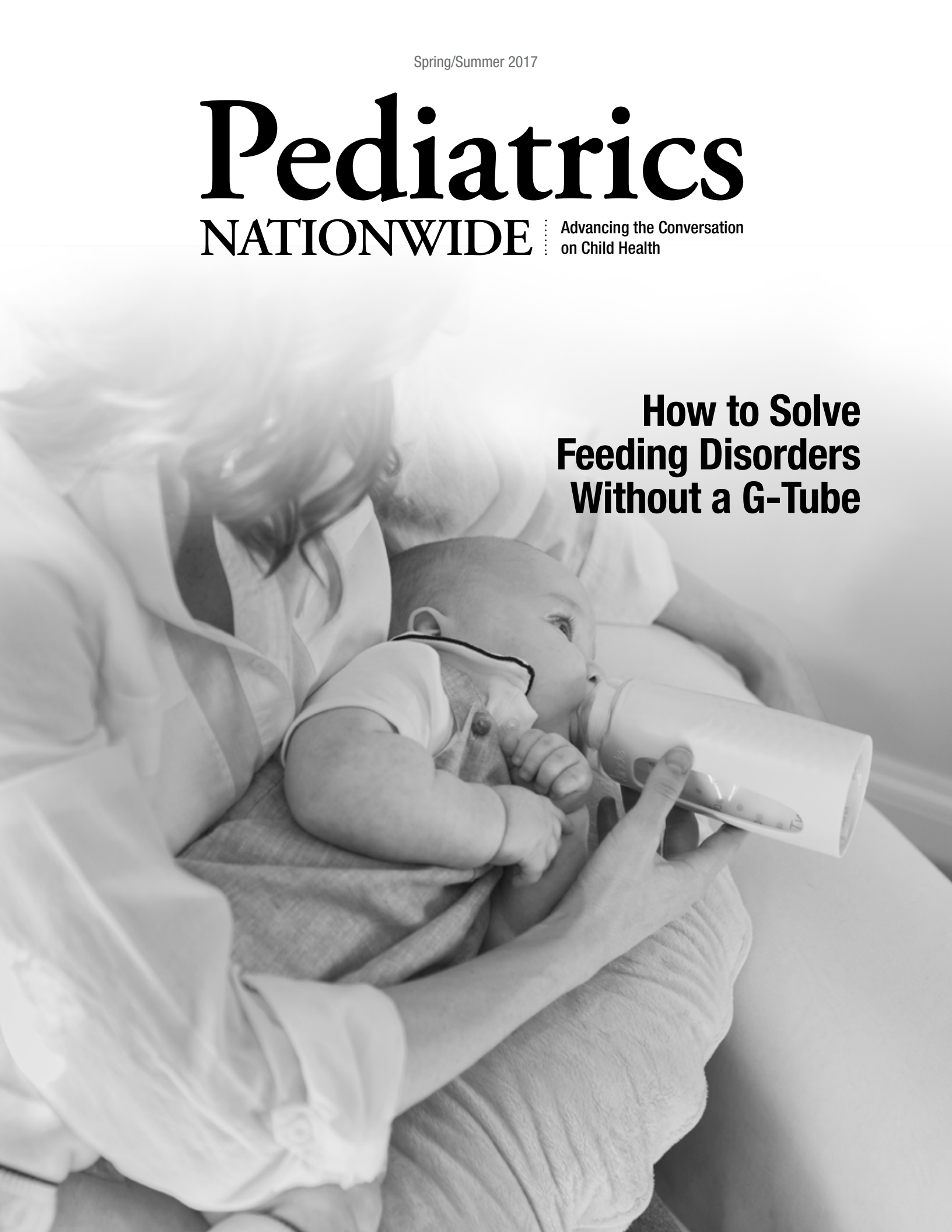
Spring/Summer 2017

Pediatrics NATIONWIDE

Advancing the Conversation on Child Health



How to Solve Feeding Disorders Without a G-Tube

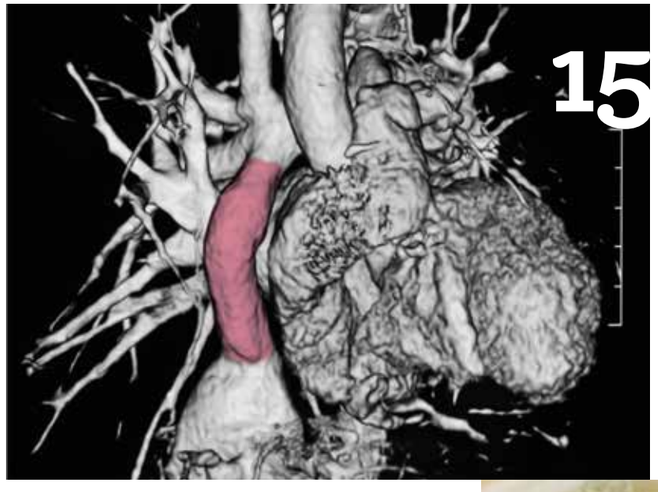
Table of Contents

18 HOW TO SOLVE FEEDING DISORDERS WITHOUT A G-TUBE

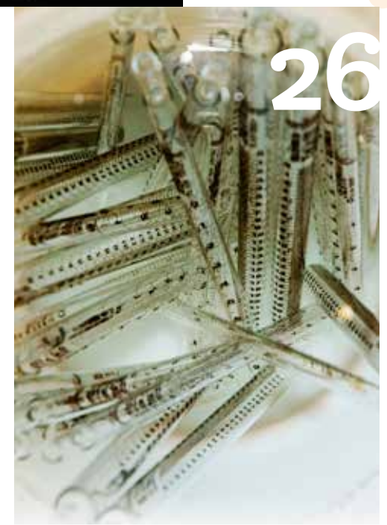
Preterm infants with feeding disorders often leave the hospital with a gastrostomy tube in place. That can lead to other problems – beyond issues in acquisition of feeding and airway protection skills, the presence of a G-tube at discharge is also associated with neurodevelopmental delays.

But innovative diagnostic tools and feeding therapies allow infants such as 8-month-old Paul Terlecky to thrive at home without a tube. Paul once had episodes of cyanosis every time he fed; now, the only modification he requires is a "side-lying" position so he can control the amount of milk he swallows.

In this issue, we explore the neonatal research that led to the tools and therapies that help Paul and infants like him.



FEATURES



DEPARTMENTS

> *Having the right people on your team can be the difference between just having a good idea and launching a successful product.*
>
> *— Christopher Shilling, MS, Director, Drug and Device Development Services, Nationwide Children's Hospital (page 29)*

> *You first have to understand what's happening when everything goes well. We do this by building models of the truly successful grafts, ones without stenosis."*
>
> *– Jay Humphrey, PhD, John C. Malone Professor of Biomedical Engineering, Yale University (page 17)*

Survey: Physical Barriers, Not Fear, Keep Homeless Youth From Receiving Care

Research survey investigates barriers to care in unstably-housed youth.

Every year, an estimated 1.6 to 1.7 million youth in the United States are living on the streets, in shelters or in other temporary living situations. Earlier studies have suggested that homeless youth do not seek medical services because of fear-based barriers – distrust of doctors, fear of being judged or misunderstood, or losing their privacy by seeking care.

However, a new survey recently published in the *Journal of Community Health* indicates that health care barriers faced by this population are not rooted in mentality but in logistics – the top cause being lack of transportation to a medical facility.

"We thought fear-based concerns would play a bigger role in youth not seeking health care," says Gayathri Chelvakumar, MD, member of the Adolescent Medicine Physician Team at Nationwide Children's Hospital and lead author of the survey. "It was surprising that it was reported so infrequently. In fact, not having transportation was an even bigger issue than cost of treatment or lack of insurance."

Dr. Chelvakumar and her team polled unstably-housed youth in three different shelters about barriers to receiving health care from a list of 14 potential choices, including "other." The responses were then classified into three categories during analysis: lack of health insurance, logistical obstacles other than health insurance, and fear-based concerns (e.g., I don't trust the doctor). The three most common responses – lack of transportation, lack of insurance, expense – fell under the first two categories.

Those who did report fear as a barrier to treatment utilized the emergency department 3.8 times more often than their peers in the past 12 months. This may be due to greater perceived anonymity and the common practice of not receiving medical attention until it becomes necessary.

"We're hoping to use this survey and further work to start creating guidelines for best practices of building programs accessible to homeless youth," adds Dr. Chelvakumar, also an assistant professor of Clinical Pediatrics at The Ohio State University College of Medicine. "Reaching these kids early can help stop homelessness now and prevent them from falling into chronic homelessness. There's currently no system at our institution to collect routinely information on patients' housing status, and part of the battle is identifying these kids so that we can connect them to resources."

"We want to make health care geographically accessible, whether that's mobile units or on-site clinics," Dr. Chelvakumar says. "I think youth input is a big piece of starting to solve this puzzle and figuring out how to offer transportation services that will be utilized. But the good news is, these are concrete issues that we can address to make sure that everyone can find their medical home."

Chelvakumar G, Ford N, Kapa HM, Lange HL, McCree AL, Bonny AE. Healthcare barriers and utilization among adolescents and young adults accessing services for homeless and runaway youth. *Journal of Community Health*. 05 Nov 2016. [Epub ahead of print]

— Brianne Moore

<5%
of youth surveyed reported fear-based barriers to seeking medical care

21%
of homeless youth have reported 4+ ED visits compared to the 9% national average (2.3 times more)

44.5%
reported using the ED or urgent care 2+ times in the past year

Does Celiac Disease Increase Risk for Functional Abdominal Pain Disorders?

Functional abdominal pain disorders (FAPDs), such as irritable bowel syndrome and functional dyspepsia, are highly prevalent around the world. In children, these disorders are associated with multiple comorbidities, poor quality of life, school absenteeism and enormous costs of care.

A recent multinational study evaluated the prevalence of FAPDs in children with celiac disease (CD) and controls found surprising results suggesting that not all types of gastrointestinal inflammation lead to FAPDs in children.

"The pathogenesis of FAPDs is not completely understood, and numerous studies in adults and children have shown that FAPDs are frequently preceded by intestinal inflammation," says Miguel Saps, MD, an attending gastroenterologist in the Division of Gastroenterology, Hepatology and Nutrition at Nationwide Children's Hospital and leader of the study, published in the *Journal of Pediatrics*. "Approximately one in three children who have a bacterial acute gastroenteritis develop FAPDs that may last for years. CD is a chronic gastrointestinal inflammation, and we were interested in establishing if CD, similarly to other sources of inflammation, predisposed children to develop FAPDs – a question that so far had no answer. The results of our study suggest that not every gastrointestinal inflammation increases the risk of developing FAPDs."

The international cohort study was a collaboration among three university hospitals in Chicago, and Messina and Verona Italy. It included three groups of 4- to 18-year-old children: (1) children with CD on a gluten-free diet for more than 6 months; (2) sibling controls without CD; and (3) unrelated controls.

"This study was an expansion of our previous work also published in the *Journal of Pediatrics*, in which we solely examined children with CD and their siblings," explains Dr. Saps, who is also the director of research in the Motility Center at Nationwide Children's. "The sample size for this study was double that, with a total of 289 children and adolescents participating from 2014 to 2015."

The Questionnaire on Pediatric Gastrointestinal Symptoms-Rome III (QPGS-RIII), which has been successfully used to identify FAPDs in children according to the Rome III criteria, was completed for each study participant. The QPGS-RIII includes questions on frequency, intensity, location and duration of GI symptoms. A validated Italian version was used in the centers in Italy.

"We found no significant difference in prevalence of chronic abdominal pain or FAPDs among children in the three groups," says Dr. Saps. "The findings of this collaborative research confirm the results of our previous, smaller study, which showed no increased risk of chronic abdominal pain and FAPDs in children with CD on a gluten-free diet compared with their siblings."

This larger prospective study sheds novel insight on FAPDs in children. "Our study suggests that the mechanisms that leads to FAPDs in children may in some cases differ from those in adults," adds Dr. Saps. "Given the high prevalence of these chronic, recurrent disorders in children, we hope to conduct additional studies to elucidate the exact mechanisms of FAPDs in children and develop prevention strategies, something that is not currently done."

Saps M, Adams P, Bonilla S, Nichols-Vinueza D. Abdominal pain and functional gastrointestinal disorders in children with celiac disease. *Journal of Pediatrics* 2013 Mar;162(3):505-509.

Saps M, Sansotta N, Bingham S, Magazzu G, Grosso C, Romano S, Pusatcioglu C, Guandalini S. Abdominal pain-associated functional gastrointestinal disorder prevalence in children and adolescents with celiac disease on gluten-free diet: a multinational study. *Journal of Pediatrics.* 2017 Mar;182:150-154.

— Tiasha Letostak, PhD

Bracing for Buckle Fractures

Shifting from casts to splints for distal radius buckle fractures has saved time and money for providers and families.

The traditional treatment for distal radius buckle fractures involves immobilization in a short- or long-arm cast. A 2015 multi-institutional study found that more than 70 percent of pediatric orthopedic specialists use this as their standard of care, and until the spring of 2016, Nationwide Children's Hospital did as well.

Research in the last decade has demonstrated that alternative, removable splinting results in similar outcomes for these stable wrist fractures, while reducing costs and eliminating the need for follow-up orthopedic visits and radiographs.

So the Department of Orthopaedics at Nationwide Children's changed its practice, in a collaborative project with Cincinnati Children's Hospital Medical Center (CCHMC). The results have been substantial.

In the five months before the project began, 20 percent of Nationwide Children's orthopedic patients with distal radius buckle fractures were treated with the removable braces. The standard of care changed in March 2016. By December 2016, more than 90 percent of patients at Nationwide Children's were treated with braces instead of casts.

A total of 231 patients were seen with buckle fractures in the first several months of the project. Applying a splint instead of a cast saved an estimated $86,118 in health care costs. This does not include the costs to families for time off work for a return visit to the orthopedic clinic.

"It's the right thing to do," says Julie Balch Samora, MD, PhD, hand and upper extremity surgeon and director of quality improvement in the Department of Orthopaedics. "Changing our practice saves money not only for families but also for the health care system. It minimizes radiation exposure, because no repeat radiographs are needed, and it eliminates any risk of cast complications. It also saves time for families, because the patients do not have to come back and see us again."

The only reason the splint rate isn't 100 percent is parent preference, according to Dr. Samora. Some families feel that because of the child's activity level, or because of sports played, a cast may offer more protection. Even for those children, orthopedic specialists at Nationwide Children's now prefer a splint, but families have the option to choose what works best for them.

Ultimately, it may be possible for children with these fractures to avoid a visit to orthopaedics altogether. A radiology report that standardizes how the fractures are described may allow the emergency department or urgent care providers to apply Velcro splints without a specialist referral. Dr. Samora is currently collaborating with the Department of Radiology at Nationwide Children's to systematically report these injuries.

— Jeb Phillips

Balancing Immune Activation and Suppression After Cardiopulmonary Bypass

Understanding how the immune system responds to CPB could dramatically impact postsurgical outcomes.

Cardiopulmonary bypass (CPB) is a relatively routine procedure, generally with favorable outcomes. However, among the risks posed to patients is the over- or under-activation of the immune system following the surgery.

Mark Hall, MD, FCCM, division chief of Critical Care at Nationwide Children's Hospital, with Ronald Bronicki, MD, FCCM, associate medical director, Cardiovascular Intensive Care Unit at Texas Children's Hospital, reviewed the common immune complications associated with CPB in the August 2016 issue of *Pediatric Critical Care Medicine*.

"The immune system becomes very activated during the process of going through the CPB machine," says Dr. Hall. "When it is in the machine, the blood is conducted through tubes made out of plastic and other synthetic materials."

Immune cells such as white blood cells and lymphocytes, as well as virtually every inflammatory pathway, become activated when in contact with these materials.

During immune activation, patients can develop systemic inflammation, the result of increased cytokine production. It is not uncommon for patients to show signs of inflammation in the immediate post-operative period, such as fever, leaky blood vessels, and organ dysfunction. Pre-existing factors, complexity of the surgery and duration of time on the CPB machine all contribute to the degree of systemic inflammation.

Additionally, this inflammation can often lead to immune suppression due to a compensatory anti-inflammatory response. This compensatory anti-inflammatory response has been demonstrated in multiple studies following CPB in children. Children who develop severe immune suppression after CPB are at increased risk for new or secondary infections in the post-operative period.

Because both the pro-inflammatory response and the compensatory anti-inflammatory response may be harmful, physicians and researchers are working to achieve a balance following CPB.

Dr. Hall says he and others are trying to understand in greater detail which patients experience severe immune suppression after CPB and who is at the greatest risk for post-operative infection and complications.

"The goal is to identify strategies that might reduce both inflammation and the immune suppression we often see after heart surgery," says Dr. Hall. "We hope to find therapies that would reduce inflammation during the procedure and its immediate aftermath. Those therapies would be short-lived and would allow the immune system to reconstitute itself quickly in the post-operative period."

Bronicli, RA, Hall M. Cardiopulmonary bypass-induced inflammatory response: Pathophysiology and treatment. *Pediatric Critical Care Medicine*. 2016 Aug;17:S272-S278.

— Mary Bates, PhD

The Maternal Microbiome: How Stress During Pregnancy Impacts Female Offspring in Adulthood

A recent study suggests a critical window of pregnancy where stress is able to influence the microbiome and intrauterine environment, with lasting behavioral consequences.

Previous research has demonstrated that stress during pregnancy changes the composition of the intestinal microbiota and is related to the emergence of behavioral disorders such as anxiety and depression.

A new study shows that microbiome changes are manifested in the mother and also found in female offspring in adulthood, with a correlation between increased maternal stress and increased anxiety-like behavior as well as cognitive alterations in adult female offspring.

"Stress during pregnancy is an adverse prenatal event that can have a negative effect on fetal neurodevelopment, with long-term behavioral impacts," says Michael Bailey, PhD, principal investigator in the Center for Microbial Pathogenesis in The Research Institute at Nationwide Children's Hospital and senior author of the study, which was published in the journal *Brain, Behavior, and Immunity*. "Stress is known to change the inflammatory state of tissues, promote the release of inflammatory mediators and cytokines from these tissues, and alter the microbiome, which has the capacity to influence behavior."

Relationships between intrauterine growth factors, hormones, and the immune system are constantly changing and essential to the healthy development of offspring, and modifications in the microbiome have been shown to impact these relationships and alter immune responses.

To elucidate whether commensal microbes are part of a maternal intrauterine environment during prenatal stress, Dr. Bailey and his colleagues examined cytokines *in utero* in both the placenta and the fetal brain of offspring.

"Interleukin-1β was increased in the placenta and fetal brain from offspring whose mothers were exposed to prenatal stress," says Tamar Gur, MD, PhD, maternal-fetal psychiatrist at The Ohio State University and first author of the study. "Since IL-1β has been shown to prevent induction of brain derived neurotrophic factor, we examined BDNF and found a decrease in the female placenta and adult amygdala, indicating an *in utero* impact on neurodevelopment that extends into adulthood."

Dr. Bailey and his team also found that gastrointestinal microbial communities differed between adult females born from stressed versus non-stressed pregnancies, and that adult female offspring exposed to prenatal stress also showed increased anxiety-like behavior and cognitive alterations.

"Our work indicates that the microbiome may be a key link between the intrauterine environment and adult behavioral changes," says Dr. Bailey, who is also an associate professor of Pediatrics at The Ohio State University. "There is a crucial time frame when stress is able to influence the microbiome and the intrauterine environment in a deleterious manner."

Dr. Gur notes that they focused on the development of anxiety-like behavior in females because anxiety is more common in women, but they plan to include data from male offspring in future studies of gestational stress.

Gur TL, Shay L, Palkar AV, Fisher S, Varaljay VA, Dowd S, Bailey MT. Prenatal stress affects placental cytokines and neurotrophins, commensal microbes, and anxiety-like behavior in adult female offspring. *Brain, Behavior, and Immunity*. 2016 Dec 24. [Epub ahead of print]

— Tiasha Letostak, PhD

In Extremely Preterm Babies, SNAP-II Score Predicts Brain Impairments at Age 10

Measures taken in first 12 hours of life are associated with a host of deficits.

Children born extremely preterm are known to be at increased risk of neurodevelopmental impairments, but not all babies born the same early date and weight are equal.

Researchers have found that for children born at less than 28 weeks, a neonatal illness severity score, The Score for Neonatal Acute Physiology-II (SNAP-II), predicts cognitive, neurological, behavioral, social and education-related deficits at 10 years of age.

The finding, by investigators of the Extremely Low Gestational Age Newborns (ELGAN) Research Study builds on earlier work showing a high SNAP-II score predicted damage found in brain scans among the same children at age 2.

This latest segment of ELGAN, a prospective observational study of 874 extreme preemies born at 14 hospitals in the Northeast, Midwest and Southeast, was recently published in the *Journal of Perinatology*.

"The association between SNAP-II and developmental impairments at 10 years was independent, after logistic regressions, from the association with gestational age," says John W. Logan, MD, a neonatologist at Nationwide Children's Hospital and lead author of the study. "That suggests physiologic instability by itself is important."

Instability reflected in SNAP-II scores is derived from common measures taken in the first 12 hours of life: urine output, presence of more than one seizure, lowest temperature, blood gas pH, blood pressure and oxygen fraction.

While the association between a SNAP-II score of 30 or more and brain damage is clear, "It's very difficult to be certain about how to interpret what we've seen," says Karl C. Kuban, MD, section chief of pediatric neurology at Boston University School of Medicine.

The researchers offer four possible explanations for the link between a high SNAP-II score and brain injuries among these children.

1. Physiologic instability may be in the causal chain between immaturity and brain injury.

2. High scores are markers for "intermediate" postnatal events, such as bacteremia/sepsis, necrotizing enterocolitis and chronic lung disease, which are associated with adverse brain outcomes.

3. SNAP-II scores convey information about immaturity/vulnerability, serving as a marker for developmentally regulated processes, such as an infant's ability to synthesize neuroprotective proteins.

4. The score is a marker for inflammation, which is developmentally regulated and puts the newborn brain at risk for multiple disturbances.

To dig further, Dr. Logan and colleagues are studying twins within the cohort. Dr. Kuban and others are studying psychiatric, behavioral and other outcomes of these patients at ages 15 and 17 while searching patients' placenta and early blood for epigenetic links.

Logan JW, Dammann O, Allred EN, Dammann C, Beam K, Joseph RM, O'Shea TM, Leviton A, Kuban KC for the ELGAN Study Investigators. Early postnatal illness severity scores predict neurodevelopmental impairments at 10 years of age in children born extremely preterm. *Journal of Perinatology*. 2017 Jan 12. [Epub ahead of print]

— Kevin Mayhood

INTERVENTION FOR MEDICALLY COMPLEX CHILDREN IMPROVES HEALTH, SAVES MONEY

THE POPULATION-BASED PROGRAM FEATURES COORDINATED CARE, EDUCATION AND FEEDING TUBE MANAGEMENT

by Kevin Mayhood

A population-based intervention for children with medical complexity in central and southeast Ohio led to fewer admissions, shorter hospital stays and a reduction of inpatient charges of nearly $11.8 million over 30 months, all while making children healthier.

Nationwide Children's Hospital and its affiliated accountable care organization, Partners For Kids (PFK), developed the quality-improvement effort, serving an average of 548 children each month, who had a neurological impairment and a percutaneous feeding tube and were covered by Medicaid.

The key steps were standardizing feeding tube management, improving family education and implementing a care coordination program within a framework that makes value of care rather than payment per service the financial incentive.

"Children with medical complexity are a challenge for families and the health care system, and they require a variety of people to help optimize their care," says Garey Noritz, MD, chief of the Section of Complex Care at Nationwide Children's and co-leader of the quality-improvement initiative. "We've found that if a system gets together and we say that we want to make a difference, we can."

Nationally, these children comprise 6.9 percent of pediatric patients receiving Medicaid but consume 40 percent of the Medicaid budget spent on children.

"The United States spends an enormous amount of money on health care and a lot are questioning whether we are spending all that money well," says Sean Gleeson, MD, president of PFK and co-leader of the initiative. "This work is focused on how can we design a system to care for each patient more effectively, give better clinical outcomes and do it in a way that requires less money."

PFK, one of the country's oldest and largest pediatric accountable care organizations, is a partnership between Nationwide Children's and more than 1,000 doctors in central and southeastern Ohio to provide care for 330,000 children covered by Medicaid. Here, community-based approaches have improved outcomes.

Ohio's Managed Medicaid plans pay a set amount per child, or capitation fee, up front to PFK. Nationwide Children's and member physicians are then responsible for allocating that money effectively to make sure all of the covered children receive the care they need.

"Generally, the better the care, the less you spend on it. But you have to be organized," Dr. Noritz says.

A study of the initiative is published in the January 2017 issue of *Pediatrics*.

To begin, patients were narrowly defined, which allowed for better tracking and reliable data. A variety of medical doctors, surgeons, nurses, neurologists, parents, administrators and dieticians were asked what would better care look like, what works, what are the current frustrations and more. As they developed the program, leaders rapidly adjusted the initiative to the realities they found.

Social workers or registered nurses were hired as care coordinators to help patients and their families navigate the health care system and reach goals delineated in each patient's treatment plan. Coordinators contacted the families at least monthly and met in person every 90 days, reassessing and updating goals each quarter.

Much of the coordinated care focused on the feeding tubes. Because the apparatus requires maintenance, different procedures for usage and an individualized nutrition plan, "they're a boondoggle for families," Dr. Noritz says. "Lots can go wrong."

Families were given structured, individualized training, including hands-on demonstrations and practice with mannequins.

Between January 2011 and December 2014, care coordinators enrolled 58 percent of the target cohort. During the first 30 months of implementation, hospital admissions for these children dropped 18 percent and average length of stay 32 percent. Total inpatient charges dropped 2.1 percent the first year, 12.2 percent the second and 15 percent during the first six months of the third.

The percentage of children with weights between the 5th and 95th percentiles, an important health marker, increased 8.2 percent.

"It shows that when you shift the model from fee for service to value-based care, that can improve things as long as the incentives are aligned correctly," Dr. Noritz says. "We incentivize better care, not more care."

The initiative was jump started with a federal grant but making care more efficient allowed the system to create a funding source that keeps the work sustainable, Dr. Gleeson says. The people hired for care coordination under the grant are now paid for from the Medicaid capitation fees and more are being hired due to the initiative's success.

"The bottom line is encouraging," Dr. Gleeson says. "We spent a lot of time and effort on this, but we felt like we did something good for the children. And it provides insight for others that there's value here."

He and Dr. Noritz, however, emphasize that each initiative must be tailored to the center and ACO involved, because all differ.

Nationwide Children's is now exploring how to bring this kind of care coordination to children covered by private health insurance.

Noritz G, Roldan D, Wheeler TA, Conkol K, Brilli RJ, Barnard J, Gleeson S. A population intervention to improve outcomes in children with medical complexity. *Pediatrics.* 2017 Jan;139(1):(e20153076).

During the first 30 months of implementation, hospital admissions for these children dropped

↓18%

average length of stay dropped

↓32%

Total inpatient charges dropped

↓2.1%

the first year

↓12.2%

the second year

↓15%

during the first six months of the third year

A NARROW FOCUS:

PERFECTING TISSUE ENGINEERED VASCULAR GRAFTS

A pair of surgeon-researchers is perfecting tissue engineered vascular grafts through bench, clinical and computational modeling studies.

by Abbie Roth

"I think the notion in translational medicine of going from bench to bedside is a little bit flawed," explains Christopher Breuer, MD, pediatric surgeon and principal investigator at Nationwide Children's Hospital. "In that any time you start to do something in humans, you're really starting all over again at some level."

For the last 23 years Dr. Breuer and Toshiharu Shinoka, MD, PhD, co-directors of the Tissue Engineering Program in The Research Institute at Nationwide Children's, have been working together to use tissue engineering techniques in congenital heart surgery. Shortly after they met at Harvard University in 1994, they developed one of the first tissue engineered blood vessels and the first tissue engineered valve.

"We were very fortunate," says Dr. Breuer. "Usually, when you try things in the laboratory they fail more often than they succeed. We were able to create functional valves and vessels in only about a year's worth of work."

Fast forward to Yale University in 2012. Drs. Breuer and Shinoka implanted the first tissue engineered vascular graft in a human patient in the United States as part of a landmark clinical trial just before moving to Nationwide Children's. Since then, Dr. Shinoka and his surgical colleagues at Nationwide Children's have implanted three additional tissue engineered vascular grafts (TEVGs) in children with single ventricle (SV) congenital heart anomalies.

"Tissue engineered vascular grafts are superior to other options for pediatric congenital heart patients for several reasons, the most important of which is the graft's growth capacity," Dr. Shinoka says. "Our grafts don't require immunosuppression or anti-rejection medications because they are made up of the patient's own cells. And they grow with the child, decreasing the number of follow-up surgeries needed with conventional grafts."

One might think the innovation stops here: the team has a working graft with growth potential in a clinical trial. But for Drs. Breuer and Shinoka, the successes in the clinic drive the bench work.

"What we learn from our patients in the clinical study is incredibly important to the bench work. While you can certainly learn a lot in theoretical and animal studies, when you get to the clinic, there's always a bit of fine tuning, some sense of starting over," Dr. Breuer says. "The ability to go back and forth between the lab and clinic is vital to our process. And that's probably the biggest distinction of our laboratory; it all sort of blends together into one project."

THE RIGHT THING FOR THE WRONG REASON

Through the combination of clinical studies and continued bench work, Drs. Breuer and Shinoka have discovered important aspects about how TEVGs respond in a human body. And they have identified the leading complication associated with TEVGs: stenosis.

After the Fontan procedure – the surgery in which the TEVG is placed – the blood flows from the heart to the body and then back to the lungs. It is oxygenated passively, not pumped through the lungs as in normal circulation.

"If narrowing of the graft occurs, less blood will flow to the lungs to be oxygenated, resulting in patients who do more poorly and have worse exercise tolerance. Having a widely open blood vessel is critical to these patients," says Dr. Shinoka. "It's the difference between children playing outside at recess or sitting on the sidelines, or worse yet, waiting for another surgery."

The team has spent 14 years studying the causes of stenosis, including the development of a mouse model.

"It might seem counterintuitive to make grafts for mice when you are already doing grafts in the clinic," says Dr. Breuer. "But there are tools available for studying mice that are simply not available in other species."

These tools and the continued bench work led to the initial discovery that they were doing the right things for the wrong reasons.

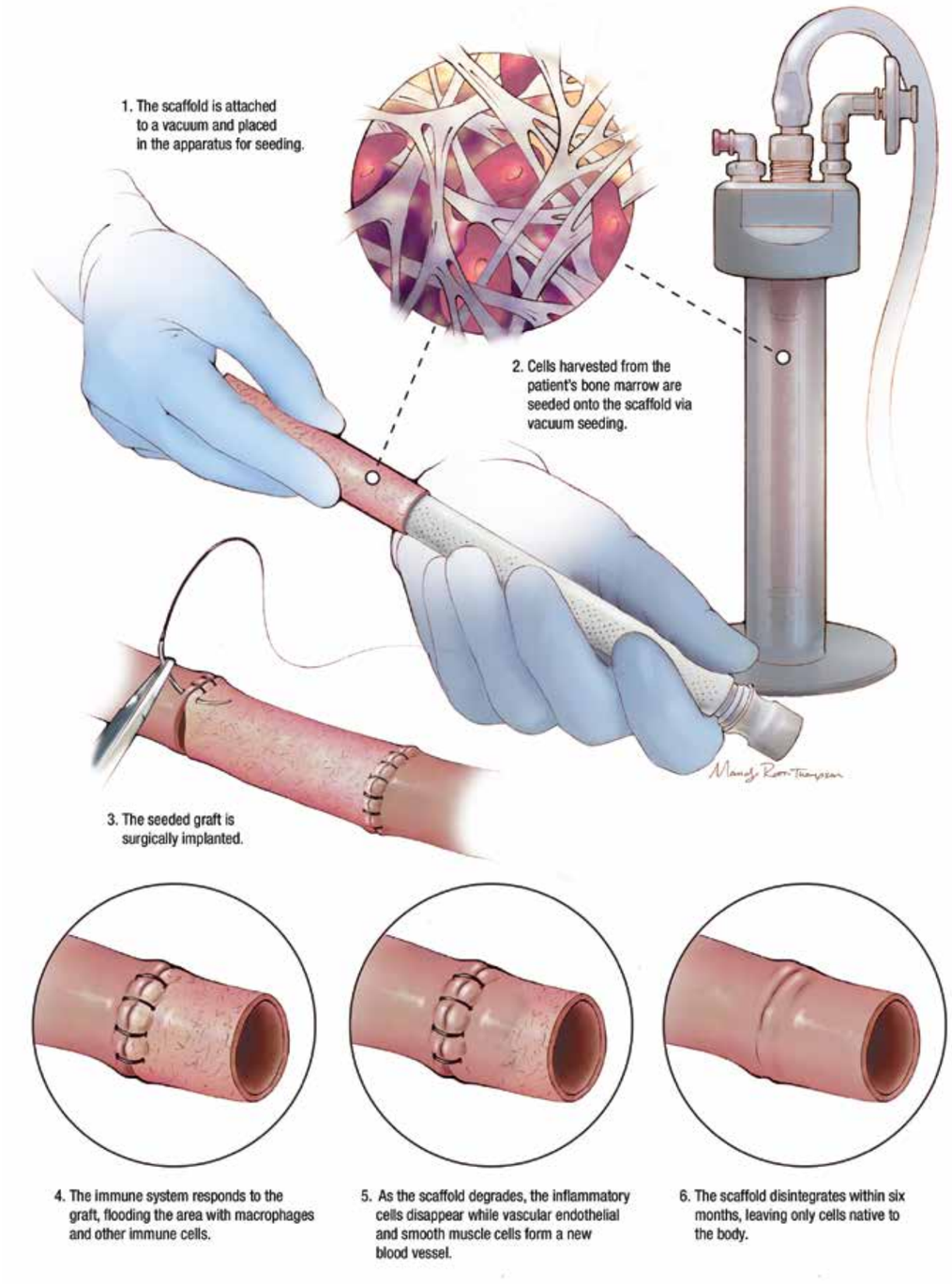
Briefly, the process of creating and implanting a TEVG involves: placing the scaffold in a vacuum, seeding it with cells obtained from the patient's bone marrow at the beginning of surgery and then placing the graft. Over the next six months, the body acts as a bioreactor to grow a new vessel. The scaffold disintegrates.

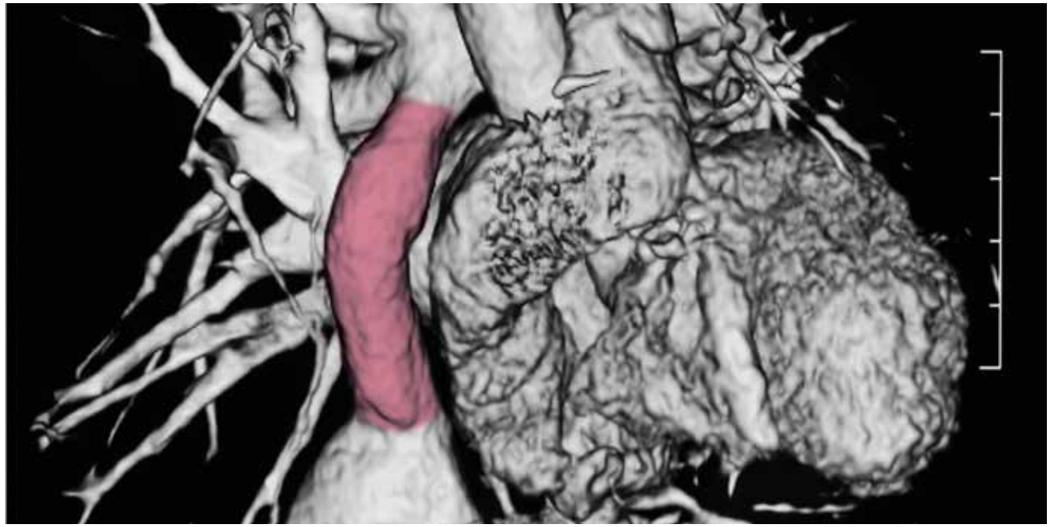
When they started, they assumed that the cells that were seeded onto the scaffold made the resulting vessel, but surprisingly, they found the host cells were the ones that made the vessel.

"WHAT WE LEARN FROM OUR PATIENTS IN THE CLINICAL STUDY IS INCREDIBLY IMPORTANT TO THE BENCH WORK. WHILE YOU CAN CERTAINLY LEARN A LOT IN THEORETICAL AND ANIMAL STUDIES, WHEN YOU GET TO THE CLINIC, THERE'S ALWAYS A BIT OF FINE TUNING, SOME SENSE OF STARTING OVER. THE ABILITY TO GO BACK AND FORTH BETWEEN THE LAB AND CLINIC IS VITAL TO OUR PROCESS. AND THAT'S PROBABLY THE BIGGEST DISTINCTION OF OUR LABORATORY; IT ALL SORT OF BLENDS TOGETHER INTO ONE PROJECT."

– Christopher Breuer, MD, pediatric surgeon and principal investigator at Nationwide Children's Hospital

SEEDING AND IMPLANTATION OF THE TEVG





Tissue engineered vascular grafts are used to create an extracardiac total cavopulmonary connection, from the inferior vena cava to the right pulmonary artery, during the Fontan procedure. The right atrium is isolated from venous return. Venous blood is passively delivered to the right pulmonary artery.

In fact, Dr. Breuer explains, "We discovered that you could make the vessels without seeding the scaffolds, but they didn't work as well and were more prone to stenosis. Our later work shows a correlation between stenosis and the number of cells seeded on the scaffold."

The scaffold is essential, but once it is in place, the body takes over and runs the show. According to Drs. Breuer and Shinoka, the cells that are the most important to the whole process are the immune cells, particularly macrophages.

"Macrophages orchestrate the whole process," says Dr. Breuer. "If you can control them, you can control vascular graft formation. It's all connected. The scaffold causes a host response. The physical and chemical properties of the scaffold affect the macrophages. The cell seeding affects the properties of the scaffold."

BLOCKING STENOSIS

In addition to understanding every component of the TEVG process, Dr. Breuer and his team have delved into learning exactly how stenosis forms.

Transforming growth factor beta (TGF-β) is a cytokine that is involved in many cellular functions, including the regulation of cell growth, proliferation, differentiation and apoptosis. It turns out, TGF-β is also integral in the formation of stenosis.

"If you block the receptor for TGF-β, you can block stenosis," Dr. Breuer says.

Another line of inquiry led to a serendipitous genetic finding. Some mice with certain mutations rarely form stenoses.

While working with mouse models, the team placed TEVGs in SCID beige mice. SCID is a mutation that essentially eliminates the immune system of the mouse. The human equivalent to the beige gene is lysosomal transport gene (LYST), which is an intracellular protein. Mutations of LYST in humans result in Chediak-Higashi syndrome, which affects many parts of the body, particularly the immune system.

"The more we used the model, the more frustrated we became. The grafts formed really well, but the stenosis I was trying to study almost never occurred," explains Dr. Breuer. "Finally I thought, 'maybe this isn't the

"YOU FIRST HAVE TO UNDERSTAND WHAT'S HAPPENING WHEN EVERYTHING GOES WELL," SAYS DR. HUMPHREY. "WE DO THIS BY BUILDING MODELS OF THE TRULY SUCCESSFUL GRAFTS, ONES WITHOUT STENOSIS."

– Jay Humphrey, PhD, John C. Malone Professor of Biomedical Engineering and chair, Yale University School of Engineering and Applied Science

problem, maybe this is the solution.' You see, it turns out that the beige mutation is very important for grafts. If you put grafts in beige mice, stenosis almost never forms. Now we're looking at how to block the beige gene, possibly with an antibody against beige protein."

REFINING THE BEDSIDE APPROACH

All of this research has led to five promising interventions that Drs. Breuer and Shinoka hope to incorporate in their clinical trial. They have submitted their data and are working with the FDA to gain approval to begin the next phase of the trial.

First, the team proposes to seed more cells on the graft before implantation. "This is fairly easy to do," says Dr. Breuer. "And we can mathematically calculate and analyze risks and benefits of altering the amount of cells seeded to reach optimization."

Secondly, they plan to address the TGF-β pathway using medications. Losartan is a clinically available medication that is already FDA approved for this patient population. The investigational drug SB431542 is still in development and, while promising, is a ways off from FDA-approval. Both drugs show promise in preventing stenosis by altering the TGF-β pathway, according to Dr. Breuer.

"The investigational drug works really well in the models," says Dr. Breuer. "But losartan is already approved and safe for this population. We've included both drugs in our petition to the FDA, but getting losartan to the clinic for the trial is likely to happen more quickly and with less risk."

Another promising drug is cilastazol, which does not target the TGF-β pathway. Instead, it targets platelets. Cilastazol is FDA-approved for adults with risk of stenosis, but it is not yet approved for use in children.

Finally, the team is working toward use of an anti-beige antibody to block the beige protein, mimicking the effect of beige genomics on the graft in the mouse model.

PERFECTING THE SCAFFOLD

In the meantime, the team continues to refine the scaffold.

"We know how important the chemical and physical properties of the scaffold are to the whole process and to how much the graft does or does not become stenotic," says Dr. Breuer. "Small adjustments to the scaffold have the potential to totally stop stenosis."

With an infinite number of ways to alter its design and structure, they looked to computational modeling and engineering principles to narrow the scope of possibilities. They partnered with Jay Humphrey, PhD, John C. Malone Professor of Biomedical Engineering and chair, Yale University School of Engineering and Applied Science, to begin a computational modeling project to describe tissue formation in the vascular graft and the body's response to the scaffold.

"You first have to understand what's happening when everything goes well," says Dr. Humphrey. "We do this by building models of the truly successful grafts, ones without stenosis."

These models will direct the future research projects to refine the design of the scaffold.

"By taking data points that are limited and finding the functional relationships that capture those data points – that describe or reflect them – we can build models that are predictive," explains Dr. Humphrey. "Once a model is validated, we can, with confidence, predict things that haven't been observed or measured."

This predictive power has the potential to move the research at a remarkable pace.

"Instead of doing a million experiments, we are letting the computers do some of the heavy lifting," says Dr. Breuer. "Then we can focus on the handful of experiments that we hope will get us to the desired result."

With a shared interest in applying engineering principles to understanding vascular function, Drs. Breuer, Shinoka and Humphrey are exploring the possibilities. By going full circle to advance the science, which ultimately advances the patient care by leaps and bounds, the team understands that the process of discovery, clinical implementation and success is a two-way street. Success is redefined by each new discovery.

"Our clinical experience with TEVGs has laid the foundation for extensive research toward the development of the ideal scaffold," says Dr. Breuer. "And our efforts to discover interventions against stenosis and optimize the scaffold design are rapidly approaching clinical translation. This is the essence of translational medicine and the hope for curing congenital heart disease."

Best C, Onwuka E, Pepper V, Sams M, Breuer J, Breuer C. Cardiovascular tissue engineering: Preclinical validation to bedside application. *Physiology.* 2016 Jan;31(1):7-15.

Hibino N, Mejias D, Pietris N, Dean E, Yi T, Shinoka T, Breuer C. The innate immune system contributes to tissue-engineered vascular graft performance. *FASEB Journal.* 2015 Jun;29(6):2431-2438.

Lee YU, de Dios Ruiz-Rosado J, Mahler N, Best CA, Tara S, Yi T, Shoji T, Sugiura T, Lee AY, Robledo-Avila F, Hibino N, Pober JS, Shinoka T, Partida-Sanchez S, Breuer CK. TGF-B receptor 1 inhibition prevents stenosis of tissue engineered vascular grafts by reducing host mononuclear phagocyte activation. *FASEB Journal.* 2016 Jul;30(7):2627-2636.

Miller KS, Khosravi R, Breuer CK, Humphrey JD. A hypothesis-driven parametric study of effects of polymeric scaffold properties on tissue engineered neovessel formation. *Acta Biomaterials*. 2015 Jan;11:283-294.

Tara S, Kurobe H, de Dios Ruiz-Rosado J, Best CA, Shoji T, Mahler N, Yi T, Lee YU, Sugiura T, Hibino N, Partida-Sanchez S, Breuer CK, Shinoka T. Cilostazol, not aspirin, prevents stenosis of bioresorbable vascular grafts in a venous model. *Atherosclerosis, Thrombosis and Vascular Biology.* 2015 Sep;35(9):2003-2010.

Drs. Breuer and Shinoka have been partners in the lab and the operating room for more than two decades. As co-directors of the Tissue Engineering Program, they lead a diverse team of scientists and surgeons in tissue engineering research spanning cardiothoracic surgery, general pediatric surgery and otolaryngology applications.

HOW TO SOLVE FEEDING DISORDERS WITHOUT A G-TUBE

By Jeb Phillips

Babies in a neonatal intensive care unit must have a safe way of receiving nutrition in order to go home. Full oral feeding is ideal, of course. But for those patients with persistent difficulty feeding by mouth, there were two primary options before 2002 to guarantee nutrients by the time of discharge.

Both had their own problems.

Option One. An infant remained an inpatient while specialists and therapists tried empiric therapy that could lead to effective feeding. Maybe an acid suppressive medication would do the trick. Maybe formula thickeners would. Few objective tests could tell providers what was underlying the baby's feeding difficulties, so doctors made educated guesses based on clinical symptoms.

Extending inpatient stays until a baby achieves oral feeds might have negative health consequences, it's expensive, and there was no way to predict how long the stay would be. In an era of medical cost containment, the first option is not much of one.

Option Two. Send the infant home eating by tube – often meaning the placement of a gastrostomy tube (G-tube) to deliver nutrition directly to the stomach. The maintenance of these tubes is associated with its own costs. They add to new parents' already considerable stress, and G-tube complications can send infants back for an inpatient stay. Crucially, a G-tube bypasses all the structures above the stomach, eliminating opportunities for a baby to develop oromotor, airway protection and related higher neural functions.

A 2016 study found that the presence of G-tube at discharge from a NICU was an independent predictor of neurodevelopmental delay at 2 years of age.

There is now a third option. Largely developed by Sudarshan Jadcherla, MD, director of the Neonatal and Infant Feeding Disorders Program at Nationwide Children's Hospital, it was 20+ years in the making. The majority of babies referred to the Nationwide Children's program since 2008 for placement of a G-tube are actually feeding by mouth at discharge.

"Not everyone can do exactly what we do, but people need to know that it is possible," says Dr. Jadcherla. "Survival of premature infants, of high-risk infants, is increasing. That is important on its own. We also need to focus on survival without morbidity, though. Our overarching, long-term vision with our feeding interventions is to improve the life of the child."

WHEN DOES A FEEDING DISORDER BEGIN?

Dr. Jadcherla, now the associate division chief of Neonatology at Nationwide Children's, started his pediatrics and pediatric gastroenterology training in Ireland, caring for children who had long-standing eating disorders.

The underlying causes were gastroenterological, neurological or cardio-respiratory, and as the child aged, behavioral components of feeding difficulties emerged. Successful therapies become more difficult to implement when all four are in play.

So Dr. Jadcherla decided to back up. He wanted to know how the neuro-gastroenterological system developed during gestation and early infancy. How does normal peristalsis even occur for a baby? How does airway protection function? What are the physiological and pathophysiological bases for airway and digestive symptoms? With answers to these and other questions, can we learn how to treat feeding issues in the neonatal time period before they become entrenched?

An early 1990s neonatology fellowship focusing on GI motility at Baylor College of Medicine, and some emerging research into neurological, airway and digestive relationships were foundational. Airways and the esophagus have common innervation, this research was showing. The gut originates early in the embryological stage, and airway and lung buds arise from that primitive gut. Stimulating the foregut means the airway and lungs can react, and vice versa.

Clinicians and researchers at the Medical College of Wisconsin, Milwaukee were pioneers in developing objective evaluations for adult swallowing and feeding disorders, including esophageal manometry. Dr. Jadcherla became a faculty member at the college and the affiliated Children's Hospital of Wisconsin in 1995, and began working to apply some adult ideas to neonates.

Among their innovations, Dr. Jadcherla and others in Wisconsin designed manometry catheters to measure esophageal motility in babies as small as 0.7 kilograms (1.5 pounds).

"At this point, I was really just trying to understand what normal looks like for infants," says Dr. Jadcherla. "We cannot objectively know what is abnormal until we understand which esophageal reflexes ensure aerodigestive protection in normal infants, or until we characterize the sensory-motor properties of these reflexes during maturation."

– Sudarshan Jadcherla, MD, director of the Neonatal and Infant Feeding Disorders Program at Nationwide Children's Hospital

"At this point, I was really just trying to understand what normal looks like for infants," says Dr. Jadcherla. "We cannot objectively know what is abnormal until we understand which esophageal reflexes ensure aerodigestive protection in normal infants, or until we characterize the sensory-motor properties of these reflexes during maturation."

In 2002, Dr. Jadcherla moved to Nationwide Children's.

CHARACTERIZING ABNORMAL

The study describing the creation of the infant-sized manometry catheter did not appear until 2003. So Dr. Jadcherla was bringing unpublished possibilities with him on his move to Ohio.

"I started working in the NICU two years before Dr. Jadcherla arrived," says Rebecca Moore, RN, and clinical research coordinator in the Innovative Feeding Disorders Research Program at Nationwide Children's. "There were no manometry studies here or anywhere else that I knew of. We didn't have many diagnostic tools that allowed us to see what feeding abilities a baby had. We only had clinical observation. A lot of babies were going home with G-tubes."

That started to change as Dr. Jadcherla continued gathering normative data at Nationwide Children's, but shifted part of his focus to characterizing abnormality in feeding. A series of studies, abstracts and presentations reported on investigations into how pharyngo-esophageal reflexes are impaired with perinatal neurological injury, in the presence of gastroesophageal reflux disease (GERD) and in infants with bronchopulmonary dysplasia (BPD).

Over the next few years, Dr. Jadcherla started formulating what was beginning to look like that third option – somewhere between an indefinite stay in the NICU and a rush to place a G-tube so a neonate could be discharged. Research from him and others suggested that a "pathophysiology-based approach" to feeding disorders was both possible and useful.

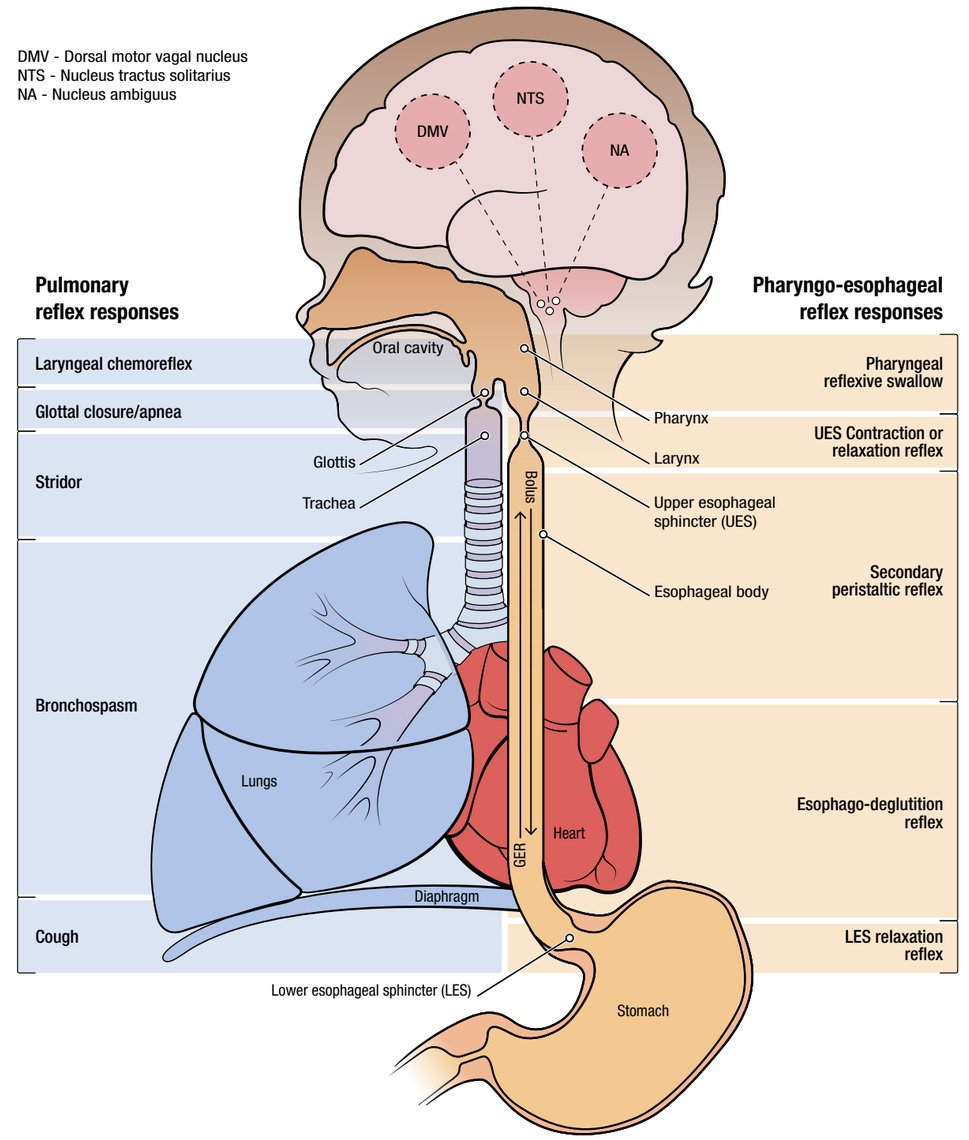
The techniques for evaluation that Dr. Jadcherla had helped create would allow specialists to map the suck-swallow-peristalsis process of an infant. The normative data he had collected would allow the abnormalities to be pinpointed: Is the issue reflux, coordination of esophageal muscles, aspiration? A combination, or something else entirely? Then a personalized therapy strategy could target the exact problems.

Dr. Jadcherla fully introduced the Neonatal and Infant Feeding Disorders Program in 2008.

PRECISION MEDICINE AT THE CRIBSIDE

When a baby is referred from the NICU with feeding problems severe enough that a G-tube may be warranted for discharge, program staff members perform a complete clinical evaluation. Special attention is paid to the volume fed, the type of feed and frequency of feeding. It's important to have a clear picture of all the feeding milestones during the patient's life, not just the current feeding situation, Dr. Jadcherla says.

Other, previously diagnosed conditions are also considered. Neurological impairment, lung disease and airway issues all may affect the neuro-aerodigestive apparatus. A video-fluoroscopic swallow study or upper GI fluoroscopy study may have already been performed, and those become



"Survival of premature infants, of high-risk infants, is increasing. That is important on its own. We also need to focus on survival without morbidity, though. Our overarching, long-term vision with our feeding interventions is to improve the life of the child."

– Sudarshan Jadcherla, MD, director of the Neonatal and Infant Feeding Disorders Program at Nationwide Children's Hospital

part of the evaluation. If they haven't been performed, they typically aren't unless a structural abnormality is suspected.

A pH impedance study is often the first diagnostic tool used for an infant referred to the program. Nearly all babies experience reflux, and GERD is a frequent clinical diagnosis when irritability, lack of weight gain or other symptoms become troublesome. The impedance study determines how acidic the refluxate is, how high it travels up the esophagus and how long it stays before a baby can clear it. A diagnosis of GERD is often made based on symptoms. These impedance studies regularly show that GERD is not the primary problem.

"GERD is diagnosed more often than it should be," says Dr. Jadcherla. "Reflux is common and can result in symptoms. Many symptoms in a premature baby appear to be troublesome because the baby has little tolerance for any symptoms. The feeding disorders themselves often have other causes."

The most in-depth study is swallow-integrated esophageal manometry with concurrent monitoring of respiration patterns, heart rate patterns and pulse oximetry. Better than any other evaluative tool currently available, this allows Dr. Jadcherla and his team to understand what happens after a bolus is introduced into the oral cavity – length and frequency of muscle contractions, reactivity to a stimulus, tone of upper and lower esophageal sphincters and, if the swallow stops before completion, where it stops.

"With this study, we are in a position to understand oral mechanics like suction and expression and peristalsis across the pharynx and esophagus," Dr. Jadcherla says.

"At the same time, we are studying airway function and heart function. We can discover where the symptoms are being caused, and we can make a treatment plan."

Sometimes, the best plan after the evaluation ends up being a G-tube anyway.

Dr. Jadcherla and colleagues have discovered and characterized important manometric markers that are associated with feeding success:

- Sphincteric response to esophageal and pharyngeal infusion
- Peristalsis induced by esophageal and pharyngeal infusion
- Secondary peristalsis induced by esophageal infusion
- Normal pharyngeal manometry
- Oral feeding challenge success
- Suck-swallow-breathe-esophageal swallow sequence

The absence of one or two of these does not mean feeding therapy will fail. The absence of most, though, suggests that a baby is not developmentally mature enough for therapies to work. A better use of time and resources would be to place a G-tube and allow the baby to grow until therapies have a better chance of making a difference, says Dr. Jadcherla.

"That can be disappointing for parents, but because we have always included parents in this decision-making process, they understand why we believe a G-tube is the appropriate option at that point," says Dr. Jadcherla. "A G-tube is not the end of our commitment to these families. In some ways, it represents the beginning. For some infants, rehabilitation cannot start until they mature and have stable breathing patterns."

When manometry and other evaluations indicate the potential for success without a G-tube, though, the feeding team begins plotting a strategy.

"REPETITION IS THE MOTHER OF SKILL"

Pharmacological treatment may be indicated in some circumstances. An acid-suppressive medication is given if the team objectively determines that reflux is abnormally acidic and is a cause of difficulties. Infants with BPD, and neurological or cardiac conditions, may have other drugs that are indicated for their diseases.

Therapy in the Neonatal and Feeding Disorders Program largely entails taking the time to fine-tune how the baby is fed by mouth and train the baby's many sucking-feeding-swallowing reflexes. That means, in the first place, adjusting volume and frequency of feeds, viscosity, nipple flow rates and caloric density.

In the second, it means a variety of occupational therapy tactics, including cue-based feeds, pacing of feeding, posture and operant conditioning.

"Repetition is the mother of skill," Dr. Jadcherla explains. "A very small quantity of oral feed can help train the neuromuscular apparatus. Even 5 mL provides the infant with sensation – taste, liquidity. The stimuli activate different neural pathways resulting in peristalsis. You must repeat these therapies to help the baby develop the neuro-aerodigestive interrelationship. You cannot try one thing, then move on to the next, without giving the baby a chance to respond."

A baby's behavioral state matters, Dr. Jadcherla says. A child using neuromuscular resources to cry is not going to focus on oral skills. A calm, bundled baby who receives eye contact from the feeder will learn more quickly.

A baby continually fed by gavage tube does not experience hunger. Hunger is a prelude to the act of feeding, so therapists adjust how often feeding occurs. A baby fed by gavage tube has also not learned to associate sucking with nutrition or the feeling of fullness. So when a tube feed does take place, a therapist may have the infant suck on a pacifier simultaneously. Sucking on a pacifier alone does not always provoke swallowing, so a small stimulus like water, milk or sucrose is included. A baby then knows that hunger, sucking, swallowing and feeling full are connected.

"Physicians and therapists can be afraid to start oral feeds, especially when infants remain on oxygen," says Moore, the research program coordinator. "We know from our own experience, and from our research, that it is developmentally appropriate, and actually good for development."

BABY PAUL

There are now nearly 100 peer-reviewed publications supporting the methods of the Neonatal and Infant Feeding Disorders Program. There is also 8-month-old Paul Terlecky.

Paul's mother, Rachel, is an emergency medicine physician at Licking County Memorial Hospital in

Paul Terlecky was born at 31-weeks gestational age and spent 8 weeks in the NICU at Kapiolani Medical Center for Women and Children before he was able to travel home to Ohio. He was fed by nasogastric tube until about a week before discharge.

"The standardized measures that Dr. Jadcherla and his colleagues gather are continuing to build toward a stronger clinical basis for treatment. I have great concerns about the variability of interpretation that still exists. We must have appropriate tests, but we also need professionals to know what they are doing with those tests."

– Joan Arvedson, PhD, program coordinator of Feeding and Swallowing Services at Children's Hospital of Wisconsin-Milwaukee

Newark, Ohio, and his father, Andrew, is an orthopedic surgeon there. The couple took a 2016 trip to Hawaii when Rachel was pregnant. Just before they were scheduled to come home, Rachel went into labor.

Paul was born at 31 weeks gestational age and spent 8 weeks in the NICU at Kapiolani Medical Center for Women and Children before he was stable enough to travel home. He was fed by nasogastric tube until a week or so before discharge. Paul had episodes of cyanosis during bottle feeding, but breast feeding was going well, Rachel says.

Six days after the return to Ohio, she noticed that he was having more severe episodes of cyanosis. They were now occurring during breast feeding. A pulse oximeter showed Paul's SPO_2 levels were dropping below 80 percent during those episodes. The Terleckys went to the Nationwide Children's Emergency Department, where Paul was admitted.

Because of Paul's age and symptoms, he was referred to Dr. Jadcherla and the feeding program. Paul underwent manometry, which showed that his nasopharynx and upper esophageal sphincter were hyper-reactive to stimulus. In essence, the reflexes that exist to protect the airway were doing too good of a job. Any tiny liquid volume was causing him to gag and cough. A fiberoptic endoscopic evaluation of swallowing (FEES) showed he was usually not aspirating with feeding.

Why the hyper-reaction now, after a period of relatively safe feeding? Lactation consultants weighed Paul before and after a short breastfeeding session and found that he was gaining an ounce in a just a few minutes. Rachel, it turned out, had a fast let-down and was providing more milk than Paul could safely swallow in the week or so since he left the NICU in Hawaii. That likely led to Paul's protective mechanisms becoming overprotective.

Dr. Jadcherla told the Terleckys that therapy could remedy this, and he led a care conference with the parents laying out the plan.

Rachel Terlecky becomes emotional when talking about it. "He took the time to connect with his patients, to make sure we felt heard and to make sure our objectives were met. I cannot say enough about the way he cared for us as a person and as a physician."

Paul took some thickened feeds from a bottle. The lactation team worked with Rachel to safely decrease her supply, including having her pump off milk before breast feeding. Paul would eat in a side-lying position, so that he (and not gravity) could control the amount of milk he was swallowing. He was discharged after nine days, and side-lying is the only modification the Terleckys still use.

"We know there are children who have G-tubes and ongoing problems," Rachel says. "I think those kids are lucky that they have Dr. Jadcherla."

THE FUTURE

What about the neonatal populations of other states or other countries?

"Institutions are starting to replicate programs like the one at Nationwide Children's Hospital and programs for older children," says Neelesh Tipnis, MD, the chair of Pediatric Gastroenterology at the University of Mississippi Medical Center who began a similar program at that institution three years ago. "When I came here, we were the fourth in the South. There are now eight pediatric motility programs. People recognize the importance of these skilled, interdisciplinary teams and how important they are in helping children reach their full potential."

Recognition, however, comes with the realization that a lot of work still must be done, says Dr. Tipnis. Dr. Jadcherla's research in the youngest population is crucial, because it provides a starting point for learning how children's feeding disorders change as they age. Significant knowledge gaps still exist across the pediatric age spectrum, however. Dr. Tipnis often first sees patients after they leave the NICU.

"Our techniques are getting better, our ability to analyze big data is getting better," Dr. Tipnis says. "We still do not have much normative data in older children, though. From a practical standpoint, as reimbursement continues to change, we are not going to be compensated for treatments that don't have objective evidence behind them."

The continuing lack of objective evidence – along with a lack of professionals experienced in interpreting evaluations and treating patients – also worries Joan Arvedson, PhD, program coordinator of Feeding and Swallowing Services at Children's Hospital of Wisconsin-Milwaukee. Dr. Arvedson is co-author of *Pediatric Swallowing and Feeding: Assessment and Management*, one of the field's best-known reference books.

"The standardized measures that Dr. Jadcherla and his colleagues gather are continuing to build toward a stronger clinical basis for treatment," she says. "I have great concerns about the variability of interpretation that still exists, particularly in videofluoroscopic swallow studies. I have concerns in some cases about the limited evidence for what some clinicians and therapists do. We must have appropriate tests, but we also need professionals to know what they are doing with those tests."

Dr. Arvedson and Dr. Jadcherla agree, in her words, that "the most developmentally, neurophysiologically appropriate therapies are what we should be focused on." Dr. Jadcherla and his colleagues at Nationwide Children's continue to caution neonatologists and pediatric gastroenterologists about the use of acid-suppressive medications, when there is mounting evidence that they are often unhelpful and may harm some children. Dr. Arvedson says that in her experience, formula thickeners are too frequently employed as the first change made, and they may have negative consequences for the GI tract or even increase risk for aspiration.

Dr. Jadcherla says one of the larger concerns in neonatal feeding disorders is how smaller institutions, or physicians in developing countries, can use these cutting-edge techniques and research to help their patients. Neonatal esophageal manometry, for example, is only possible in a few major research institutions.

"We need a multicenter trial to come up with simplified criteria," he says. "We can disseminate the knowledge we have now, so people can at least try to make educated guesses. But can our methods be used in the absence of the resources only available at a few institutions? For example, if an institution does not have the resources to do any objective evaluations, and a neonate with a feeding disorder is likely to go home with a G-tube, can we at least give an optimal post-menstrual age for G-tube placement?"

Nationwide Children's has now embarked on a single-center, randomized, controlled trial to investigate diagnosis and treatment of GERD in infants. Dr. Jadcherla continues to study the mechanisms of aspiration during swallowing and how aspiration can be rectified.

And day to day, he sees children like Paul who can learn to feed well when given personalized treatment.

"Our work to improve the quality of these babies' lives continues," Dr. Jadcherla says.

Jadcherla SR, Khot T, Moore R, Malkar M, Gulati IK, Slaughter JL. Feeding methods at discharge predict long-term feeding and neurodevelopmental outcomes in preterm infants referred for gastrostomy evaluation. *The Journal of Pediatrics.* 2017 Feb; 181:125-130.

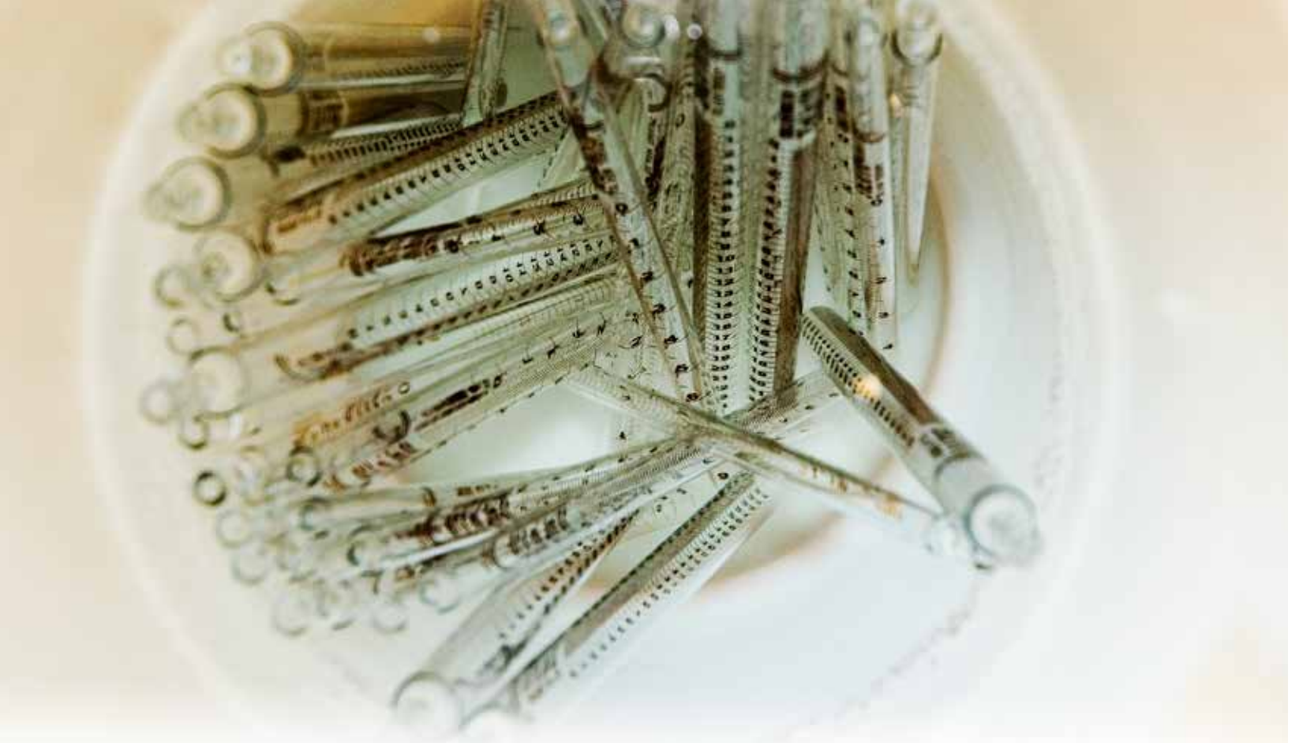
Jadcherla SR, Peng J, Moore R, Saavedra J, Shepherd E, Fernandez S, Erdman SH, DiLorenzo C. Impact of personalized feeding program in 100 NICU infants: pathophysiology-based approach for better outcomes. *Journal of Pediatric Gastroenterology and Nutrition.* 2012 Jan; 54(1):62-70.

Jadcherla SR, Stoner E, Gupta A, Bates DG, Fernandez S, Di Lorenzo C, Linscheid T. Evaluation and management of neonatal dysphagia: impact of pharyngoesophageal motility studies and multidisciplinary feeding strategy. *Journal of Pediatric Gastroenterology and Nutrition.* 2009 Feb; 48(2):186-192.

Jadcherla SR, Duong HQ, Hoffmann RG, Shaker R. Esophageal body and upper esophageal sphincter motor responses to esophageal provocation during maturation in preterm newborns. *The Journal of Pediatrics.* 2003 Jul; 143(1):31-38.

Jadcherla SR and Rudolph CD. Gastroesophageal reflux in the preterm neonate. *NeoReviews.* 2005 Feb; 6(2): e87-e98.

Jadcherla SR, Hasenstab KA, Sitaram S, Clouse BJ, Slaughter JL, Shaker R. Effect of nasal noninvasive respiratory support methods on pharyngeal provocation-induced aerodigestive reflexes in infants *The American Journal of Physiology - Gastrointestinal and Liver Physiology.* 2016 Jun 1; 310(11):G1006-G1014.



Discovery to Drug Development:

Expanding the Role of Academic Centers

AS MORE RESEARCHERS AT ACADEMIC CENTERS BECOME INVOLVED IN DRUG DEVELOPMENT, INSTITUTIONS ARE RESPONDING WITH SUPPORT AND GUIDANCE

By Abbie Roth

Researchers at academic institutions regularly make discoveries about disease processes and potential therapeutic agents. Translational medicine is focused on moving these discoveries out of the laboratory and into the clinic where they can potentially help patients. But creating a new treatment or medication – drug development – is a completely different process with its own set of challenges as compared to research work common in the academic setting.

Academic research and drug discovery diverge in key ways – from the primary goals and objectives to how they are funded and the institutional support required. And as more researchers embrace the opportunity to pursue drug development at academic centers as a way to move their discoveries from the lab bench to the patient bedside, institutions and the pharmaceutical industry are responding.

"We, at academic centers, have a unique opportunity to develop new drugs and repurpose old drugs for patients desperately in need of them," says Christopher Shilling, MS, director of Drug and Device Development Services at The Research Institute at Nationwide Children's Hospital. "Drug discoveries are continuously happening in academic centers. The challenge is moving these discoveries into a drug development process more common in the industry. This is a particularly viable option for patients with rare diseases in which the pharmaceutical industry is not investing."

THINKING STEPS AHEAD

Academic centers with the right resources can conduct the right studies to bring down the risk level for industry to invest in drugs at early investigational stages. In order to do so, strategy and intention are needed to bridge the gap from academic research to drug development.

"Most researchers aren't trained to think about how to approach developing something as a therapy versus doing scientific research on the agent," says Chad Bennett, PhD, director of medicinal chemistry for the Drug Development Institute (DDI) at The Ohio State University Comprehensive Cancer Center – Arthur G. James Cancer Hospital and Richard J. Solove Research Institute (OSUCCC – James). "The sooner a researcher begins to think about the criteria and information the FDA and pharmaceutical industry will want, the better off he or she will be to develop the needed experiments."

Academic centers are increasingly investing in drug development, shifting resources and forming programs through which researchers can get the support they need.

"At the DDI, we seek out and support research technologies developed at OSU and vet them for potential commercial and clinical success," says Dr. Bennett. "Everyone on our team has a background in pharma, so we can guide and support the researchers through the process."

Beyond counseling investigators, setting up milestones and adding team members, the DDI provides investment funds to supplement the grants earned by the researchers.

"Our plan is to move the product through development as quickly as possible," explains Dr. Bennett. "Once we have secured an intellectual property patent, the clock is ticking. Many times research grant money doesn't support the type of experiments needed to get the drug into a phase 1 clinical trial as quickly as we need it to. So we supplement with investment dollars that are based on achieving milestones in the development pathway."

In doing so, the DDI team assists investigators in both furthering their academic careers and getting drugs to the marketplace.

At Nationwide Children's, the Drug and Device Development Services team aims to engage researchers early on in the process.

"We start from the researchers' vision of what the product would be as a commercial entity," says Shilling. "Then, we guide the researchers to take the required steps to make their work more acceptable by federal regulators and valued from a commercial viewpoint. We go from an initial research concept to engaging the right people, and then guide them towards the appropriate next steps."

> "We, at academic centers, have a unique opportunity to develop new drugs and repurpose old drugs for patients desperately in need of them."
>
> *– Christopher Shilling, MS, director of Drug and Device Development Services at The Research Institute at Nationwide Children's Hospital*

"Most researchers aren't trained to think about how to approach developing something as a therapy versus doing scientific research on the agent. The sooner a researcher begins to think about the criteria and information the FDA and pharmaceutical industry will want, the better off he or she will be to develop the needed experiments."

– Chad Bennett, PhD, director of medicinal chemistry for the Drug Development Institute at The Ohio State University Comprehensive Cancer Center – Arthur G. James Cancer Hospital and Richard J. Solove Research Institute.

Researchers at Nationwide Children's are encouraged to consider what studies would need to be done to get a drug product to market as they are writing their grants, explains Shilling. In this way, grant funding may support some of the activities needed for drug development.

Another key area of focus for the program is building relationships with the U.S. Food and Drug Administration (FDA) and educating all faculty about the opportunities to work with the FDA.

In the pharmaceutical industry, checkpoints, reviews and quality checks are designed with the FDA process in mind. Vetting the potential product is done continuously during development, which is a challenge for academic centers. According to Shilling, academic centers have great researchers doing high-quality research, but lack some of the resources for vetting that are common in industry.

"Our approach is to train researchers to be FDA compliant, to be proactive in doing things in ways that will help ensure a smooth process when the time comes to go to the FDA," says Shilling. "To be most successful, we want them to look years ahead of their initial research question."

MOVING INTO THE MARKETPLACE

Both Shilling and Dr. Bennett note that academic centers can only take drug development so far and that partnering with pharmaceutical companies, either big pharma or smaller start-ups, is essential to getting the product to market.

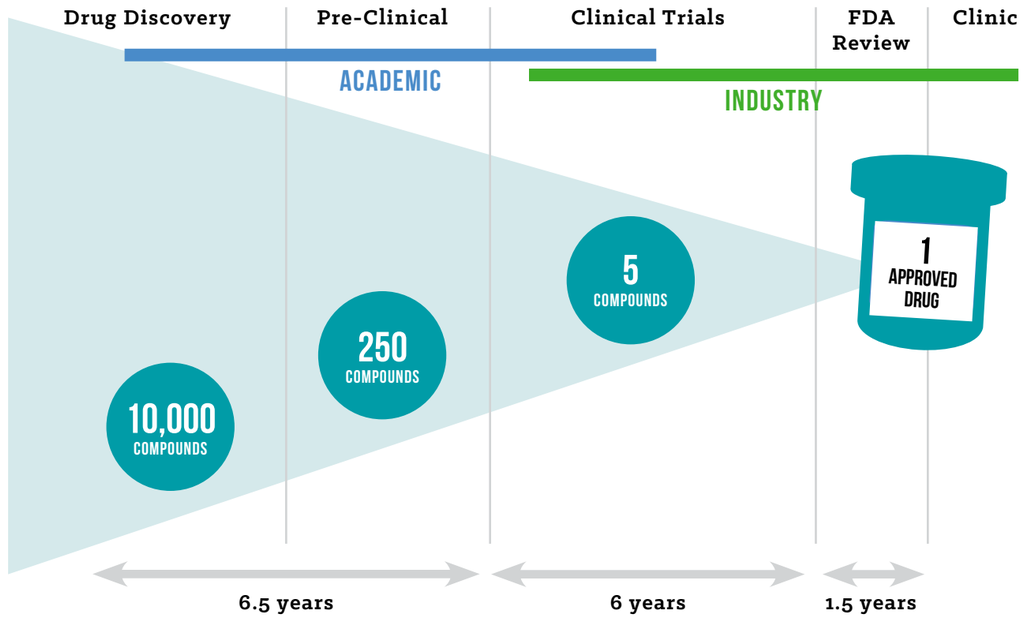
"At an academic center, we can't bring the drugs and devices that we develop all the way to market. We need to create partnerships. This involves engaging with technology commercialization resources at the academic centers to help find and curate industry partnerships," says Shilling.

Part of that enticement for industry partners is to show a lower investment risk to increased value proposition.

"By vetting the drugs and getting them into early stage clinical trials, we are able to show preliminary safety and efficacy, making them more appealing to companies looking to invest," says Shilling.

"If we can decrease the risk associated with an investigational drug, we'll be more successful in finding a partner to bring it to market," says Dr. Bennett. "The competitive landscape, however, plays a significant role in when the partnerships are likely to happen."

THERAPEUTIC DEVELOPMENT PIPELINE



For drugs developed for very small patient populations, large pharmaceutical companies may never be the ideal partner. An increasing number of start-ups, often formed by angel investors or funded by patient foundations or advocacy groups, may be more willing to take on the risk of a developmental drug for a small patient population. Bigger companies are in the space, but they tend to wait – it is uncommon for them to invest where high risk is maintained, according to Shilling.

These higher risk, smaller patient population scenarios are also new ground for the FDA.

"One question the FDA has yet to answer is how to regulate personalized medicine," says Shilling. "In most cases, even with a small patient population, a potential therapeutic must still follow the traditional FDA process. But in cases where your drug intends to only treat a single individual, there's no clear process for that."

"We are in the unique position to be at the table for early conversations about how to manage and regulate these personalized medicine products, both within our institution and nationally," he elaborates. "We've had early conversations about personalized medicine drug development and are hopeful to see these conversations continue with the FDA."

Regardless of the size of the prospective patient population, Shilling and Bennett agree that it's never too early to consider what the research should look like as a product. That vision, combined with the right tools and resources will help make the process more efficient.

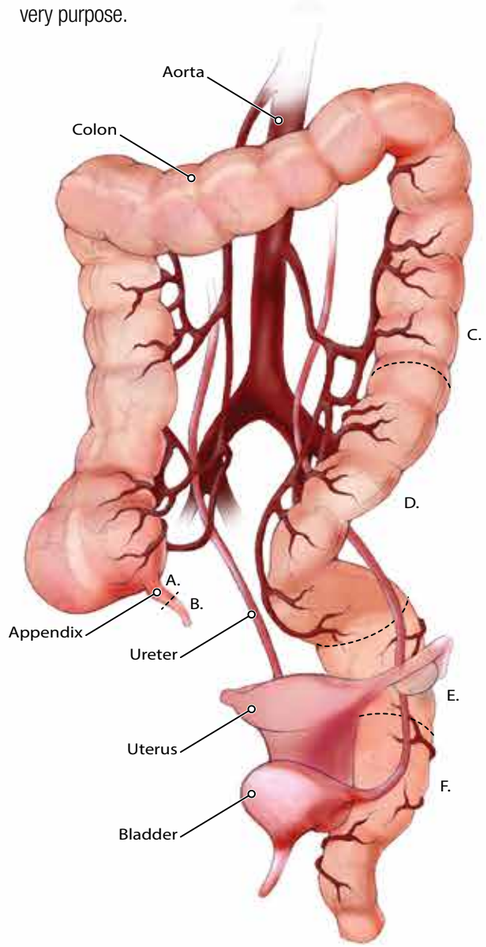
"Having the right people on your team can be the difference between just having a good idea and launching a successful product," says Shilling. "It's never too soon to reach out."

Three Procedures, One Surgery

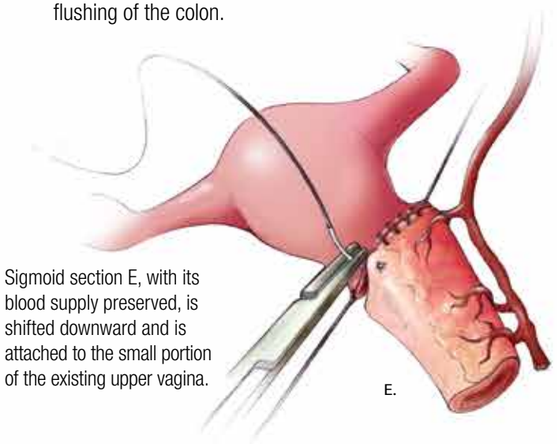
Colorectal Surgery, Urology and Gynecology coordinate to save tissue and time.

A child with a complex colorectal and pelvic condition may require several surgeries over months or years before they are able to successfully manage their urine and stool. With advance planning and coordination it can be possible to treat many issues at once and conserve tissue. The Center for Colorectal and Pelvic Reconstruction at Nationwide Children's Hospital brings medical and surgical teams together for this very purpose.

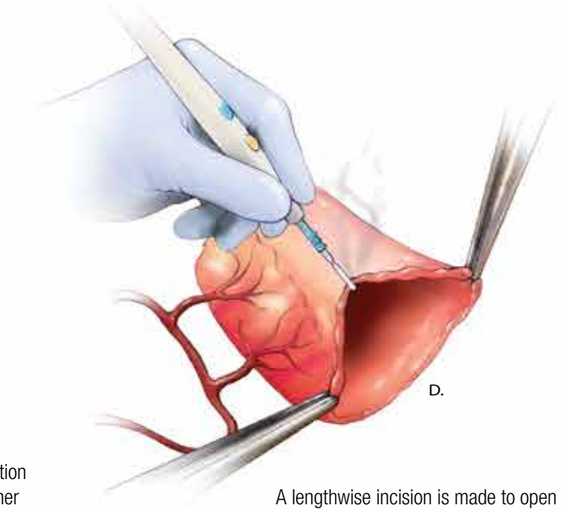
Shown here is a representative collaboration: A 5-year-old girl presented with a dysfunctional sigmoid colon leading to fecal soiling, a small, overactive bladder resulting in urinary incontinence, and distal vaginal atresia (or absent lower vagina). In a single eight-hour operation colorectal, urological and gynecological surgeons used portions of the dysfunctional sigmoid colon to both augment the bladder and create a neovagina. Appendix tissue, meanwhile, became channels that both allowed for catheterization of the bladder and for flushing of the colon.



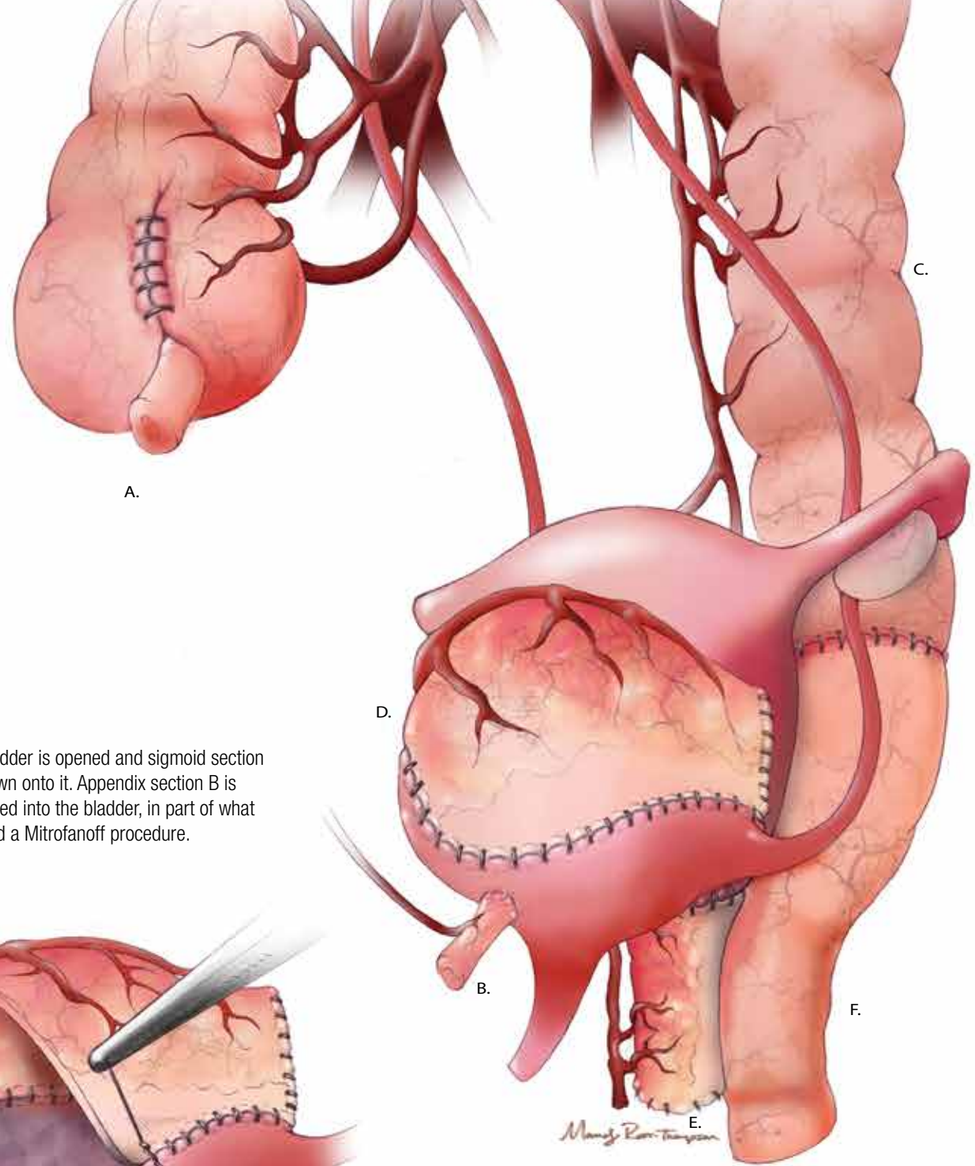
Presurgical anatomy. Surgeons identify one sigmoid colon section D to become an augmenting "patch" for the bladder and another sigmoid section E to become the neovagina. The appendix section A is attached to the cecum for enema flushing, while another section B will be implanted in the bladder for catheter access.



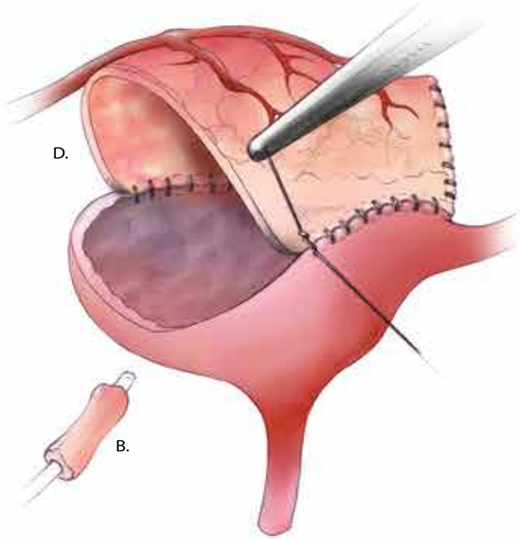
Sigmoid section E, with its blood supply preserved, is shifted downward and is attached to the small portion of the existing upper vagina.



A lengthwise incision is made to open the sigmoid section D. Its blood supply is also preserved, so that it can be rotated around to become part of the bladder.



The bladder is opened and sigmoid section D is sewn onto it. Appendix section B is implanted into the bladder, in part of what is called a Mitrofanoff procedure.



Postsurgical anatomy. The cecum was plicated around appendix section A, which is now attached to the umbilicus for enema flushing (Malone procedure); section B is implanted in the bladder for catheter access; sigmoid colon section D has become part of the bladder; sigmoid colon section E has become part of the vagina; and colon section C and the rectum (F) have been attached as an anastomosis.

With daily enema flushing of the colon and clean intermittent catheterization of the bladder, the patient is now "socially continent," or able to remain clean and dry in her regular activities.

The Equity Equation

By Deena J. Chisolm, PhD

Deena J. Chisolm, PhD, director of the Center for Population Health and Equity Research at Nationwide Children's Hospital, applies a health equity approach to improving infant mortality outcomes.

Health care quality and outcomes differ by race, ethnicity, wealth and place of residence. In fact, we know that health outcomes such as life expectancy, health-related quality of life and infant mortality are more defined by a person's zip code than by their genetic code.

The field of health disparities research was developed to unite clinicians, health services researchers, epidemiologists, social scientists and others in the pursuit of understanding what differences exist, why they exist and what we can do about them. Yet even given a number of notable health disparity reductions in the past decade, many large gaps still exist.

Why? In part, because we've been looking at the gaps without focusing on the world in which those gaps exist. This realization has spawned a movement to change our focus from health disparities to health equity.

A health equity approach starts with the belief that everyone should have a fair opportunity to live a long, healthy life that is not compromised because of their race, ethnicity, gender, income, sexual orientation, neighborhood or any other social condition. Health equity research is designed to study how we achieve that vision. It changes our "lens" from the difference to the solution. Health equity research uses diverse data sources to identify health inequities and tests interventions to learn which approaches work best in which populations to reduce those inequities. Ultimately, this research informs health care and health policy designed to maximize health across all populations.

"Closing the gap requires implementing interventions that have the greatest impact in the populations that have the greatest opportunity for improvement."

– Deena J. Chisolm, PhD

In 2016, The Research Institute at Nationwide Children's formalized its commitment to research and advocacy in the area of health equity with the establishment of the Center for Population Health and Equity Research. As an epidemiologist and health services researcher, I combine clinical data and community input to learn what works and what doesn't to maximize health across all populations.

As part of my work, I apply the health equity lens to one of Ohio's greatest public health challenges, infant mortality. Infant mortality (IM) is defined as death of an infant in its first year of life. In Ohio, nearly half of these deaths are associated with premature birth (46.3 percent). Other leading causes included sleep related deaths (16.0 percent) and birth defects (14.8 percent).

According to the Ohio Department of Health's most recent infant mortality report, the state's 2015 infant mortality rate was 7.2 mortalities for each 1,000 live births, ranking 45th in the nation, and the IM rate in black births was 2.7 times higher than that in white births (5.5 per 1,000 vs. 15.1 per 1,000). Over the past two decades, the state has done a commendable job reducing the overall rate, which was as high as 9.8 in 1990, but the black-white difference has remained frustratingly consistent.

This is why:

Different populations have different infant mortality rates because they face different health and social factors that influence infant mortality risks. This means that "one size fits all" can help improve overall performance in populations but may not close the gaps.

For example, an intervention that reduces infant mortality by 10 percent for both black and white populations, will yield decreases to 13.6 and 5.0, respectively. This is a great improvement but a notable gap remains. Closing the gap requires implementing interventions that have the greatest impact in the populations that have the greatest opportunity for improvement. To reach a goal of 5 per 1,000 IM in both black and white births, we would need to implement interventions that generate a 10 percent improvement for white births and a 67 percent improvement for black births. This is a daunting challenge that some would argue is unreasonable, but the health equity lens provides us with a framework for meeting the challenge head on.

The health equity lens moves us from doing the same thing for everyone to doing the right thing for everyone. It leads us to think bigger about what that right thing is and to customize our approaches to the needs of our diverse communities.

For infant mortality, we can think about intervening at three levels: (1) we can continue to improve the quality of health care provided to premature infants and babies with congenital anomalies or traumatic injury; (2) we can continue to improve the care of expecting mothers by enhancing access to high quality prenatal care, education and support; and (3) we can improve the communities in which our future moms and dads live by improving the economic, educational and employment environments so that parents have the best potential for better birth outcomes before pregnancies happen.

In collaboration with state and local governmental and community partners, we are addressing each of these levels with a combination of innovative approaches to neonatal and infant care as well as engaged approaches to improving social determinants of health. Importantly, we are also conducting research to measure the success of our strategies. Through intervention, research and review, we can reach our goal of best outcomes for all babies.

Stay informed. Keep up-to-date. Read more. Visit **PediatricsNationwide.org** for exclusive online content, physician commentaries and more.

Best Practices in Severe BPD Treatment

by Jeb Phillips

Infants with severe bronchopulmonary dysplasia (BPD) have high risks of late morbidities and mortality, but the best ways to manage these vulnerable patients are still debated. In fact, it's not always clear how to define "severe BPD." In a recently published comprehensive review, the Bronchopulmonary Dysplasia Collaborative offers guidance for neonatologists regarding evidence-based approaches for treatment of patients with BPD.
PediatricsNationwide.org/BPD-Collaborative

Human Trafficking: How Many Victims Have You Treated?

by Abbie Roth

According to a report published in the *Annals of Health Law*, 88 percent of sex trafficking survivors reported contact with a medical provider during the period of exploitation. Megan Letson, MD, MEd, division chief of Child and Family Advocacy at Nationwide Children's, shares the challenges associated with helping human trafficking victims as well as ways physicians and other health care workers can make an impact for these children and adolescents. **PediatricsNationwide.org/Human-Trafficking**

Cognitive Behavioral Therapy Can Help Kids With Persistent Post-concussive Symptoms

by Mary Bates

For most children and adolescents who experience concussions, symptoms resolve after a week or two. However, a small subset of children has persistent symptoms lasting for months or even years after the injury. These symptoms can be disruptive and stressful, impacting many areas of their lives. In a recent pilot study, a psychological intervention was found to improve patients' function and quality of life, even years after a concussion.
PediatricsNationwide.org/CBT-Concussions

"Science knows no country, because knowledge belongs to humanity, and is the torch which illuminates the world."

– Louis Pasteur

Help us advance the conversation on child health.

Follow *Pediatrics Nationwide* on Twitter @NCHforDocs

to stay up-to-date on pediatric research, clinical advances, practice tools, case studies, patient

Pediatrics NATIONWIDE Advancing the Conversation on Child Health

Publishers
Jan Arthur
Tonya Lawson-Howard

Editor/Writer
Abbie Roth

Staff Writers
Tiasha Letostak
Jeb Phillips

Contributing Writers
Mary Bates
Brianne Moore
Kevin Mayhood

Art Director and Designer
Tanya Burgess Bender

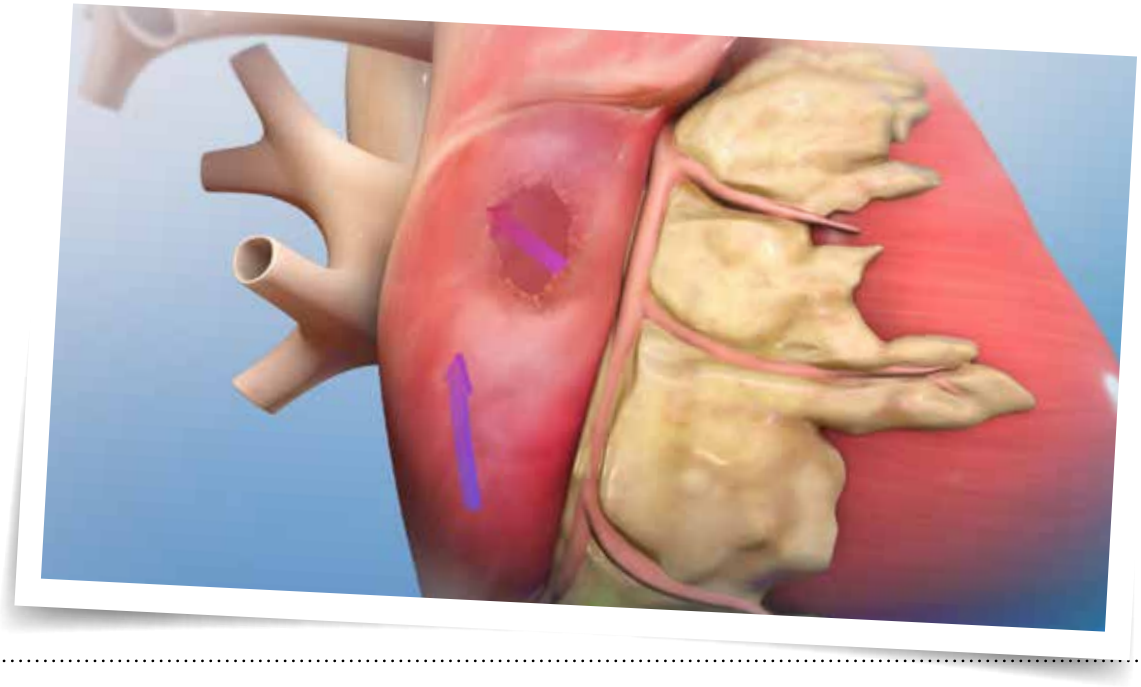
Photographers
Brad Smith
Dan Smith

Illustrator
Mandy Root-Thompson

PEDIATRICS NATIONWIDE is published by Nationwide Children's Hospital, 700 Children's Drive, Columbus, Ohio 43205-2696. All opinions and recommendations stated in these articles are those of the authors and interviewees – not necessarily of the editors, the medical staff or the administration of Nationwide Children's. Inclusion of products, services or medications in this publication should not be considered an endorsement by Nationwide Children's. These articles are not intended to be medical advice and physicians should be consulted in all cases.

NATIONWIDE CHILDREN'S
When your child needs a hospital, everything matters.℠

Nationwide Children's Hospital
700 Children's Drive
Columbus, Ohio 43205-2696



3D Animation Prepares Families for Single Ventricle Surgery

Treating infants born with hypoplastic left heart syndrome is a complicated charge, involving multiple procedures and surgeries over several years. The Hybrid approach spares the newborn open heart surgery until he or she is older and bigger. Patient and family education is a large component of The Heart Center's approach to single ventricle care. The development of three-dimensional animations to educate families about the details of the procedure ensures that families can make informed decisions about their child's care. **NationwideChildrens.org/Hybrid-Stage-1-Animation**.