the duration between the diagnostic and administrative dates.

Results: A total of 1,056 women contributed to this study. Of these, 189 were diagnosed with breast and 40 with endometrial cancers. An additional 268 women had BBC. For breast cancer, using the first algorithm we calculated the sensitivity of 95.2% and specificity of 96.4%. Application of the second algorithm yielded a sensitivity of 94.2% and a specificity of 97.6%. For the third one, our calculations indicated 89.0% sensitivity and 97.9% specificity. Our analyses based on the same algorithms yielded similar sensitivity and specificity for endometrial cancer. For BBC, we calculated a sensitivity of 82.5% and a specificity of 56.7% based on the first, 73.1% sensitivity and a specificity of 71.9% for the second and 38.8% and a specificity of 90.5% for the third algorithms. The average duration between diagnostic and administrative dates for incident breast, endometrial cancers and BBC was 0.65, 0.01, and 0.31 years, respectively.

Conclusions: Our initial findings confirm the validity and potential utility of EHR for population based cancer research. The algorithm of "2+ ICD-9 Coding System" yielded the most efficient process. The observed lower sensitivity and specificity for BBC potentially can be attributed to the wider pathologic spectrum of BBC. The relatively short duration between the EHR and diagnostic dates suggests of unbiased interchangeability of dates.

Principal Investigator: Wannian Yang

Title: HECT E3 ubiquitin ligase Nedd4-1 ubiquitinates ACK and regulates EGF-induced degradation of EGFR and ACK

Department and Institution: Weis Center for Research, Geisinger Health System
Co-investigators: Qiong Lin, Jian Wang, Chandra Childress, Marius Sudol, David J. Carey
Background: ACK1 (activated Cdc42-associated tyrosine kinase 1) (also Tnk2) is an ubiquitin-binding protein and plays an important role in ligand-induced and ubiquitination-mediated degradation of epidermal growth factor receptor (EGFR).
Aims: 1. To determine interaction of ACK1 with and ubiquitination of ACK1 by the E3 ubiquitin ligase Nedd4-1. 2. To determine the role of interaction between ACK1 and Nedd4-1 and the ubiquitination of ACK1 in regulation of EGFR degradation.
Methods: GST-fusion protein pulldown and co-immunoprecipitaion assays were used in analysis of the interaction. An in vitro ubiquitination assay was developed for detection of ubiquitination.
Results: ACK1 is ubiquitinated by HECT E3 ubiquitin ligase Nedd4-1 and degraded along with EGFR in response to EGF stimulation. ACK1 interacts with Nedd4-1 through a conserved PPXY WW binding motif. The WW3 domain in Nedd4-1 is critical for binding to ACK1. Although ACK1 binds to both Nedd4-,1 and Nedd4-2 (also Nedd4L), Nedd4-1 is the E3 ubiquitin ligase for ubiquitination of ACK1 in cells.mInterestingly, deletion of the sterile alpha motif (SAM) domain at the N-terminus dramatically reducedmthe ubiquitination of ACK1 by Nedd4-1 while deletion of the Uba domain dramatically enhanced the ubiquitination. Use of proteasomal and lysosomal inhibitors demonstrated that EGF-induced ACK1 degradation is processed by lysosomes, not proteasomes. RNAi knockdown of Nedd4-1, not Nedd4-2, inhibited degradation of both EGFR and ACK1, and overexpression of ACK1 mutants that are deficient in either binding to or ubiquitination by Nedd4-1 blocked EGF-induced degradation of EGFR.
Conclusions: Nedd4-1 regulates EGFR degradation through interaction with and ubiquitination of ACK1.