

NEC SYMPOSIUM 2019

BREAKING DOWN THE BARRIERS OF NEC PREVENTION & TREATMENT

SYMPOSIUM SUMMARY
JUNE 2 - 5, 2019



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NEC SYMPOSIUM 2019

The NEC Society presented the NEC Symposium in Ann Arbor, Michigan, June 2 - 5, 2019 with generous support from the Patient-Centered Outcomes Research Institute (PCORI), National Institute of Child and Human Development (NICHD), and Section of Pediatric Surgery at the University of Michigan. This was the second internationally attended conference hosted by the NEC Society.

The 2019 Symposium attracted 217 diverse participants from Japan, Brazil, Sweden, the United Kingdom, Australia, China, Mexico, Canada, and 30 U.S. states. Participants included neonatologists, pediatric surgeons, pediatric cardiologists, nurses, dietitians, nonprofits, industry, lactation consultants, scientists, trainees and students, 20 patient-families impacted by NEC, as well as representatives from PCORI, NICHD, the Food and Drug Administration, and Vermont Oxford Network.

Unlike other medical conferences, the NEC Symposium - like the NEC Society - is led by parents. Every participant at the NEC Symposium is valued for the unique perspective and expertise s/he brings to the NEC community. The NEC Society refers to medical conferences that fully integrate and empower all stakeholders as "All-In Meetings".

When everyone in the NEC community has a voice and we all work together, we can accomplish so much more than we can as individuals. Together, we can create a **World Without NEC!**



MOVING THE FIELD FORWARD

PROJECTS EVOLVING FROM THE 2019 NEC SYMPOSIUM

The NEC Society has established the biennial NEC Symposia to drive research that matters to patient-families who have been personally impacted by this devastating disease. A number of patient-driven projects are evolving from the NEC Symposium in Ann Arbor, including research focused on:

The label “Human Milk Fortifier”

NEC in cardiac and term babies

Long-term outcomes and NEC survivors over two years of age

Establishing a NEC Advocacy Day in Washington DC

Building the NEC Society’s Research Collaborative’s capacity to conduct patient-centered research



HUMAN CONNECTION

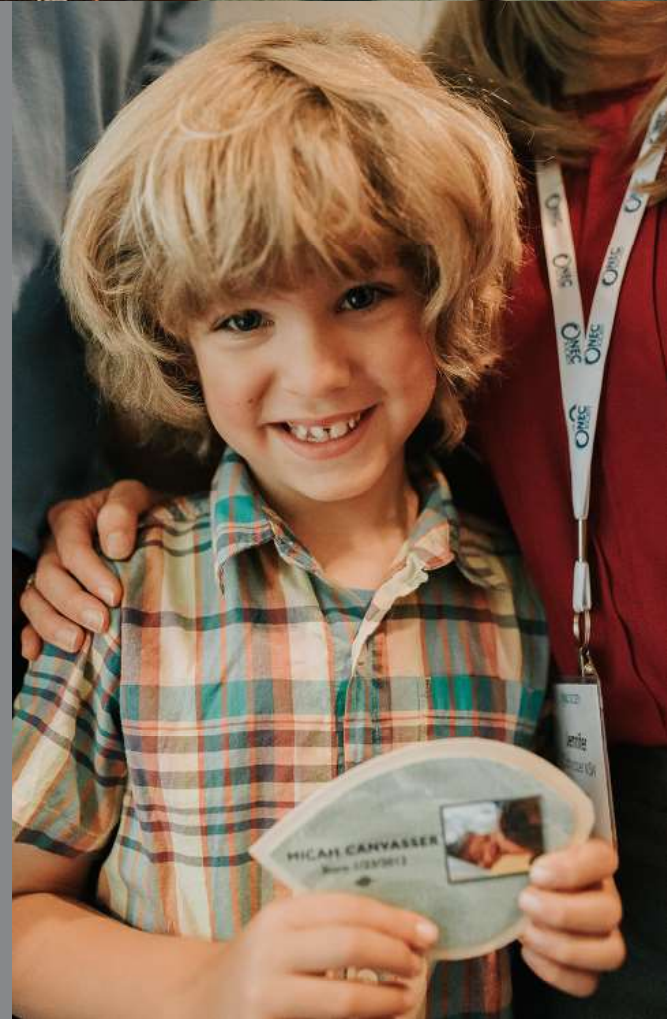
The NEC Symposium provided an inclusive venue for all stakeholders in the NEC community to connect with and learn from each other. By working together, across disciplines, we broaden our outlook and achieve more than we ever could as individuals. The Symposium united clinicians, researchers, patient-families, industry, non-profits, and others to move our work to the next level, together.





TREE OF COURAGE


The Tree of Courage display greeted all who entered the Symposium. Artist Leslie Napolitano created the original Tree of Courage painting to honor her grandson, who was lost to the disease, and all who cared for him. The painting now represents all of the babies and families who face this devastating disease and the incredible providers who care for them. Each leaf on the Tree honors a baby impacted by NEC, humanizing the disease, and reminding all of us why we do this work.



DEDICATED SESSIONS

Each session at the Symposium was dedicated to a baby affected by NEC. This not only honoured those touched by this disease, but it kept all attendees focused on the true devastation of NEC and the urgency of our work.





Dedicated to Paige and Patrick Bibbee
NEC: Recent Breakthroughs and Promising
Directions

Dedicated to Desmond Boatright
Evaluating Strategies to Increase the Use of
Mothers Own Milk

Dedicated to Micah Canvasser
Opportunities for the Federal Government to
Help Advance NEC Research

Dedicated to Brooks Cavellini
NEC Risk: Early Identification and Risk
Stratification

Dedicated to Sophie Clinick
Advancing the Needs of Patient-Families
through the NEC Society Research Collaborative

Dedicated to Elijah Correa
Innovative Quality Improvement Projects in the
NICU

Dedicated to Keaton, Dorian, and Aiden
Davis
Probiotics and NEC: What We Learn From
Experience Resulting In Litigation

Dedicated to Reid Denchik
Diagnosing NEC: Diagnostic Criteria, Proposed
Changes, and Emerging Diagnostic Tools

Dedicated to Leyden Dlugolecki
Medically Fragile Term Infants with NEC

Dedicated to Guy Ferguson
New Directions in NEC with Early Investigators
Committed to Bridging the Gap from Bench to
Bedside

Dedicated to Matilda Grant
Risks and Benefits of Probiotic Use in Fragile
Infants

Dedicated to Linseigh Green
Tools to Support Families with NEC Survivors

Dedicated to Seth Grogan
Adding Fortifier to Human Milk: How to
Optimize Safety

Dedicated to Henry Gu
Uniting Providers and Patient-Families
Towards NEC Prevention and Improved
Outcomes

Dedicated to Hope Marie Luchsinger
Advancing the Needs of Patient-Families
through the NEC Society Research
Collaborative

Dedicated to Makenna Mebane
Defining NEC: Using Patient-Family Driven
Outcome Measures

Dedicated to Lydia and Carol Nell
Mechanistic Studies into the Prevention and
Treatment of NEC

Dedicated to Sarah Rose Raab
Promising Novel Therapies for NEC in
Preclinical and Clinical Trials

Dedicated to Antonio Rosito
How Human Milk Protects Against NEC:
Breaking Down the Science

Dedicated to Kaleb and Kadence
Soash
Empowering Families and Driving Patient-
Centered Outcomes Research

Dedicated to Freddie Spruce
International Opportunities to Improve NEC
Practices and the Patient-Family Experience

Dedicated to Colton Tanner
NEC Advocacy and the Prioritization of
Resources

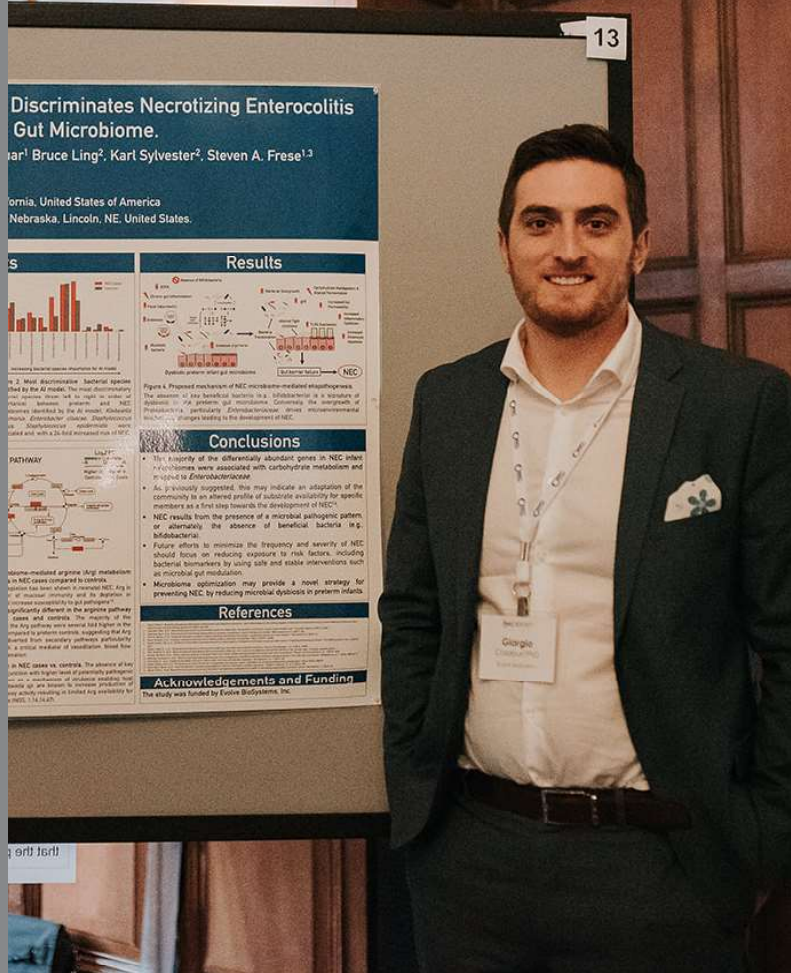
Dedicated to Charlie and Bobby
Vernon
Disparities in the Care of Fragile Infants and
Opportunities to Overcome Them

Dedicated to Lakevia Ward
NEC Biorepository: A New Tool to Improve
Our Understanding of the Disease

POSTER SESSION

The Symposium featured over 40 research posters. A wide range of exciting new work was on display. Four posters from patient-families were also integrated, sharing personal stories of NEC and providing an opportunity to learn from their experiences.

Additionally, the NEC Symposium welcomed nearly 40 trainees, with 8 of them receiving a scholarship to participate in the Symposium, thanks to funding from the R13 NICHD award. A networking dinner was held to allow this next generation of investigators to meet and network with NEC Symposium faculty.







THE NEC SOCIETY IS GRATEFUL FOR PCORI'S GENEROUS SUPPORT!

Welcome address by Anne Trontell, PCORI

The Patient-Centered Outcomes Research Institute (PCORI) is a 501(c)1 nongovernmental, nonprofit organization established by the 2010 Patient Protection and Affordable Care Act. PCORI is dedicated to advancing patient-centered outcomes research that:

Engages patients and other stakeholders throughout the research process

Seeks answers about what works best for patients, based on their concerns and circumstances

Compares the effectiveness and safety of treatment and health care delivery options

Since 2015, PCORI has served as a springboard for the NEC Society, supporting the organization in its earliest years. The NEC Society received PCORI Engagement Awards for North America's first NEC Symposium at UC Davis in 2017, as well as the NEC Symposium at the University of Michigan in 2019.

After receiving support from PCORI, the 2019 NEC Symposium also earned an R13 conference-support



grant from the National Institute of Child Health and Human Development (NICHD). With the NICHD's R13 funding, the NEC Society was able to award eight trainee travel scholarships, as well as provide an additional 27 trainees with a special registration rate.

The NEC Society and PCORI share the vision of integrating and empowering patient-families in the research process. The NEC Society is deeply grateful for PCORI's generous support and looks forward to continuing to advance research that is relevant and meaningful to our families who have been personally impacted by this devastating disease.



MECHANISTIC STUDIES INTO THE PREVENTION AND TREATMENT OF NEC

Facilitated by Steven McElroy, Agostino Pierro, and Akhil Maheshwari, with presentations from Christopher Gayer, David Hackam, Catherine Hunter, Camilia Martin, Isabelle De Plaen, Misty Good, Mark Underwood, Matthew Ralls, Doug Burrin, Venkatesh Sampath. Dedicated to Lydia & Carol Nell

NEC has been known as a disease process for the past 50 years, but we are still struggling to understand how it begins, why some babies get it, and why some babies develop more severe NEC than others. Mechanistic research in both infants and animal models is essential to furthering our understanding of NEC. This session brought together 15 scientists from across the US, Canada, and Japan to discuss their recent findings that have significance to NEC. This group of esteemed researchers ranged from new investigators to scientists who have devoted over 30 years to studying the disease. Topics discussed included understanding why neurodevelopment delays occur after NEC, understanding how feeding and IV nutrition can impact susceptibility to bowel disease, understanding the role of the blood flow in the gut to disease development, understanding the role of maintaining cellular integrity to prevent NEC, the role maternal inflammation can play in later development of NEC, the genes that may be involved in increasing the risk of developing NEC, probiotics to prevent bowel injury, and the role of anemia in development of intestinal injury.

RECENT BREAKTHROUGHS AND PROMISING DIRECTIONS

Mark Underwood

Dedicated to Paige and Patrick Bibbee

The purpose of the keynote address was to summarize some of the key breakthroughs in NEC research since the first NEC symposium at UC Davis in 2017. Over 1000 papers with necrotizing enterocolitis as a keyword have been published in that two-year period! First, the definition of NEC has been refined to improve the quality of data for clinical research. These refinements will allow the NEC community to determine the best biomarkers and the most effective preventive strategies for infants with classic preterm NEC while encouraging separate studies of spontaneous intestinal perforation, feeding intolerance, septic ileus and atypical NEC (e.g. onset before 2 weeks or after 36 weeks corrected gestational age). Second, the evidence supporting efficacy of specific interventions in preventing NEC was reviewed: delayed cord clamping (improved mortality but no impact on NEC), human milk oligosaccharides (yes in rodents, no



in piglets, unclear in humans), non-HMO prebiotics (improved mortality but no impact on NEC), lactoferrin (no), and probiotics (yes). Finally, updates on the role of the microbiota in NEC, the potential of a vaccine that could be given in pregnancy to stimulate production of protective antibodies in mom's milk, and evidence that we are making progress in reducing NEC incidence were presented.



DISPARITIES IN THE CARE OF FRAGILE INFANTS AND OPPORTUNITIES TO OVERCOME THEM

Jochen Profit, Krista Sigurdson, Lelis Vernon
Dedicated to Charles and Bobby Vernon

Racial and ethnic disparities in neonatal outcomes originate in inequities in social determinants of health, as well as differential access to quality neonatal care. Minority mothers and neonates may receive care from facilities that treat patients with poorer quality of care or may receive worse quality of care than white mothers within the same facility. Qualitative work reveals accounts of disparate care based on racial or ethnic identity among other factors that suggest disparate access to family-centered care. Increasing the use of mother's milk offers a promising avenue for alleviating disparities in NEC. Family partners are a key component of quality improvement efforts as they are able to provide experiential accounts of care delivery and practical solutions. The California Perinatal Quality Care Collaborative (CPQCC), a statewide network of NICUs and High-Risk Infant Follow-up clinics committed to improving the quality of care for vulnerable infants, is launching a health equity task force to design interventions to address the areas of inequity revealed in the literature and our research.

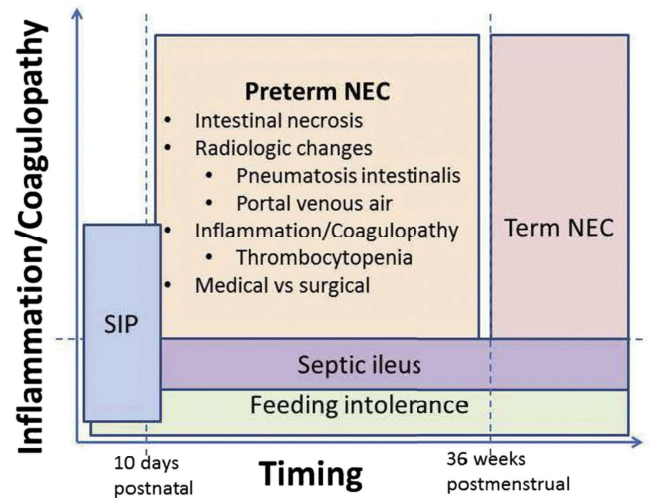
“Attending a conference with patient-family involvement was completely life-changing for me, and will have an enormous impact on my practice well beyond NEC.”
- 2019 NEC Symposium attendee

DEFINING NEC: USING PATIENT-FAMILY DRIVEN OUTCOME MEASURES

Steven McElroy, Ravi Patel, and Simone Rosito
Dedicated to Makenna Mebane

The Defining NEC session highlighted the need to improve how we apply diagnostic criteria to define NEC. The session reviewed existing NEC definitions and staging criteria and explored the importance of precise and explicit disease definitions, while acknowledging disease states often exist across a spectrum. In addition, the session highlighted why it is critical to engage patient-families in defining NEC outcome measures that can be used to evaluate NEC definitions. Drs. Patel and McElroy highlighted the limitations of Bell staging, including the presence of pneumoperitoneum resulting from spontaneous intestinal perforation, high incidence of Stage I NEC, the uncertainty around the presence of pneumatosis, and the baseline risk not being accounted for (e.g. gestational age). Dr. McElroy shared another way of thinking about and defining NEC, as presented in **Necrotizing Enterocolitis: Using Regulatory Science and Drug Development to Improve Outcomes** by Caplan, et al. Eight critical considerations for redefining NEC were presented, including:

1. Address spontaneous intestinal perforation
2. Account for the spectrum of disease
3. Differentiate infants with non-specific symptoms (e.g. Bell stage I) that are likely due to other causes.
4. Incorporate baseline-risk (e.g. risk-stratification) into definitions



5. Describe how to address uncertainty regarding the presence of pneumatosis
6. Identify better approaches to estimate pre-test probability of NEC to guide the need for additional diagnostic testing (e.g. x-ray, ultrasound)
7. Compare performance of case-definitions in classifying an important set of outcomes among infants with NEC.
8. Assessment of predictive ability of diagnostic measures to guide inclusion.

In conclusion, by engaging patient-families, we can define a set of patient-centered outcomes among infants with NEC. We can use such outcomes to compare existing NEC definitions, working towards consensus and refining existing NEC definitions.



DIAGNOSING NEC: DIAGNOSTIC CRITERIA, PROPOSED CHANGES, AND EMERGING DIAGNOSTIC TOOLS

Jae Kim, Karl Sylvester, and Cristal Grogan
Dedicated to Reid Denchik

Not only is NEC a complex, multifactorial, severe disease that develops rapidly, it is also difficult to accurately diagnose. The ability to accurately diagnose NEC is critical to providing high quality, tailored healthcare to our most vulnerable infants. Early biomarkers offer hope for identifying and preventing NEC, but unfortunately, at this point, still require years of additional research before routine utilization in the NICU. Accordingly, bowel ultrasound offers a promising and readily available tool for improving our ability to diagnose NEC. Bowel ultrasounds offer clinicians the ability to see unique features of bowel wall architecture (thickness and echogenicity, pneumatosis intestinalis) as well as bowel function (motility and blood perfusion). Yet, for many reasons, most NICUs are not using ultrasound to help diagnose NEC. Clear protocols must be established, by both the radiology and neonatal community before this diagnostic tool can be widely adopted. For this reason,

patient-families to engage in research and advocacy efforts that can help to advance the development, adoption, and integration into clinical practice of improved diagnostic approaches to NEC, such as bowel ultrasound.

RISK AND BENEFITS OF PROBIOTIC USE IN FRAGILE INFANTS

Jae Kim, Ravi Patel, Mark Underwood, Erin Umberger. Dedicated to Matilda Grant

Probiotic use varies widely in NICUs, with some routinely administering probiotics to all premature infants and others waiting for more definitive evidence or better probiotic products. In clinical trials and observational studies, probiotics have been shown to reduce the risk of NEC and death in preterm infants. Nevertheless, and for a variety of reasons, many NICUs do not routinely administer probiotics to neonates most susceptible to NEC. In light of the variability in practice regarding probiotics, it is critical to engage parents in decision-making and ensure they understand the rationale around whether their baby will receive probiotics. A concise

“Phenomenal conference! Can’t wait for the 2021 NEC Symposium!”

- 2019 NEC Symposium attendee



summary for NICU parents regarding an overview of NEC as well as the risks and benefits of human milk and probiotics can be found at NECsociety.org



NEW DIRECTIONS IN NEC WITH EARLY INVESTIGATORS COMMITTED TO BRIDGING THE TRANSLATIONAL GAP FROM BENCH TO BEDSIDE

Hala Chaaban, Misty Good, David Hackam, Troy Markel, Colin Martin, Heather Denchik, Heather Tanner. Dedicated to Guy Ferguson

To kick off this session, Misty Good presented exciting findings from her laboratory on a novel approach to preventing and treating NEC by enhancing epithelial regeneration. The Good lab has discovered that by manipulating the cytokine

environment in the intestine, the inflammatory response can be dampened during NEC, and she is working with the Food and Drug Administration to pursue a clinical trial on this new therapeutic for NEC. The next speaker, Chelsea Qinjie Zhou, discussed their studies evaluating the role of TLR4 signaling in both the intestinal epithelium and in the brain during NEC. Their work is particularly exciting because it begins to shed light on the mechanisms behind long-term cognitive impairment after NEC. Troy Markel discussed new results from his laboratory where they are evaluating the role of hydrogen sulfide as a key mediator in facilitating host protection following the mesenteric ischemia seen in NEC. To close the session, Neonatologist Hala Chaaban presented her work on how antibiotics inhibit intestinal development and increase the susceptibility to intestinal injury in neonatal mice. Dr. Chaaban highlighted how prolonged antibiotic exposure in premature infants is associated with increased mortality and necrotizing enterocolitis, emphasizing the risk of excessive antibiotic usage in neonates and the importance of antibiotic stewardship in neonatal care. Taken together, this session described new approaches from early investigators who are committed to translating their research findings from the bench to the bedside in hopes of improving outcomes for premature and medically fragile infants.

EMPOWERING FAMILIES AND DRIVING PATIENT-CENTERED OUTCOMES RESEARCH

Noah Canvasser, Heather Denchik, Linseigh Green and Mark Underwood.

Dedicated to Kaleb and Kadence Soash

This session featured personal narratives from individuals who have been impacted by NEC. Linseigh Green, a recent graduate of NYU, survived NEC as an infant and has struggled with complications from the disease throughout her life. Linseigh highlighted the lack of information and resources available to long-term survivors of NEC and the clinicians who care for these patients after two years of age. Heather Denchik, a registered nurse and mother of a young NEC survivor, helped Symposium participants realize that NEC is a lifechanging, family diagnosis. Noah Canvasser, a urologist and father who lost his 11-month-old son to complications of NEC, emphasized the importance of collaboration and empowering families. Dr. Underwood facilitated a discussion with Linseigh, Heather, and Noah,



exploring strategies to engage families in advancing patient-centered research in the NEC community. This powerful session illustrated how families live with the results of their baby's NEC diagnosis for a lifetime and has led to the NEC Society's project on long-term NEC survivors and outcomes.



EVALUATING STRATEGIES TO INCREASE THE USE OF MOTHERS OWN MILK IN THE NICU

Jennifer Canvasser, Paula Meier, Aloka Patel

Dedicated to Desmond Boatright

Mothers own milk (MOM) offers the most protection against necrotizing enterocolitis. Several strategies were presented to help optimize the use of MOM in the NICU with babies at risk of NEC. To build and protect the mother's milk supply, it is critical for clinicians to encourage

and help the mother to begin expressing milk as soon as possible after birth. Mothers should begin learning about the protective benefits of breast milk – including how it protects against NEC in vulnerable infants – as early as possible, ideally prenatally. Intensive lactation education can be essential for nurses, allowing them to serve as adjuncts to Board Certified Lactation Consultants.

Furthermore, MOM provides more than a potentially lifesaving intervention for vulnerable neonates, it can also serve as a source of empowerment for parents. In the NICU, parents must hand over nearly all of their parental responsibilities to professionals, which can further elicit parents' feelings of shame, anxiety, and guilt. Pumping and providing milk is the one thing that only parents can do for their infant. Accordingly, MOM can provide an avenue to bring parents in as a critical part of their infant's care team.

As they provide MOM, NEC Society parents have been able to better bond with their infant, build their sense of self-efficacy and confidence, while also gaining a deeper understanding of how they can contribute to their infant's care.

UNITING PROVIDERS AND PATIENT-FAMILIES TOWARDS NEC PREVENTION AND IMPROVED OUTCOMES

Roger Soll

Dedicated to Henry Gu

The Vermont Oxford Network (VON) is a nonprofit voluntary collaboration of health care professionals working together as an interdisciplinary community to change the landscape of neonatal care. Composed of 1200 units and 39 countries, VON uses the learn-measure-improve-share methodology to help improve outcomes in neonatal ICUs throughout the world, with patient-families at the center of this process.

The rate of NEC in babies within the VON database has been relatively stagnant. There has been an increased use of a peritoneal drain over the past decade; however, the mortality with surgical NEC remains around a third, compared to 20% with medical NEC and about 5% without NEC. Though the use of breastmilk at discharge has increased over time, it remains below 60% and has not changed for the past 5 years. Only about 15% of units have incorporated routine use of probiotics with their babies most vulnerable to NEC.

At 18-24 months of age, the rates of growth failure in surgical and medical NEC match those without NEC; however, the rates of severe neurodevelopment disability, medical re-hospitalization, post-discharge surgery and post-discharge tube feeds are all much greater in the population with NEC and highest with



surgical NEC. Furthermore, in “big” babies (birth weight >2500 grams), the prevalence of surgical NEC is greater than chromosomal abnormalities, sepsis, or congenital heart defects.

To decrease the rates of NEC, information on probiotic use, which has been steadily increasing, should be provided to families. As part of the NEC homeroom, the key drivers to decrease NEC were determined to be use of mother’s milk, increasing knowledge of milk composition, antibiotic stewardship, family engagement and partnership. Key measures include the family participation in rounds and human milk feeding at discharge. Finally, addressing disparities through focusing on family barriers such as transportation, mental and physical health, childcare, addiction, and social and home environments.



PROMISING NOVEL THERAPIES FOR NEC IN PRECLINICAL AND CLINICAL TRIALS

Gail Besner, Eamonn Connolly, and Ryan Raab

Dedicated to Sarah Rose Raab

This session investigated a current clinical trial of probiotic therapy for NEC followed by a description of a next generation activated bacterial therapeutic (ABT) probiotic therapy for NEC. An important area of interest in the prevention of NEC is the use of probiotics, which have the potential to alter the abnormal intestinal microbiome that exists in premature babies that develop NEC. In some parts of the world, the use of probiotics has become standard of care, however only ~15% of NICUs in the US currently use probiotics routinely.

Despite some encouraging results from both human and animal studies, there remains a significant lack of data on the use of probiotics, and there are currently no FDA approved probiotic products available for premature infants. Dr. Eamonn Connolly, Chief Scientific Officer of Infant Bacterial Therapeutics (IBT), provided

a detailed overview of the company's impressive efforts in bringing studies of *Lactobacillus reuteri* (Lr) to Phase 3 clinical trials under FDA guidance.

This multi-institutional Phase 3 randomized, double-blind, placebo-controlled clinical trial termed "The Connection Study" has the potential to lead to the first FDA approved probiotic preparation for NEC prevention in the nursery. Multiple NICUs in the US and abroad will participate in this study.

To date, all probiotic clinical trials have administered probiotics in their planktonic (free-living) state, and require multiple doses of administration to see a beneficial effect. In animal studies, Besner and colleagues have demonstrated that delivery of Lr in its biofilm state, induced by adherence of the bacteria to maltose-loaded microspheres, leads to a significant decrease in the

incidence and severity of NEC compared to delivery of free-living Lr, with decreased intestinal permeability and inflammation, beneficial alterations in the intestinal microbiome, and improvements in neurodevelopmental deficits in NEC survivors. Notably, these beneficial effects occurred after administration of only one single dose of the probiotic.

These findings support the potential for an improved next-generation microbiome therapy for NEC, with approval to begin Phase 1 human clinical trials for this therapy pending. Further information regarding promising novel therapies for NEC including promotion of intestinal microvasculature, mitigating neurological injury, identifying genetic associations, metabolomic profiling, and an important parent's perspective, will be presented in a manuscript titled, "Hope on the Horizon: Promising Novel Therapies for Necrotizing Enterocolitis" in *Pediatric Research*.



HOW HUMAN MILK PROTECTS AGAINST NEC: BREAKING DOWN THE SCIENCE

Tarah Colaizy, Christina Valentine, and Simone Rosito
Dedicated to Antonio Rosito

Compared to the term infant, the gut of a preterm baby has poor peristalsis, a leaky mucosal barrier, an impaired repair capacity and a disordered pro-inflammatory state. Human milk offers protection by promoting maturation of gut motility, increasing cell division and epithelial differentiation, and providing compounds that enhance immune function and maturity.

Human milk is primarily cells (white blood cells), sugar (oligosaccharides), lipid (gangliosides), and proteins

(growth factors, secretory IgA, lactoferrin, and lysozyme represent 30% -- compared 5% in bovine milk). Macrophages make up 40-60% of cells in the colostrum and 80-90% in mature milk with colostrum containing 1×10^5 cells compared to 1×10^3 in mature milk.

Use of colostrum increases brush border enzyme activities and gene expression changes to downregulate pro-inflammatory IL-1 alpha, IL-6, TNF-alpha, and TLR-4 in the intestine compared to TPN and formula. Secretory IgA in milk represents 25%-50% of maternal daily production and interestingly 75% is not digested but is secreted in feces. Finally, exosomes – vesicles found in human milk – are internalized by human intestinal cells, improving enterocyte proliferation and decreasing the histologic severity of NEC.

When mother's own milk is not available, pasteurized donor milk should be provided. In the DOMInO trial published in *JAMA* 2016, the incidence of NEC decreased from 6.6% to 1.7% when donor milk was used instead of formula as a supplement to mother's milk. In the 2018 Cochrane review, preterm formula had a 64% increased risk of NEC (RR 1.64, 1.03-2.61) when used instead of fortified donor milk in very low birth weight infants. Finally, using a MonteCarlo simulation, the use of breastfeeding has \$1.5 billion cost savings, with \$16 million of direct cost savings in surgical NEC alone.

OPPORTUNITIES FOR THE FEDERAL GOVERNMENT TO HELP ADVANCE NEC RESEARCH

Gerri Baer, Tonse Raju, and Jennifer Canvasser
Dedicated to Micah Canvasser

Dr. Tonse Raju discussed the need for additional funding for NEC research studies and explained some of the challenges related to conducting the clinical studies. Seven different National Institutes of Health (NIH) Institutes fund NEC research, including the National Institute of Child Health and Development (NICHD), contributing approximately 50% of NIH NEC funding. The key challenges of conducting NEC trials mirror the challenges of conducting trials in other rare diseases, including pace of recruitment, funding duration, and the need for well-conceived multi-site collaboration. Dr. Gerri Baer presented opportunities for interaction with the FDA to advance NEC research. The Orphan Product Designation program provides financial incentives to drug and biologic developers to innovate for conditions affecting less than 200,000 people per year in the United States. The Office of Orphan Product Development also offers



grants for clinical trials and natural history studies to support rare disease product development. FDA has initiatives and guidance documents to assist in incorporating the patient and family voice in the agency's understanding of clinically meaningful improvements. Both NIH and FDA help to fund and facilitate pediatric clinical trial networks, that offer trial-ready sites and help expedite studies.



PROBIOTICS AND NEC: WHAT WE LEARN FROM EXPERIENCE RESULTING IN LITIGATION

Matthew Bizzarro, Adam Masin, Jennifer Canvasser
Dedicated to Keaton, Dorian, and Aiden Davis

Matthew Bizzarro, the Medical Director of the NICU at Yale New Haven Hospital, and Adam Masin, a partner at Shipman & Goodwin LLP, spoke about the lessons that families, physicians, nurses, and product manufacturers can learn from a lawsuit resulting from the use of probiotics to prevent NEC.

Dr. Bizzarro focused on the hospital's careful decision to use probiotics, how the hospital handled the patient's case to determine that a fungal contamination had occurred, and how the hospital informed the family and regulators about the incident.

Mr. Masin concentrated on the hospital's and the FDA's investigation into the incident, and conveyed issues raised during the hospital's successful defense of the litigation relating to its use of probiotics.

"I found inspiration from the patient-families. To have a meeting, driven by patient-families, which addresses a topic in a multidimensional manner should be the "new model" to be followed. Engaging families and sharing stories, dedicating sessions, needs to become the norm."

- 2019 NEC Symposium attendee

ADDING FORTIFIER TO HUMAN MILK: HOW TO OPTIMIZE SAFETY

Amy Hair, Jae Kim, Sarah Taylor, and Cristal Grogan
Dedicated to Seth Grogan

Fortification of human milk with a multi-nutrient fortifier is an evidence-based method to protect preterm infant growth. Since preterm infant growth is positively associated with neurodevelopment, fortification is an expectation in neonatal care. A human milk-based fortifier (HMBF) added to mother's milk, which is supplemented as needed with donor human milk, allows preterm infants to receive an exclusive human milk diet. When compared to a diet of human milk supplemented with formula as needed and fortified with bovine-based fortifier (B-BF), the exclusive human milk diet has been associated with less necrotizing enterocolitis. However, a study to assess whether HMBF is associated with decreased necrotizing enterocolitis when compared to B-BF added to human milk, with no formula, has yet to be performed. Nonetheless, the potential for HMBF to protect the preterm infant has compelled numerous



centers to feed HMBF instead of B-BF to at least the most at-risk preterm infants. Parents of infants who developed necrotizing enterocolitis recommend that the label "human milk fortifier" be revised to clearly differentiate between HMBF and B-BF. It is essential for parents to be informed about fortification and the known risks and benefits.



NEC RISK EARLY IDENTIFICATION AND RISK STRATIFICATION

Sheila M. Gephart, Karl Sylvester, and Lelis Bauza'
Vernon
Dedicated to Brooks Cavellini

Necrotizing enterocolitis (NEC) can be challenging to diagnose in part because of varying presentations and early symptoms that are non-specific. Risk factors for NEC are

diverse with some being non-modifiable (gestational age, birth weight, race, growth restriction, etc.), others influenced by NICU practices (lower risk with human milk exposure, use of feeding protocols, influenced by unit NEC incidence). Communicating an infant's NEC risk to heighten concern when symptoms develop is not systematic in most NICUs. This session began with Sheila Gephart, PhD, RN, describing the cycle of rescue and how a risk score could standardize risk awareness and communication about NEC symptoms. She presented research describing the validation and testing of GutCheckNEC, one NEC risk score, and how it was related to severity of illness but was able to differentiate risk for the worst NEC from as early as the third day of life. Karl Sylvester, MD, then discussed recent peer reviewed updates to standardizing NEC diagnosis. He emphasized the need for greater definition and tools to define evolving NEC risk prior to symptoms in order to facilitate the development of NEC-preventing therapeutics. Dr. Sylvester closed by presenting promising new results in defining the composite metabolic risks of prematurity and nutritional exposures with the hope of being able to more precisely identify emerging NEC in fragile infants.

INTERNATIONAL OPPORTUNITIES TO IMPROVE NEC PRACTICES AND THE PATIENT-FAMILY EXPERIENCE

Wakako Eklund, Minseh Khashu, Agostino Pierro, and Lelis Bauza' Vernon
Dedicated to Freddie Spruce

NEC is a scourge of premature infants not only in the US, but worldwide. However, it is interesting that rates of NEC vary significantly across the globe. While the rate of NEC in the US, Canada, Italy, and Australia is around 7-9%, the rate of NEC in Japan is around 2%. There is currently little understanding why this difference occurs.

This session was dedicated to Freddie Spruce and was intended to bring together representatives from the US, Canada, England, Brazil, and Japan to discuss practices in their countries that may be unique. Topics ex-



plored included NICU size and configuration, feeding approaches, community and parental engagements, surgical approaches to NEC, and strategies to drive patient-centered NEC research on a global scale.



PRIORITIES FOR DRIVING PATIENT-CENTERED RESEARCH AND NEC PREVENTION

Jennifer Canvasser, Samir Gadepalli, Erin Umberger

The NEC Society aims to utilize the NEC Symposia to drive research and improved care practices for infants at risk of NEC. In the NEC Society's ongoing effort to build a world without this devastating disease, this closing session outlined critical next steps:

1. Build the NEC Society Research Collaborative's capacity and resources to advance NEC research.
2. Promote diversification and continuity of research by attracting new talent to the NEC field.
3. Identify and promote quality standards and best practices so we can better #preventNEC
4. Provide opportunities for NEC Society patient-families to use their voice to drive change.

In addition to these four key areas, the NEC Society will also focus on projects that improve our understanding of long-term outcomes in NEC survivors who are more than two years of age, full-term NEC, and how we can move closer to identifying and implementing universal high-quality standards of care.

Every individual attending the 2019 NEC Symposium left with a responsibility to harness the knowledge they gained during the conference to help advocate, improve care, and drive research. Only by working together, will we be able to live in a World Without NEC.

"The NEC Symposium is one of the best conferences I have ever attended. The presentations were all high-yield and very helpful."

- 2019 NEC Symposium attendee

WORKGROUPS

Workgroups were interactive sessions where all stakeholders engaged in discussions to deeply explore one topic. The goal of the workgroups was to bring forth novel ideas and approaches that will lead to new projects, research, and collaborations to move the field forward. As the NEC Society Research Collaborative builds its capacity to drive research, it will take on the workgroups' projects.

NEC Biorepository: A New Tool to Improve Our Understanding of the Disease

Facilitators: Misty Good, Sunyoung Kim, Troy Markel, Matthew Ralls, and Erin Umberger

Dedicated to Lakevia Ward

The goal of the NEC Society Biorepository is to promote, facilitate, and accelerate clinical-translational observational studies of NEC in humans. To achieve these goals, the NEC Society Biorepository, led by Dr. Misty Good, has developed the infrastructure for a NEC specimen biobank with linked clinical metadata to execute large prospective clinical studies. Dr. Good discussed how the NEC Society Biorepository has emerged to advance collaboration among institutions through the shared use of biologic samples in the dedicated pursuit of molecular indicators of disease and to gain greater pathophysiologic insights through research. Drs. Good and Kim have collaborated on a prospective biomarker discovery project that has already led to two grant applications and three manuscripts. Importantly, Erin Umberger also discussed the parental perspective on involvement in research studies. Having parents' input on everything from study design to the consent form can be extremely helpful. Additionally, communication back to the families after enrollment with any findings, outcomes, and manuscripts is essential to them. We will promote our published collaborative studies on the NEC Society Biorepository website to help facilitate communication and provide a "Year in Review" update for families. In summary, the NEC Society Biorepository will provide a comprehensive framework for sharing biological samples and clinical data through a robust and secure system that supports the investigation of large translational research studies on NEC, while integrating the family perspective in our approach.



Innovative Quality Improvement Projects in the NICU

Facilitators: Minesh Khashu, Robert E. Schumacher, and Ryan Raab

Dedicated to Elijah Correa

The QI workgroup improved understanding of how to use quality improvement projects to prevent and improve NEC outcomes. Participants utilized a Driver Diagram to explore primary and secondary drivers and priorities. A driver diagram is the visual representation of shared knowledge and explores all possible aspects that may impact on success for delivering a particular smart aim. Participants developed various change ideas and appropriate metrics. Drs. Khashu and Schumacher have offered on-going support via email to interested teams who are interested in advancing their QI and NEC work. Recommended priorities include developing a driver diagram to cover all aspects of QI work in relation to NEC, improving human milk and colostrum use, minimizing intestinal dysbiosis (less unnecessary antibiotic use, H2 blockers etc), standardizing feeding regimens, exploring the routine use of probiotics, adopting the early use of ultrasound for NEC diagnosis, and empowering patient-families with adequate information so they can contribute as a member of their baby's care team.

NEC Advocacy and the Prioritization of Resources

Facilitators: Samir Gadepalli, Camilia Martin, Heather Denchik, Heather Tanner

Dedicated to Colton Tanner

Parents need adequate information about necrotizing enterocolitis, including the potential risks and protective factors as early as possible. The common experience of learning about these issues as they are experienced disarms the family and medical team in proactively advocating for the best medical care. Furthermore, the resources and funding dedicated to understanding, preventing, and treating NEC has been inadequate for decades. To improve outcomes for our most vulnerable neonates, we will need to collect and publish structured, compelling data, and utilize the patient-family voice to increase the visibility of NEC on a national level with federal institutions that prioritize health care and research dollars, including Congress and NIH.

Advancing the Needs of Patient-Families through the NEC Research Collaborative

Facilitators: Jae Kim, Ravi Patel, Anne Trontell, Jennifer Canvasser

Dedicated to Hope Marie Luchsinger and Sophie Clinick

The NEC Society Research Collaborative, a group of about 50 diverse investigators who are committed to driving NEC research as one collective team, presents the NEC community with a unique and exciting opportunity to advance the field. This workgroup focused on identifying priority areas of research that are meaningful to families who have been impacted by NEC. Research focused on improving communication about the potential risks and protective factors, as well as specific strategies that allow parents to best contribute as a member of their baby's care team, are of high priority. Furthermore, this workgroup revealed that establishing, disseminating, and broadly implementing high quality standards of care for infant's at risk of NEC is of utmost importance to diverse NEC stakeholders.

Medically Fragile Term Infants with NEC

Facilitators: Amy Hair, Steven McElroy, Simone Rosito

Dedicated to Leyden Dlugolecki

NEC is most often seen in preterm infants. However, around 10% of infants who develop NEC are born at term. There is minimal information and resources available regarding term NEC. As a result of this session, the NEC Society will raise awareness about term NEC and Cardiac NEC. The NEC Society will develop a research project focused on term NEC and contribute to the limited literature available (currently 35 articles and very few articles about Cardiac NEC). Furthermore, a small group of parents and providers including nurses, NNPs, physicians and researchers have volunteered to create a workgroup called “Term NEC interest group” focusing on advancing the research in the field of medical fragile term infants with NEC. Providers should discuss NEC early with parents especially Cardiac infants that are at high risk for NEC. Parents of premature and medically fragile term-infants need to be empowered and informed about the risks and protective factors associated with NEC.

Tools to Support Families with NEC Survivors

Facilitators: Wakako Eklund, Sheila Gephart, Cristal Grogan, Lelis Bauzá Vernon, Linseigh Green

Dedicated to Linseigh Green

This workgroup focused on identifying core challenges and opportunities survivors face post-NEC, potential solutions to address them, and prioritizing next steps for the NEC clinical and research community. Sessions were led by Sheila Gephart, PhD, RN and Wakako Eklund, DNP, NNP-BC and invigorated by the perspectives shared by survivors, Linseigh Green, and parents of NEC survivors, Lelis Bauza' Vernon and Cristal Grogan. The workgroup included NEC survivors, survivor's parents, nurses, nurse practitioners, social workers, and physicians (both surgeons and neonatologists). Discourse centered on answering three key questions:

- 1. What specific health problems did parents and survivors navigate in the first three years after NEC?**
- 2. How would you describe the support that you received? Was it helpful and was there support you needed that you didn't get?**
- 3. Long-term, what challenges did you encounter related to healthcare, education, support and advocacy?**

Survivors and families faced challenges that extended far beyond the NICU. Linseigh Green emphasized the need for better information sharing and care coordination by stating, “My parents should have left the NICU with more than a bill.” Early on, survivors and families grappled with central line complications and infections, threats of neurodevelopmental delay, and the extreme need to fight and coordinate care across huge healthcare teams of “ologists.” Long-term these complications didn't disappear. Many experienced allergic sensitivities, bowel dysfunction, and neurological impacts. Parents experienced post-NEC traumatic stress, unavailable and ill-fit psychological counsel, and needs for information and support. From school age to young adulthood, survivors emphasized their frustration and few resources to establish credibility for one's symptoms to emergency care clinicians and educators who often knew nothing about NEC and if they did, labeled it as exclusively a problem of neonates. Survivors needed to know how to take care of themselves, make sense of and self-manage their symptoms and often found that they

needed more accessible research findings. The workgroup identified multiple solutions to address the challenges and prioritized the need for better support, better transitional care, research to examine long-term challenges, and an information campaign to increase awareness of NEC's impacts beyond the neonatal period. Plans are underway for NEC Society projects to address these priorities.





The NEC Society encouraged the Symposium's professional photographer to bring and nurse her baby anywhere, anytime throughout the meeting. The NEC Society is proud to support mothers.



Unlike other medical conferences, the NEC Symposium – like the NEC Society – is led by parents. Jennifer Canvasser and Erin Umberger co-chaired the NEC Symposium in partnership with Samir Gadepalli, MD, MS, MBA, a pediatric surgeon at the University of Michigan. Jennifer and Erin organized the minute details of the NEC Symposium, from drafting the agenda to awarding scholarships for students, residents, and fellows to attend the meeting. With support from the NEC Society’s Scientific Advisory Council, Jennifer and Erin executed a scientifically robust, clinically relevant, patient-integrated Symposium.

Every participant at the NEC Symposium is valued for the unique perspective and expertise s/he brings to the NEC community. As such, nurses, dietitians, lactation consultants, and other nonprofit organizations are valued at the NEC Symposium and recognized as fundamental to the NEC Society’s vision of a world without NEC. Patient-families are not simply included at the meeting, they are fully integrated and empowered to use their voice.

The academic, scientific, and clinical faculty and participants are expected to authentically engage with patient-families throughout the planning and implementation stages of the NEC Symposium. The faculty and participants from the scientific community universally express appreciation for this process, with many noting that no other scientific meeting has such a powerful, compelling impact. Nearly 70% of participants report planning to implement a new research project or different care practice as a result of their participation at the NEC Symposium.

In this way, the NEC Symposium is remarkably different from any other medical conference, and the NEC Society’s success can be replicated!

Those who participated in the two NEC symposia recognize the value of scientific conferences that integrate the patient-family voice and other diverse stakeholders, therefore the NEC Society has formalized a framework for other societies to model the same approach to integrating patient-families and hosting an All-In Meeting.

NEC Society's 10-steps to hosting an All-In Meeting:

1. Break down the hierarchy. Ensure everyone is empowered to participate, listen, and be heard. It is helpful for All-In Meetings to engage their faculty and participants by first name.
2. Integrate patient-families.
 - a. Start from the beginning and maintain integration throughout the planning, implementation, evaluation, and dissemination stages.
 - b. Dedicate each session to a patient or family impacted by the disease.
 - c. Pair each session with a patient-family representative. Empower that representative to contribute to the session, provide feedback on content, and/or speak from the podium. Support clinicians and researchers with tools and advice on how to integrate their patient-family representative.
 - d. Give patient-families the opportunity to ask the first question during discussions and Q&A time.
 - e. Design and feature patient-family posters to integrate among the academic posters.
 - f. Visibly honor patient-families throughout the meeting by using photos, videos, and quotes.
 - g. Empower patient-families with information, tools, and resources to build their skills and confidence. Host a pre-meeting webinar and take responsibility for ensuring your patient-families have the information and support they need to contribute to your All-In Meeting.
 - h. Foster relationships between patient-families by helping them get to know each other and serve as resources to each other. Start this process well before the face-to-face All-In Meeting and suggest tools that will help them cultivate their relationships after the meeting, including social media platforms.
 - i. Create opportunities for patient-families and researchers to collaborate on research projects.
 - j. Be mindful of word choice and how language can be interpreted by patient-families.
3. Prioritize funds to support patient-families. Select a core group of patient-families and fund their participation.

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4. Intentionally elevate the voices of women, people of color, and individuals with rare or unique experiences to share. They will bring critical insight to your All-In Meeting and exponentially advance your work.
5. Make it relevant and personal. Use real stories to draw in participants so they feel a sense of ownership and belonging. Break down technical, scientific presentations so that the meaning and implications can be understood by everyone in the room.
6. Invest in building relationships. Take the time to establish trust and rapport by hosting networking events. Promote diversification and continuity of research by attracting new talent to the field.
7. Support and include nursing mothers. Encourage mothers to bring their babies to your All-In Meeting and emphasize they are welcome to nurse anywhere, anytime.
8. Demonstrate the impact, progress, and opportunities. Use live polling tools to help participants understand the impact of their work.
9. Capitalize on the expertise in the room. Facilitate dialogue away from the podium by providing multiple and varied opportunities for informal discussion at circular tables where everyone can participate.
10. Remain receptive and responsive to constructive criticism. Create a non-judgmental culture where honesty is valued. Feedback can be difficult, but the discomfort creates an impetus for improved care practices and research.

The NEC Symposium conducted an evaluation at the conclusion of the meeting and one anonymous piece of feedback helps to illuminate how an All-In Meeting can help to humanize medicine:

“I may not remember all of the great science discussed at the meeting, but I will always remember ALL of the patient-family stories. And I will remember how the meeting made me feel and that will make me a better provider.”

All-In Meetings give us the rare opportunity to engage in face-to-face dialogue with diverse stakeholders and patient-families who share a deep and common vision. We can present the most innovative research and cutting-edge care techniques, while also feeling the real-life consequences of this disease as patient-families use their experience to advance the field. The NEC Society encourages other organizations to use the NEC Society’s 10-step guide to hosting an All-In Meeting and give their participants a transformative experience that grounds and enlightens us, and reminds every person in the room of why we are here.

Jennifer Canvasser
MSW

Samir Gadepalli
MD, MBA

Erin Umberger
M.Arch

2019 NEC Symposium Co-Chairs





THANK YOU

TO OUR EXHIBITORS!



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THANK YOU

OUR TEAM

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