Marshfield Clinic®

Research Institute

2024

Summer Research Internship Program (SRIP) Symposium

August 6-7, 2024

Froehlke Auditorium

August 6, 2024

3-4:00 p.m. Meet interns in-person in the POD.

August 7, 2024
Presentation Schedule

10:00 a.m. Welcome –
Jennifer Meece, PhD
Executive Director & Chief Research Officer
Marshfield Clinic Research Institute

Jeff VanWormer, PhD
SRIP Director
Marshfield Clinic Research Institute

Gary Ratts
Koller Trust

10:20 a.m. Cameron Lee
Mentored by: Maria Sundaram, PhD
Characteristics of Medically-Attended Respiratory Infections in High-Risk Adults

10:50 a.m. Shravani Gummaraju
Mentored by: Jeff VanWormer, PhD
Adverse Childhood Experiences in Rural and Farm Families in Wisconsin

11:20 a.m. Jason Xu
Mentored by: Rohit Sharma, MD
Comparing Clinical Outcomes of Robotic Assisted Procedure and Open Laparotomy in CytoReductive Surgery (CRS) and Heated IntraPeritoneal Chemotherapy (HIPEC) for Peritoneal Carcinomatosis (PC)

Presentation Schedule

11:50 a.m. Break

12:00 p.m. Anna Isberg
Mentored by: Jeremy Pomeroy, PhD
Non-Hyperphagic Factors Influencing Hyperphagia Questionnaire Scores in Bardet-Biedl Syndrome

12:30 p.m. Bright Asante
Mentored by: Tonia Carter, PhD
Assessment of Candidate Genetic Variants in Orofacial Clefts

1:00 p.m. Susmitha Bommini
Mentored by: Scott Hebbring, PhD and Brooke Delgoffe, MS
Utility of Family Data Extracted from Hospital Records

1:30 p.m. Closing and luncheon to follow

Thank You To Our Program Donors

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Please consider joining us in making this opportunity available next year and beyond by including this program in your charitable giving plans.

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Characteristics of Medically-Attended Respiratory Infections in High-Risk Adults

Cameron Lee, Maria Sundaram, *Clinical Epidemiology and Population Health*

Background: The similar clinical presentation of different respiratory viruses makes precise diagnoses difficult without dedicated laboratory testing. Laboratory testing for seasonal respiratory viruses, however, is not routine in clinical environments. This limited testing results in knowledge gaps of the burden of these respiratory viruses in adults. The purpose of this study is to understand the symptoms and severe outcomes of medically-attended respiratory infections caused by human metapneumovirus, parainfluenza virus, adenovirus, and other non-influenza, non-RSV respiratory pathogens, in adults with underlying high-risk conditions.

Methods: We conducted an observational study to examine the characteristics of non-influenza, non-RSV medically-attended acute respiratory infections (MAARI) in adults with high-risk conditions. This analysis used data from re-tested respiratory specimens, collected from high-risk adults that participated in the flu vaccination effectiveness (FluVE) study from 2015-16 through 2019-20 winter seasons. Electronic health records were linked to VE study information, including laboratory viruses, from enrolled participants. We conducted univariate analyses to identify a) demographic characteristics and underlying health conditions associated with non-influenza, non-RSV respiratory pathogen infection and severe outcomes and b) the relationship between infection and non-influenza, non-RSV respiratory pathogens and severe outcomes. Additionally, we used multivariable logistic regression modeling to examine associations between underlying high-risk conditions and risk of contracting each pathogen.

Results: There were 3,575 participants in this study with complete information available for analysis. In primary analyses, we found that most sociodemographic characteristics did not have statistically significant ($p < 0.05$) associations with non-influenza, non-RSV respiratory pathogens. Secondary analyses did not reveal any statistically meaningful relationships between hospitalization and ICU admissions according to infection status for any pathogen. We observed several instances of high-risk conditions showing a statistically significant relationship with specific pathogens. Individuals with seasonal coronavirus infection were more likely to have underlying chronic respiratory disease ($p < 0.01$), and individuals with adenovirus infection were more likely to have underlying cardiovascular disease ($p < 0.01$), compared to individuals not infected with those pathogens. Furthermore, having any respiratory condition showed a decrease in relative risk for human metapneumovirus (CI: 0.5 – 0.9) and an increase in relative risk for seasonal coronaviruses (1.1-1.7) compared to individuals testing negative for both these pathogens, respectively.

Conclusions: We did not identify consistent statistically significant relationships between sociodemographic characteristics or severe illness outcomes and infection with non-influenza, non-RSV respiratory pathogens. Future research should investigate the relationships between underlying disease and potential outcomes of respiratory infections.

Adverse Childhood Experiences in Rural and Farm Families in Wisconsin

Shravani Gummaraju, Jeff VanWormer, *Clinical Epidemiology & Population Health*

Background: Adverse childhood experiences (ACEs) are seminal events that can occur in early life, including forms of neglect, physical, sexual, and emotional abuse. ACEs routinely result in negative health consequences, including increased risks of many chronic conditions in adulthood. While there are some established social determinants of ACEs (e.g., parental substance abuse, poverty), the degree to which residency impacts the risk of ACEs is not well understood. Nearly 20% children and adolescents in the U.S. live in rural areas, but evidence is mixed on how the burden of ACEs differ between rural and urban youth. Furthermore, no studies have examined the burden of ACEs in those who live on farms, a hazardous subset of rural environments. The purpose of this study was to examine the association between ACEs and rural/farm residency in north-central Wisconsin youth.

Method: Cross-sectional analyses were conducted using medical records data from an existing cohort of children and adolescents (age 0-17 years) in a 20-county region of north-central Wisconsin. Medically attended ACEs were identified by screening for groups of diagnostic codes indicative of emotional, physical, or sexual abuse, as well as neglect, observed between 2017 and 2023. The ACE cases were further chart audited for validation and a multivariable logistic regression was used to examine associations between rural/farm residence and ACEs.

Results: The sample included 5,990 individuals who lived on a farm, 52,614 who lived in a rural area, and 42,788 who lived in a non-rural area. Overall, ACEs were observed in 2,677 participants (2.7%). In the final adjusted model, the risk of an ACE was significantly higher in (non-farm) rural youth as compared to both farm (adjusted odds ratio [aOR] [95% confidence interval; CI] = 0.72 [0.60, 0.89], $p = 0.001$) and non-rural (aOR [CI] = 0.86 [0.78, 0.95], $p < 0.001$) youth. Specifically, rural (non-farm) youth had the highest risk of an ACE at 169 (CI: 158, 182) per 10,000, whereas farm youth had the had the lowest risk of an ACE at 123 (CI: 102, 149) per 10,000.

Conclusions: Compared to their farm and non-rural counterparts, youth who lived in rural areas had a significantly higher risk of an ACE. Additional prospective studies are needed to identify causal elements within different child rearing environments that may promote or protect against ACEs.

Comparing Clinical Outcomes of Robotic Assisted Procedure and Open Laparotomy in CytoReductive Surgery (CRS) and Heated IntraPeritoneal Chemotherapy (HIPEC) for Peritoneal Carcinomatosis (PC)

Jason Xu, Rohit Sharma, *Cancer Care Research Center*

Background: Peritoneal carcinomatosis (PC) is a severe cancer, typically of abdominal origin, that has metastasized to the peritoneum. Before the advent of two advanced therapies, CytoReductive Surgery (CRS) and Heated IntraPEritoneal Chemotherapy (HIPEC), PC was considered a terminal illness within just a few years. Both CRS and HIPEC have demonstrated promising outcomes for various patients with PC, but the extensive abdominal incision performed during the open laparotomic version of these procedures has, in some studies, been associated with higher mortality, morbidity, and prolonged hospitalization. More recent studies have shown that robotic CRS and HIPEC is both feasible and safe. Robotic CRS/HIPEC may also provide superior visualization and range of motion intraoperatively, but only a few studies have been done that have compared open vs. robotic CRS/HIEPC on postoperative outcomes.

Methods: A retrospective cohort was assembled of PC patients who received CRS/HIPEC since 2008 at a single institution, the Marshfield Clinic Health System (MCHS) in central Wisconsin. Demographic and clinic data were extracted and entered into a database, stratified by patients who received robotic or open CRS/HIPEC. Statistical analyses were conducted using the SAS statistical software. Univariate and multivariable regression models were used to assess associations between open vs. robotic CRS/HIPEC on key outcomes, including hospital stay, blood loss, operative time, and 90-day readmissions.

Results: There were 85 patients, 70 in the open and 15 in the robotic CRS/HIPEC groups, who met study eligibility criteria. In univariate analyses, only underlying peritoneal carcinomatosis index (PCI) significantly differed between groups. Demographic and clinical characteristics were statistically similar. In multivariable analyses where patients with high PCI score were excluded, there were significant differences in estimated blood loss Open group 346 ml vs. Robotic group 169 ml ($p = 0.028$), and operative time open group 8.5 hours vs. Robotic group 10.5 hours ($p = 0.0015$).

Conclusions: More confirmatory research is needed in larger samples, but robotic CRS/HIPEC is associated with significantly reduced blood loss relative to open laparotomic approach. Despite the robotic approach taking a longer time to complete, it may also result in shorter hospital stays and less risk of rehospitalization.

Non-Hyperphagic Factors Influencing Hyperphagia Questionnaire Scores in Bardet-Biedl Syndrome

Anna Isberg, Jeremy Pomeroy, *Fritz Wenzel Center for Clinical Research*

Background: Bardet-Biedl Syndrome (BBS) is a rare heterogeneous genetic disorder with widespread symptoms, including obesity and hyperphagia, or excessive appetite. Hyperphagia symptoms and intensity are typically assessed using questionnaires, but the degree to which other factors such as age, neurocognitive functioning, language delays, and BBS genotypes influence questionnaire scores is unknown. The purpose of this study was to identify non-hyperphagic factors that influenced hyperphagia questionnaire scores in children with BBS.

Methods: Data from participants in the Clinical Registry Investigating Bardet-Biedl Syndrome (CRIBBS) who were age 4-17 years was used in this analysis. Interviews with a parent or caregiver of the person with BBS included the Hyperphagia Questionnaire (HQ), the Social Communication Questionnaire (SCQ), items about speech and language development, and genetic testing results. Spearman's correlations and Wilcoxon tests were used to evaluate associations between HQ scores (total and subscale scores) and various non-hyperphagic factors, including age, SCQ scores, language development, and pathogenic variants in BBS1 or BBS10 genes.

Results: All HQ scores were significantly correlated with age, including total ($n=131$, $r=-0.36$, $p<0.001$), as well as subscale scores for drive ($r=-0.40$, $p<0.001$), behavior ($r=-0.29$, $p=0.009$), and severity ($r=-0.21$, $p=0.0182$). In addition, HQ total ($n=68$, $r=0.34$, $p=0.0049$), drive ($r=0.31$, $p=0.0115$), and behavior ($r=0.35$, $p=0.0044$) scores were significantly correlated with SCQ scores after controlling for age. Participants who were reported to get frustrated or upset when not understood by others had significantly higher HQ drive ($n=161$, Wilcoxon two sample test $p=0.0416$) subscale scores than participants not reported to get frustrated or upset. Participants reported to know when others felt sick or sad had significantly lower HQ total ($n=163$, Wilcoxon two sample test $p=0.0002$), drive ($p=0.0002$), behavior ($p=0.0025$), and severity ($p=0.001$) scores than those not reported to know. There were no significant differences in HQ scores between participants with BBS1 or BBS10 genotypes.

Conclusions: Younger ages and higher SCQ scores were significantly correlated with higher HQ scores. Participants with some speech and language deficits also had significantly higher HQ scores, while no significant association between BBS genotypes and HQ scores emerged. These non-hyperphagic factors may prevent hyperphagia from being validly assessed using extant hyperphagia questionnaires, and likely need to be considered further to guide the clinical development of personalized therapies.

Assessment of Candidate Genetic Variants in Orofacial Clefts

Bright Asante, Tonia Carter, *Center for Precision Medicine Research*

Background: Orofacial clefts remain one of the most prevalent birth defects, both in the United States and globally. Non-syndromic oral clefts present more frequently, occurring in as high as 70% of all cleft cases. Previous studies have established strong genetic links to the development of orofacial clefts, but how the numerous unique genetic alterations contribute to the expression of orofacial clefts remains understudied. In this study, we investigated how copy number variants (CNVs), as a genetic alteration, were associated with non-syndromic cleft lip and/or palate.

Methods: Data on CNVs in non-syndromic cleft cases from two distinct population groups, Filipino and European, were extracted from a previous study on orofacial clefts. Using an in-house Linux server, BEDTOOLS, Unix code, and several R packages, a computational pipeline was implemented to: (1) identify overlapping CNV gains and losses in patients (i.e., CNV regions shared by two or more patients), (2) assess whether patient CNV overlaps occur by chance, by comparing the Z-scores of patient CNV overlaps with the Z-scores of a random sample of (1,000) CNV overlaps, (3) prioritize genes encompassed by patient overlapping CNVs, (4) assess the likelihood of patient overlapping CNVs to occur in regions of the genome with high variability, and, (5) perform gene ontology analysis to determine biological pathways enriched in genes prioritized in patient overlapping CNVs.

Results: Filipino cleft palate only (CPO) patients shared more overlaps with CNV gains (2448) than CNV losses (474). Comparing Z-scores and p-values for both groups observed, along with the randomly selected 1,000 CNV overlaps, showed that both losses and gains that appeared in patient CNVs did not occur by chance (Z-score = 595.2892, p = 0.0068 for CNV gains; Z-score = 361.7982, p =1.820e-08 for CNV losses). Specifically, there were 183 and 61 genes impacted by CNV gains and losses respectively, for Filipino CPO patients. Of these, 48 have been reported in previous studies (18 were homologs associated with cleft phenotypes in mice).

Conclusions: Z-score comparisons showed that patient CNV overlaps differ significantly, suggesting that at least some of the genomic regions of the overlaps contain genes relevant to orofacial clefts. In addition, the approach used to prioritize genes identified some cleft-associated genes that were known previously, further validating the pipeline. The prioritized genes with no known association with lip or palate observed in prior scientific literature are novel candidates to explore and confirm in future studies designed to isolate genetic contributions to the development of oral clefts.

Utility of Family Data Extracted from Hospital Records

Susmitha Bommini, Scott Hebbring and Brooke Delgoffe, *Center for Precision Medicine Research & Office of Research Computing and Analytics*

Background: Family histories serve as a valuable resource for identifying and managing disease risks in genetic research. Traditional methods of obtaining information on family histories, however, are cumbersome. Previous studies revealed the use of electronic health records (EHR) data to generate E–pedigrees using the family mapping algorithm (FMA). While EHRs offer standardized data collected through pre-defined formats, they often lack historical depth in time periods prior to EHR implementation. To help fill such historical gaps, this project focused on utilization of hospital paper records. Although paper records contain a wealth of longitudinal, family health data that predated the EHR, they present significant challenges for utilization. The purpose of this project is to create actionable family history datasets from paper records for use in the FMA.

Methods: Paper records were reviewed by staff to create the electronic data used in this project. Personal identifiers (names, addresses, and contact information) were extracted along with other temporal information and placed in electronic forms in a REDCap database. Then we conducted exploratory data analysis. Due to non-standard formats, these paper records needed extensive pre-processing to make the data trustworthy. Our data included information from birth and non-birth (primary patient) records. A single paper chart can define multiple sets of identifiers: baby, mother, and father (for birth records), patients being seen (adult/child), and their multiple emergency contacts. We re-organized the data to treat sets of identifiers listed in different capacities in a record as a unique person longitudinally and populate necessary fields from corresponding sources. We created unique identifiers for each individual to ensure consistency across different input files. Given the limited availability and missingness of time variables, we employed logical conditions to construct timeframes across the information fields. Additionally, extensive data cleaning was performed to standardize each variable due to high prevalence of manual data entry errors. We used various data pre-processing and mapping techniques to de-identify the data and produce final structured datasets.

Results: With the utilization of SAS, Python, and MS Excel, we transformed unstructured paper records data into an actionable format for use in predicting family members. From around 67k records, we identified 100k+ individuals. Input files (names, demographics, addresses, emergency contacts, and patient information) were created in compliance to FMA requirements.

Conclusions: This approach of integration of paper records data with an EHR underscores the effective utilization of family data in genetic research. Further steps in this extensive project include additional data cleaning and transformation techniques to enhance the quality and accuracy of input data and improve the algorithm’s ability to construct E-pedigrees.

2024
Research Interns

Top (left-to-right): Shravani Gummaraju, Anna Isberg, Susmitha Bommini

Bottom (left-to-right): Bright Asante, Cameron Lee, Jason Xu

SRIP Selection Committee

Peggy Hatfield, PhD

Steven Kaiser

Laurel Hoeth

Huong McLean, PhD

We would like to thank the Selection Committee members for their impartial review of applicants, the 2024 mentors, and Jeff VanWormer, PhD and Seth Langreck for administering the program.