Children's Foundation Research Institute

Research Matters

Spring 2024

Life-Changing Potential

First clinical trial for SCN2A treatment held at Le Bonheur Children's Neuroscience Institute

Just like other 4-year-olds, Sophia Cope enjoys being outside and watching Elmo, and her favorite colors are red, blue and green. But in one crucial way, she is one of a kind. Sophia is one of about 1,000 known cases of epilepsy caused by a mutation in the SCN2A gene. And now she is a participant in a clinical trial of the first medication to target this gene directly. If determined to be effective, this medication has the potential to change the lives of children with her diagnosis.

Sophia Cope was one of the first children to participate in the EMBRAVE study for a gene therapy that addresses a genetic epilepsy caused by a mutation in the SCN2A gene.

"This is the first time we have a therapy that we think can address the underlying cause to improve seizures and start seeing developmental improvement," said James Wheless, MD, co-director of Le Bonheur's Neuroscience Institute and principal investigator of the study. "If we can prove that it works, we can identify children who need intervention in the first week of life to stop developmental decline as early as possible."

Le Bonheur Children's is the only site in the world to enroll children in this phase of the EMBRAVE study for the medication PRAX-222 from Praxis Precision Medicines, Inc., with the goal of improving seizure control and development for children with this rare genetic epilepsy. Preliminary data has already shown success for patients with a 43% median reduction in seizures vs. baseline, an increased number of days without seizures and significant seizure reduction after just one dose.

SCN2A is the gene that directs the creation of sodium channel proteins in the brain, which control the flow of sodium ions to neurons. Mutations in the gene can cause too many or too few sodium ions to flow through the channels, causing epilepsy and developmental delay. In Sophia's case, the gene caused her brain to overproduce sodium ions.

Children with an SCN2A mutation are typically born with no symptoms but start seizing within the first few days of life. Mutation of the gene can also lead to developmental delays that are further exacerbated by the presence of drug-resistant seizures.

Thanks to the Families SCN2A Foundation, the Copes learned about the EMBRAVE trial that might address the underlying genetic mutation causing Sophia's medical conditions. And the only place in the world to participate in the trial was the hospital where their current neurologist, Amy McGregor, MD, was located — Le Bonheur Children's.

The EMBRAVE study is investigating the efficacy and safety of the medication PRAX-222. This drug is a novel treatment called an anti-sense oligonucleotide (ASO), which targets genes at the mRNA level to affect protein expression. In this case, the ASO hopes to target the SCN2A gene to decrease its expression, which would then decrease the sodium ions causing the symptoms.

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THE UNIVERSITY OF TENNESSEE HEALTH SCIENCE CENTER

Le Bonheur Children's Hospital

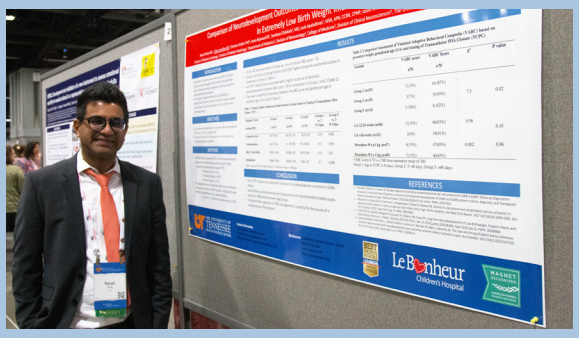
Le Bonheur Heart Institute experts present research at World Congress of Pediatric Cardiology and Cardiac Surgery

Pediatric experts from Le Bonheur's Heart Institute and the University of Tennessee Health Science Center presented lectures, posters and abstracts on recent research at the World Congress of Pediatric Cardiology and Cardiac Surgery in Washington, D.C.

The World Congress is traditionally held every four years and is a large international meeting with the goal of being the most comprehensive, up-to-date and technologically advanced meeting for pediatric and congenital heart disease. This is the first time the World Congress was held in the continental United States.

As a part of the World Congress, Le Bonheur's Heart Institute had multiple experts who presented posters of their research. This included physicians, advanced practice nurses, fellows, residents and medical students, who all have worked on research to improve the care of children in Le Bonheur's Heart Institute.

Neurodevelopment Outcomes Based on Timing of Transcatheter PDA Closure in Extremely Low Birth Weight Infants



Le Bonheur Pediatric Cardiologist Ranjit Philip, MD

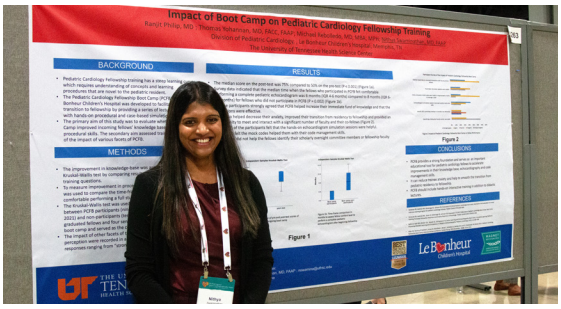
For extremely low birth weight infants with a large patent ductus arteriosus (PDA), a blood vessel in the heart that normally closes at birth, one consequence can be long-term neurodevelopment impact because of the decreased oxygen to the brain. Pediatric Cardiologist Ranjit Philip, MD, conducted a study that sought to find out if the timing of transcatheter PDA closure (TCPC) impacted the risk of a detrimental neurodevelopment outcome.

In this retrospective study, late TCPC (greater than 60 days of age) had a 38% higher incidence of poor neurodevelopment outcomes compared to younger age groups. Results showed that closing the PDA early makes a difference in the neurodevelopment of the child.

Impact of Boot Camp on Pediatric Cardiology Fellowship Training

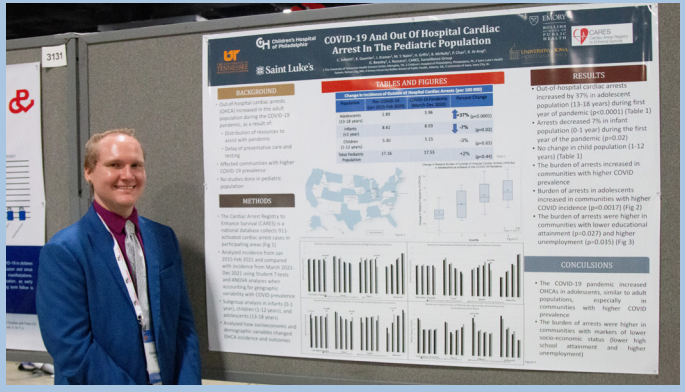
Le Bonheur's Pediatric Cardiology Fellowship Boot Camp was developed to facilitate transition to fellowship by providing a series of lectures with hands-on procedural and case-based simulations. Research from Pediatric Cardiologist Nithya Swaminathan, MD, FAAP, looked to see if the boot camp participants scored higher on a knowledge-based test and whether they were more comfortable during their transition.

Her results showed that the Pediatric Cardiology Fellowship Boot Camp provided a strong foundation for pediatric cardiology fellows to accelerate their knowledge and skills, including scoring higher on the post-test and reducing trainee anxiety during the transition from residency to fellowship.



Le Bonheur Pediatric Cardiologist Nithya Swaminathan, MD, FAAP

COVID-19 and Out of Hospital Cardiac Arrest in the Pediatric Population

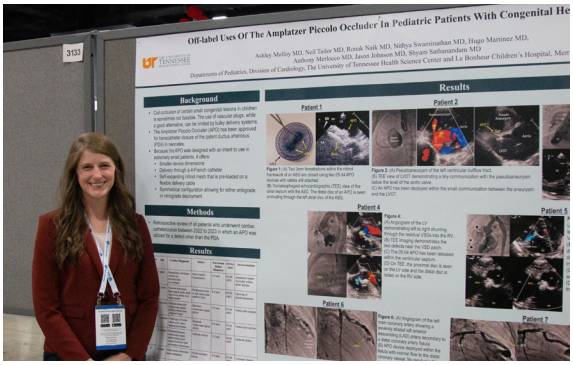


Le Bonheur Pediatric Cardiology Fellow Christopher Schmitt, MD

Out-of-hospital cardiac arrests (OHCA) increased in the adult population during the COVID-19 pandemic as a result of the distribution of resources to manage the pandemic and a delay in adults seeking preventative care and testing. Pediatric Cardiology Fellow Christopher Schmitt, MD, sought to review OHCA in the pediatric population by analyzing 911-activated cardiac arrest cases in infants, children and adolescents and then exploring how socioeconomic and demographic variables changed OHCA incidence and outcomes.

Results showed that OHCA increased by 37% in adolescents (13-18 years) and 7% in infants (0-1 years) with no change in children (1-12 years). Similar to adult populations, OHCA increased in communities with higher COVID prevalence and in communities with markers of lower socioeconomic status.

Off-Label uses of the Amplatzer Piccolo™ Occluder in Pediatric Patients with Congenital Heart Disease



Le Bonheur Interventional Cardiologist Ashley Kiene, MD

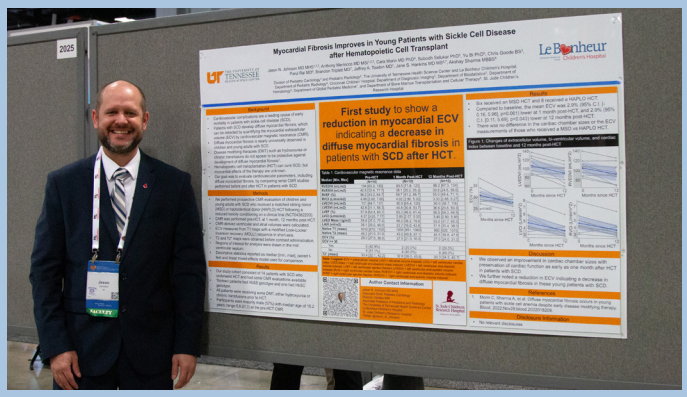
The Amplatzer Piccolo™ Occluder (APO) device has been approved for the transcatheter closure of the patent ductus arteriosus (PDA) in neonates. Le Bonheur Interventional Cardiologist Ashley Kiene, MD, reviewed patients who underwent cardiac catheterization in which an APO was used for a defect other than PDA. Because the APO was designed for very small patients, it offers advantages in its delivery and size for other heart defects.

Kiene's review showed that the device was successfully used in atrial septal defect, ventricular septal defect, coronary fistula and pseudoaneurysm, among others. The study found that APO has the potential to be an alternative to existing treatments and devices for these conditions.

Myocardial Fibrosis Improves in Young Patients with Sickle Cell Disease after Hematopoietic Cell Transplant

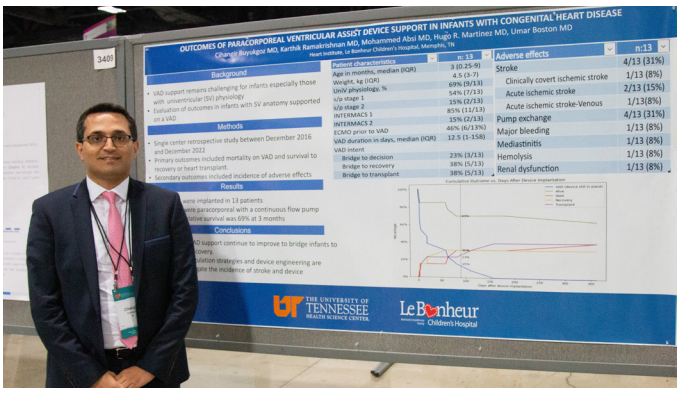
In collaboration with St. Jude Children's Research Hospital, Le Bonheur Associate Chief of Cardiology and Director of Cardiac MRI Jason N. Johnson, MD, MHS, reviewed the MRIs of 14 patients with sickle cell disease (SCD) who underwent hematopoietic cell transplantation (HCT). Patients with SCD develop diffuse myocardial fibrosis, which can be detected by measuring the myocardial extracellular volume (ECV) via cardiovascular MRI. The goal of the study was to evaluate cardiovascular parameters, including diffuse myocardial fibrosis by reviewing MRI studies before and after HCT.

The results showed a reduction in ECV indicating a decrease in diffuse myocardial fibrosis in these patients. This is the first study to show such a reduction in SCD patients after HCT. Johnson says this means the heart is remodeling and shrinking back to typical size and function after stem cell transplant.



Le Bonheur Associate Chief of Cardiology and Director of Cardiac MRI Jason N. Johnson, MD, MHS

Outcomes of Paracorporeal Ventricular Assist Device Support in Infants with Congenital Heart Disease



Le Bonheur Cardiology Fellow Cihangir Buyukgoz, MD

Ventricular assist device (VAD) support is challenging in infants but especially those with single ventricle defects. Le Bonheur Cardiology Fellow Cihangir Buyukgoz, MD, sought to evaluate the outcomes of infants on VAD with single ventricle anatomy. The primary outcomes he reviewed were mortality on VAD and survival to recovery or heart transplant, and the secondary outcomes included incidence of adverse effects such as stroke or pump exchange.

Thirteen patients were implanted with a VAD and the cumulative survival was 69% after three months on VAD. The technology available for infant VAD support continues to improve to bridge infants to transplant or recovery. Better anti-coagulation strategies and device engineering led to better outcomes and fewer adverse effects.

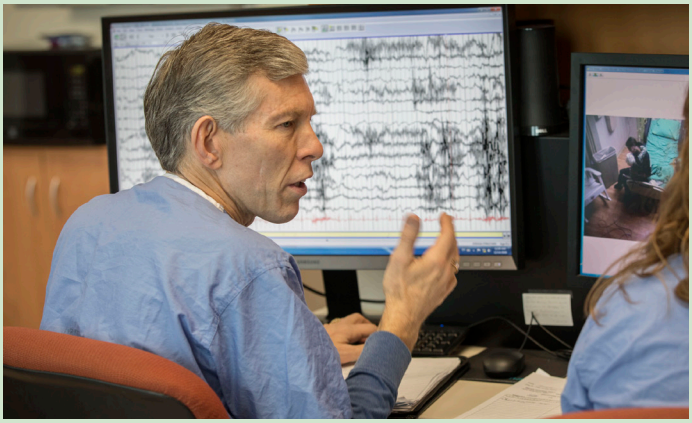
"Life-Changing Potential," continued from page 1

Delivered by intrathecal injection, trial participants will receive a dose of one milligram of PRAX-222 each month for four months. Patients are observed inpatient for at least 24 hours after the injection. Once this phase of the trial is complete, the U.S. Food & Drug Administration (FDA) will reevaluate PRAX-222 to determine if it can continue to the next phase of clinical trials.

"We have a deep track record of research in pediatric epilepsy, including intimate knowledge of taking a pre-commercial product and walking it through the regulatory phases required by the FDA," said Wheless. "We also have a system for caring for children in a clinical trial with a very well-developed multidisciplinary program and experience delivering other ASO-based therapies for genetic epilepsies."

If PRAX-222 is proved to impact the expression of the SCN2A gene, it has massive implications for children like Sophia. The drug could address the intractable seizures that occur multiple times a day. If diagnosed and treated early enough, the medication has the potential to drastically slow the developmental decline that is also associated with this gene's mutation.

"We hope that it will provide enough of a fix for Sophia that she can still grow and reach what we call 'inch-stones,' sitting up, getting rid of her trach and becoming more active," said Sophia's mom, Michaela. "It's great to think about how this can impact my child, but it's also great to be a part of something that could get answers to help others."



Le Bonheur Co-Director of the Neuroscience Institute and Chief of Pediatric Neurology James Wheless, MD, is principal investigator on the first study to address a genetic epilepsy caused by a mutation in the SCN2A gene.

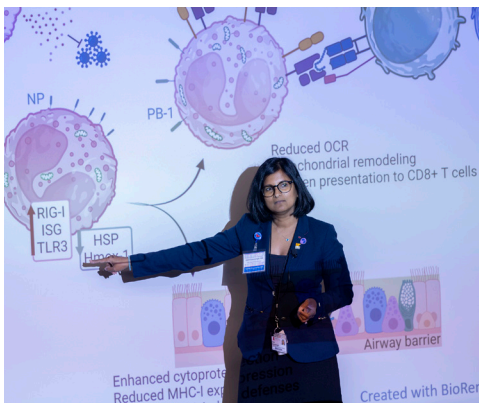
The Cope family says that they have already seen a reduction in the number and intensity of Sophia's seizures and that she is awake more and very alert.

"Sophia has become more vocal as well — I believe that she has found her voice!" said Michaela. "She has made sounds before, but not often at all. Now we get to hear her on a daily basis and even several times a day."

CFRI holds 12th annual Pediatric Research Day

Recently, Le Bonheur Children's, the University of Tennessee Health Science Center Department of Pediatrics and the Children's Foundation Research Institute held the 12th annual Pediatric Research Day led by Le Bonheur Researcher Amali Samarasinghe, PhD. This year's theme was "Research and Diversity: Superpowers When Linked." This day was an opportunity for Le Bonheur physicians and staff to come together to learn more about the groundbreaking research taking place within the institution.

This year's keynote speaker was Russell Ledet, MD, PhD, MBA, who received the James C. Hunt Visiting Distinguished Professorship. In his keynote address he shared his journey in medicine as a minority, from security guard to triple-boarded resident.



Contact us

If you have any research news or announcements you would like to include in an upcoming issue of *Research Matters*, please email Andrew Gienapp at Andrew.Gienapp@lebonheur.org.