American Academy of Pediatrics
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Research Committee Report

May 27, 2020

Much appreciation to our dedicated reviewers for 2020

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In This Issue

2020 Marshall Klaus Neonatal-Perinatal Medicine

On behalf of the American Academy of Pediatrics (AAP), Section on Neonatal-Perinatal Medicine (SoNPM) and this year's Klaus Neonatal-Perinatal Research Fund supporters, we would like to congratulate the recipients of the 2020 Marshall Klaus Neonatal-Perinatal Research Award! The Research Committee received 48 very strong applications and all applicants deserve recognition for their already strong bios, outstanding mentors, and exciting projects. Thanks to our sponsors, this year we were able to fund the top 10 ranked fellows with the $5,000 research award. The money will be used towards supplies etc. to support the proposed research project.

Special thank you to the award sponsors

Klaus Bench or Clinical Research Award

AAP, Johnson & Johnson Pediatric Institute, Mead Johnson Nutrition

Beth Israel Deaconess Neonatology Education Research Award

Brodsky & Martin's *Neonatology Review* Series

Health Services Research Award

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Marshall Klaus Bench or Clinical Research Awardees

Geoanna M. Bautista, MD

University of California, Los Angeles (UCLA), Los Angeles, CA

Title: *The Role of Piezo1 in Biomechanical Stretching of the Small Bowel*

Mentor: Martin Martin, MD, MPP

Personal Statement: As a budding physician scientist, I have always been particularly motivated to understand, treat, and manage children born with congenital anomalies, malformations and postnatal insults that can occur in the gastrointestinal tract. Prior to medical school, I pursued an opportunity to work with Drs. Michael Harrison and Tippi MacKenzie at the UCSF Fetal Treatment Center. I specifically studied the potential role of maternal-fetal cell trafficking and presence of cytokines in various congenital anomalies including congenital diaphragmatic hernia (CDH) and gastroschisis. During medical school, my growing scientific curiosity subsequently led me to pursue an opportunity to

spend a summer at the Karolinska Institute in Stockholm, Sweden in order to further my experience in tissue engineering and use of stem cells, specifically working with the diaphragm and esophagus, and gained valuable skills to apply for my subsequent research pursuits. Since starting my neonatology fellowship, I have been fortunate enough to have Dr. Martin G. Martin as my mentor, who has done exciting work with intestinal disorders that can specifically affect the neonatal population. The aim of my project has been to further our understanding of the mechanical and functional properties of the intestinal tract, specifically looking at the role of Piezo1 in the mechanotransduction induced growth and adaptation of the intestine. My overarching goal in my research is to establish novel targets for potential new therapies and solutions in neonates suffering from short gut syndromes, small bowel obstruction (SBO), GI anomalies and motility disorders. The Marshall Klaus Award will help me with these goals and open up new opportunities to continue my trajectory as a physician scientist in Neonatology.

Abstract: This project is looking at the role of Piezo1 in the gastrointestinal tract. Piezo1 is a recently discovered mechanosensitive cation channel that has been implicated in stretch induced changes in other mechanosensitive tissues. Our preliminary data suggests that Piezo1 in the smooth muscle cells of the small bowel of humans and mice is important for the maintenance of regular, rhythmic SMC contractions/Ca2+ flux particularly when the muscularis is acutely stretched. In the *in vivo* setting, Piezo1 expressed in smooth muscle cells partly mediates epithelial, crypt and stem cell expansion during homeostatic and chronic stretched conditions. This data improves our understanding of how mechanosensitive channels mediate stretch induced contractions, and this may have implications for future therapies for patients with small bowel obstruction (SBO) and/or short bowel syndrome (SBS). We will continue to further elucidate the role of Piezo1 in the other layers of the GI tract specifically in the epithelium and determine its role in specific disorders associated with intestinal dysmotility.

Danielle Callaway, MD, MPH

Children's Hospital of Philadelphia, Philadeplphia, PA

Title: *Epigenetic Mechanisms of Alveolar Epithelial Cell Plasticity and Injury Susceptibility in Bronchopulmonary Dysplasia*

Mentor: Edward Morrisey, PhD

Personal Statement: My overall goal is to become a clinician-scientist who can translate experiences with patients in the neonatal intensive care unit into novel findings in the laboratory, particularly involving pulmonary diseases such as bronchopulmonary dysplasia (BPD). My scientific career thus far in graduate school and residency has revolved around exploring how oxygen and oxidative stress can lead to pathology in various organ systems. As a Neonatal-Perinatal Medicine fellow at the Children's Hospital of Philadelphia, I have the opportunity to further my knowledge of oxygen-induced pathology and neonatal pulmonary disease in the laboratory of Dr. Edward Morrisey. Here, I will be well-equipped to answer important questions on pulmonary regeneration and alveolar epithelial cell plasticity in a model

of BPD. I will expand my scientific skill set to include the thoughtful use of specific transgenic mouse models to address cell fate after injury. Further, I will have access to the laboratory's incredible expertise in next-generation sequencing and single-cell bioinformatics with a large repository of shared data in both mouse and human tissue. Through the work on this project, I will also examine how epigenetics contributes to alveolar epithelial cell fate, helping to lay the groundwork for a new area of exploration in the laboratory. Support from the Marshall Klaus Award will help me continue along my path in becoming a productive and compassionate neonatal clinician-scientist that can use my work to positively impact the outcomes of premature infants.

Abstract: Bronchopulmonary dysplasia (BPD) is a chronic respiratory disease of premature neonates characterized by arrested alveolar development. Survivors of BPD have life-long sequelae, including increased susceptibility to respiratory pathogens, but the underlying mechanisms are not fully understood. Neonatal mice exposed to hyperoxia represent a well-studied model of BPD. Our lab is the first to show that during alveolar repair following neonatal hyperoxic injury, there is evidence of alveolar type (AT) 1 reprogramming into AT2 cells that contributes to diminished surface area for gas exchange. We hypothesize that the AT1 reprogramming induces a cellular change, possibly via epigenetic mechanisms, that contributes to altered alveolar regeneration and increased injury susceptibility secondary to viral pathogens. This project will first seek to delineate how alveolar structure is altered long-term following neonatal hyperoxia, followed by examination of alveolar epithelial cell responses after influenza infection. Lineage tracing studies of AT1 and AT2 cells as well as pulmonary function tests will be performed in animals exposed to hyperoxia and then infected with influenza either before the completion of alveologenesis (P14) or after (P60). In Aim 2, potential molecular mechanisms will be identified by examining robust data sets of single-cell RNA seq acquired from all stages of pulmonary development and mouse pups exposed to hyperoxia. Specifically, the data sets will be queried for epigenetic transcription factors since they have been shown to be important mediators during alveolar epithelial cell differentiation. Candidates will then be verified using data acquired from Aim 1 of this proposal. Identification of potential epigenetic mechanisms that lead to more severe respiratory viral infections in BPD survivors has the potential to lead to new therapeutic intervention and improve the lives of this fragile patient population.

Meredith Campbell, MD

Vanderbilt University Medical Center, Nashville, TN

Title: *Cardiopulmonary Dysfunction in Former Extremely Premature Infants*

Mentor: Eric Austin, MD, MSCI

Personal Statement: I am honored to receive the generous support of the Marshall Klaus Award, which will serve as an excellent foundation for my pursuit of an academic career as a physician-scientist. Under the guidance of my mentors Drs. Eric Austin and Jennifer Sucre, we crafted a proposal to test the central hypothesis that premature birth disrupts normal cardiopulmonary development and results in detectable right ventricular and pulmonary vascular abnormalities in mid-childhood. This project will serve as a platform from which I will gain experience in study design, grant proposals, data collection,

data analysis, and manuscript writing. In order to acquire tools essential to performing patient-oriented, hypothesis-driven clinical and translational research in an ever-changing practice environment, I am also pursuing Vanderbilt's Master of Science in Clinical Investigation (MSCI) program, a two-year program that I will complete during my fellowship. The MSCI offers a three-pronged approach to medical scientist training ideal for this point of my career: fundamental courses (e.g., epidemiology, biostatistics, and clinical trial design), mentorship, and a mentored research project. The Marshall Klaus Neonatal-Perinatal Research Award will support my professional trajectory as a physician-scientist, and will help to cultivate a productive, independently funded research career.

Abstract: Prematurity complicates approximately 10% of U.S. births, with over 400,000 premature infants born each year. Among those born prematurely, extremely low gestational age neonates (ELGANs; born before 28 weeks gestation) are at risk for significant adverse consequences of premature birth, including bronchopulmonary dysplasia, the most common lung disease of infancy. Prematurity is associated with changes in lung development, specifically decreased alveolarization, and decreased pulmonary vascular growth, which increase the risk of pulmonary hypertension during infancy—particularly among those with bronchopulmonary dysplasia or other neonatal insults. While not all ELGANs develop bronchopulmonary dysplasia, there is a growing understanding of the impact of prematurity upon the airways throughout life; however, much less is known about the cardiopulmonary consequences of premature birth beyond infancy. We propose to expand our studies of former ELGANs to test the central hypothesis that premature birth perturbs normal cardiopulmonary development, resulting in detectable right ventricular abnormalities during mid-childhood. Identification of high-risk infants earlier in their course may provide a critical window for applying therapies to prevent progressive pulmonary vascular disease and improve mortality.

Agnes S. Chao, MD

Duke University Medical Center, Durham, NC

Title: *Therapeutic Potential of Oxysterols in Neonatal White Matter Injury*

Mentor: Eric Benner MD, PhD

Personal Statement: Through research during medical school, residency, and now fellowship, I have developed an interest in basic science and translational research designed to improve the neurodevelopmental outcomes of high-risk neonates. Neonatal sepsis and chronic hypoxia are common complications of preterm birth, placing newborns at an increased risk for poor neurodevelopmental outcomes, such as cerebral palsy, profound cognitive delay, and/ or neurosensory impairment. Novel drug development in neonates is challenging due to appropriate concern for safety, thus our lab decided to look into compounds present in human maternal breast milk, such as oxysterols. In our in vitro experiments, we found that oxysterols are able to direct neural stem cells into the oligodendrocyte lineage. In our in vivo experiments we were able to show that oxysterols can rescue neonatal white matter injury both clinically and via stereological methods. In addition to expanding efficacy testing

into a human genetic background using human brain organoids through the support of the Marshall Klaus Neonatal-Perinatal Research Award, I'm also expanding efficacy testing of oxysterol-induced oligodendrogenesis into a model of neonatal hypoxia. Completion of these experiments will lead to a better understanding of the complex mechanisms of oxysterol-mediated repair in neonatal white matter injury and bring us closer to a novel and safe therapeutic strategy to prevent associated neurological deficits. I plan to continue my research under the mentorship of Dr. Eric Benner and under the support of our Duke Pediatric Departmental T32, with the goal of becoming an independent physician-scientist.

Abstract: Neonatal white matter injury (WMI) is the most common brain injury leading to poor neurologic outcomes in premature infants, such as cerebral palsy (CP), cognitive deficits, and neurosensory impairment. Risk factors include chronic hypoxia due to lung immaturity and systemic inflammatory disease resulting from sepsis, necrotizing enterocolitis, or bowel perforation. There are no treatment options available and developing novel drug therapies for neonates is challenged by appropriate concerns for safety. To address this challenge, we discovered specific breast milk-associated oxysterols that induce oligodendrocyte production from postnatal neural stem cells. Using both pharmacologic and genetic approaches, we identified sonic hedgehog signaling through its downstream effector, Gli2, as a key molecular mechanism driving oxysterol-induced oligodendrogenesis. Subsequently, we determined that treatment with 20-αHydroxycholesterol (20HC) rescues motor deficits in a mouse model of inflammatory neonatal WMI, through stimulating the production of stem cell-derived oligodendrocytes. To date, all of our work has been conducted in murine models or murine neural stem cells in vitro. The goal of this project is to understand the fate of oligodendrocyte lineages within the human brain organoid system and determine the efficacy of 20HC treatment on oligodendrogenesis in human neural stem cells. Innovative use of the recently described human brain organoid system will allow testing of 20HC in an environment that most approaches the human brain without the use of human subjects, taking us one step closer to translating oxysterols into a safe and effective therapy for neonatal WMI.

Lauren C. Frazer, MD, PhD

Brigham and Women's Hospital, Boston, MA

Title: *Role for Specialized Pro-Resolving Mediators in Recovery from Neonatal Lung Injury*

Mentor: Bruce Levy, MD

Personal Statement: My primary career goal is to become an independent investigator who conducts clinically relevant research focused on neonatal immunology and who is a leader in the field of newborn medicine. I completed a PhD in immunology as a part of the medical scientist training program at the University of Pittsburgh. I hope to apply my basic science training towards answering clinically relevant questions and to ultimately improve outcomes for neonates. My current research focus is on exploring the mechanisms utilized by a class of bioactive lipids known as Specialized Pro-Resolving Mediators (SPMs) in enhancing resolution of inflammation and recovery from tissue injury. SPMs are derived from essential fatty acids via a series of enzyme mediated steps. Exploration of these

pathways in neonates and characterization of how they function in the hyperoxia model of Bronchopulmonary Dysplasia (BPD) represents a step towards a potential new therapy for BPD where novel therapies with reduced side effects are urgently needed. I will complete this project with the mentorship of Dr. Bruce Levy at Brigham and Women's Hospital and Dr. Cami Martin at Beth Israel Deaconess Hospital. The Marshall Klaus Perinatal Research Award will provide invaluable support towards accomplishing the goals of this project.

Abstract: The overarching goal of this project is to gain a better understanding of endogenous mechanisms of resolution of inflammation and tissue recovery that occur in response to hyperoxia in neonates. Modulation of the immune response and of epithelial cell injury by a class of lipids known as Specialized Pro-Resolving Mediators (SPMs) will be explored. We will also determine how the pathways of SPM biosynthesis change over the course of development and in response to hyperoxia. Upon completion of this project, we hope to have made progress towards a novel therapy for prevention or treatment of BPD.

Lila Nolan, MD

Washington University in St. Louis, St. Louis, MO

Title: *The Immunoregulatory Role of CD11c+ Immune cells in Aryl Hydrocarbon Receptor Signaling during Necrotizing Enterocolitis*

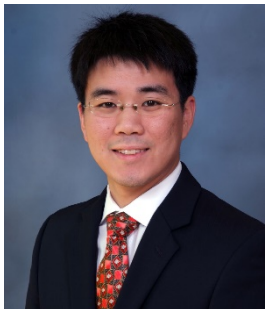
Mentor: Misty Good, MD, MS

Personal Statement: I am currently a fellow in the Neonatal-Perinatal Medicine program at the Washington University School of Medicine in St. Louis. My research interests involve the study of the cellular and molecular mechanisms involved in the pathogenesis of necrotizing enterocolitis (NEC), which remains a leading cause of high morbidity and mortality in premature neonates. I joined the laboratory of Dr. Misty Good upon starting fellowship and currently study the mechanisms by which dietary aryl hydrocarbon receptor (AhR) ligands mediate protection against intestinal inflammation using a murine model of NEC. This investigation will introduce a novel therapeutic for infants with NEC and will advance the current understanding of NEC pathogenesis. An abstract describing these findings was accepted for a platform presentation at the 2020 Pediatric Academic Society's Annual Meeting and was recognized with the SPR Basic Research Award for Fellows. I am currently supported by Dr. Gary Silverman's T32 training grant for pediatric physician-scientists at the Washington University School of Medicine. I have most recently published a manuscript in Shock entitled, "Exploring Clinically Relevant Experimental Models of Neonatal Shock and Necrotizing Enterocolitis" and in Nutrients entitled, "Immunomodulating Features of Maternal Breast Milk and Protection Against Necrotizing Enterocolitis." In the long term, I aspire a career as a neonatologist-scientist to contribute to the discovery of preventative and therapeutic factors in NEC in order to protect our most vulnerable population.

Abstract: This project aims to describe the role of aryl hydrocarbon receptor (AhR) signaling in CD11c+ immune cells during necrotizing enterocolitis. Necrotizing enterocolitis remains a leading cause of morbidity and mortality in premature infants, but the role of AhR signaling during NEC has not yet been established. We aim to use an established murine model of experimental NEC to evaluate the role of exogenous dietary ligands and cell-specific AhR knockouts on the inflammatory condition during NEC.

Timothy A. Wang, MD

Cincinnati Children's Hospital Medical Center, Cincinnati, OH



Title: *Role of IL-22 in Alveolar Repair and Regeneration in the Newborn Lung*

Mentor: Hitesh Deshmukh, MD, PhD

Personal Statement: I am a 2nd year neonatology fellow at Cincinnati Children's Hospital Medical Center. My career in research encompassed both basic science and clinical research spanning various fields. However, during my clinical pediatric training, I was drawn to the care of premature infants and began to ask a fundamental question as to why premature infants are more susceptible to infections. Previously, it had been hypothesized that the neonatal immune system was "immature", but more recent evidence has found that the neonatal immune system is rather in a unique state of development during which commensal bacteria may play a significant role. After matching into neonatology fellowship at Cincinnati, my passion to understand the basis of neonatal susceptibility and interest in the development of neonatal immunity led me to join Dr. Hitesh Deshmukh's laboratory, which has long term interest in understanding the role of commensal bacteria on the development of lung mucosal immunity. Our lab has recently shown that dysbiosis in our murine models leads to increased susceptibility to respiratory infections and that this could be reversed with interleukin (IL)-22 treatment. Along with my previous research experiences, I am now using an ex vivo model with lung organoids to help define the mechanistic pathway of IL-22 and identify potential therapeutic interventions with the goal of promoting lung healing for neonates. Along with Dr. Deshmukh, I am excited to be joined by Drs. Jeffrey Whitsett and Alan Jobe as mentors in my research and development from a neonatology fellow to an independent physician scientist.

Abstract: Bacterial pneumonia kills more than 1 million newborns each year. Increased neonatal susceptibility to pneumonia is directly linked to unique neonatal immunity, specifically lung mucosal defenses. Moreover, external factors from modern childbirth practices such as cesarean deliveries and increased use of antibiotics in early life, alter the pattern of intestinal commensal colonization in newborns, and are associated with increased risk of pneumonia. Colonization by commensal bacteria is hypothesized to be critical for postnatal development of neonate's immune system, but the underlying mechanisms remain unclear. Our laboratory recently reported that exposure to commensal bacteria immediately after birth is necessary for a robust host defense against bacterial pneumonia of neonatal mice. This crucial window was characterized by an abrupt influx of interleukin (IL)-22 producing group 3 innate lymphoid cells (IL-22+ILC3) into the lungs of newborn mice. Disruption of postnatal commensal colonization by use of antibiotics interrupted the postnatal accumulation of IL-22+ILC3 and resulted in increased susceptibility. This increased susceptibility could be reversed by either transfer of commensal bacteria after birth or by treatment with recombinant IL-22. The alveolar epithelium is composed of alveolar type I cells (AT1) that are flat and facilitate gas exchange and alveolar type II cells (AT2) that secrete surfactant. Reepithelialization of the alveolus is dependent on generation of new AT1 cells. Following epithelial destruction, the AT2 cell proliferates and differentiates into AT1 cells, thereby acting as a progenitor cell and promoting alveolar epithelial repair. AT2 cells express IL-22 receptor (IL22R) and thus represent potential targets for IL-22 signaling. These data inform the hypothesis that AT2 cells are critical targets of IL-22 in alveolar repair and regeneration following bacterial pneumonia

Newborn Medicine Education Awardee

Catherine G. Caruso, DO

Oregon Health and Science University, Portland, OR

Title: *Assessing Neonatal Delivery Room Management Using an Entrustable Professional Activity (EPA) Assessment Tool*

Mentor: Patty Carney, PhD

Personal Statement: I am currently a second year Neonatal-Perinatal Medicine fellow at Oregon Health and Science University, where I also completed my pediatric residency and chief resident year. My research interests focus on improving outcomes for neonates through clinical research, medical education (evaluation and procedural competency), and quality improvement work. I plan to pursue my passion for medical education via a career in academic medicine encompassing teaching, leadership, and research. As such, I am currently working towards a Master of Medical Education degree through the University of Cincinnati.

Neonatal resuscitation is a critical and required skill for pediatrics residents as many will go on to take positions that require delivery attendance. Unfortunately, pediatric residents site lack of opportunities for hands-on experience and presence of other providers as some of the barriers to achieving confidence and competence in delivery management. Furthermore, residency programs do not have a standardized method of assessing and monitoring

progression towards competence. This project applies an Entrustable Professional Activity (EPA) framework to delivery room management and aims to design, implement, and evaluate the effectiveness of an assessment tool in tracking pediatric resident progression towards entrustment. It is my hope that this project will increase resident participation and leadership in delivery room management, allow for assessment and tracking of competence, speed acquisition of skills, and foster independent neonatal resuscitation management.
This project integrates and builds upon my interests in education and neonatal resuscitation and allows me to develop critical research skills that will serve me in my career. I am honored to have been selected as a recipient of the Marshall Klaus Award and am grateful for the support of this award and community.

Abstract: There are a variety of barriers that prevent pediatric residents rotating through the Neonatal Intensive Care Unit from gaining adequate experience in neonatal delivery room management and resuscitation despite the importance of this skill for graduation and future independent practice. Furthermore, there is no standard method for assessing resident progression towards competency.

This project applies the work-based assessment framework of an Entrustable Professional Activity (EPA) to delivery room management via the design, implementation, and evaluation of an assessment tool. We will evaluate this tool for effectiveness in the ability to track resident progression towards competency and make entrustment decisions (awarding increased responsibility). A final component of the study aims to explore resident and assessor experiences in this pilot program through surveys and focus groups. This work will build upon and add to the growing body of literature supporting the development and implementation of EPAs.

Health Services Research Awardees

Yarden S. Fraiman, MD, MPH

Boston Children's Hospital, Boston, MA

Title: *The Impact of Race and Ethnicity on High-Risk Infant Follow-up Participation in a National Sample*

Mentor: Jonathan S. Litt, MD, MPH

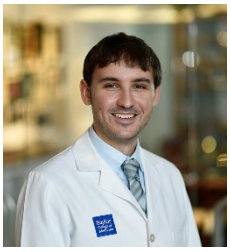
Personal Statement: My career goal is to become a physician-researcher in the field of health services research focused on racial and ethnic disparities in neonatal care. I am particularly interested in identifying system-level, modifiable factors, that contribute to, sustain, and perpetuate disparities in the field of neonatology.
While completing my residency training in the Boston Combined Residency Program at Boston Children's Hospital and Boston Medical Center, the largest safety-net hospital in New England, I witnessed firsthand the impact of community, family, socioeconomic and social factors, perhaps to a larger extent than biology, on neonatal care, health, and outcomes. There, I also learned how innovative, evidence-based, targeted interventions can make a difference in improving care and reducing disparities. I am currently a fellow in the Harvard Perinatal-Neonatal Fellowship Training Program, as well as the Harvard-Wide Pediatric Health Services Research Fellowship. Coupled with my additional training at the Harvard T.H. Chan School of Public Health where I am pursuing a Master's in Public Health, I hope to develop and utilize advanced research methods, grounded in Eco social

epidemiological theory, to identify community- and population-level modifiable social factors as unique targets for interventions to eliminate disparities and increase equity.
My current project, under the mentorship of Dr. Jonathan S. Litt, will explore racial and ethnic disparities in infant follow up program participation, a critical component of neonatal care. Our project will specifically seek to identify individual- and hospital-level factors that contribute to successful infant follow up program participation. With the support of the Marshall Klaus Award, this project will be the first step in a career that seeks to identify modifiable social factors, amenable to community and population based interventions, to close the racial- and ethnic-based gaps that continue to persist in neonatal care.

Abstract: Infant follow up programs are an essential component of the care provided to high-risk infants discharged from neonatal intensive care units (NICU). These programs are recommended by the AAP and participation is associated with increased participation in neurodevelopmental programs such as Early Intervention and also with improved long-term outcomes. Studies of neonatal care and outcomes have highlighted racial and ethnic disparities in the care of infants. Preliminary studies have identified low rates of participation in infant follow up programs and have identified racial and ethnic disparities in participation. Through the use of a national sample of high-risk infant follow up programs, we seek to explore racial and ethnic disparities in successful infant follow up program participation and examine individual and hospital level factors that contribute to disparities.

Brian C. King, MD

Baylor College of Medicine, Houston, TX



Title: *Using Wisely - Echocardiography in Preterm Infants*

Mentor: Jonathan Slaughter, MD, MPH

Personal Statement: My long-term research goal is to improve the value of neonatal patient care by incorporating utilization patterns, costs, and effectiveness data to determine the clinical utility of specific interventions and diagnostic tests and identify opportunities to reduce waste.

Abstract: Echocardiography is a highly utilized, high cost diagnostic modality responsible for almost 30% of total imaging costs in the very preterm population. In contrast, routine use of brain MRI in the preterm population has been included in national conversations about reducing wasteful spending, yet contributes less than 2% to total imaging costs in the same population. There is limited evidence in the literature assessing how clinicians use echocardiography and specifically how frequently it leads to changes in clinical management. This proposed work will utilize the Pediatric Health Information System (PHIS) database, a large billing database of US children's hospital.

Respectfully submitted by:

Joern-Hendrik Weitkamp, MD
Chair, Research Committee SoNPM