Pediatrics NATIONWIDE

Advancing the Conversation on Child Health | Spring/Summer 2024

Optimizing Prenatal and Neonatal Care for Infants With Treatable Rare Diseases

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A publication of Nationwide Children's Hospital

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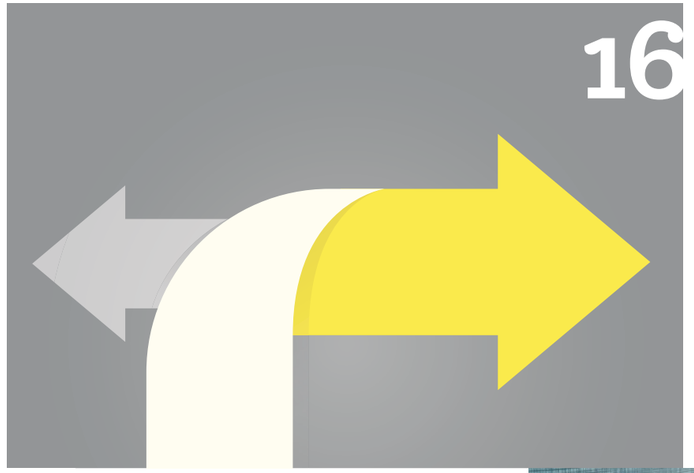
Ghaith, pictured with his mother, was born on March 29, 2023, via uncomplicated Cesarean section at Nationwide Children's Hospital. Ten minutes later, he made history by receiving his first infusion of a medication that effectively halted the damage that had started to accumulate in his brain as a result of molybdenum cofactor deficiency (MoCD) type A. Ghaith received the earliest administration of treatment for MoCD known to the team at Nationwide Children's.



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> When you start with a child who can't stay out of the hospital, and then you get them through a major abdominoplasty and genitourinary surgical reconstruction, and they heal and are chasing their siblings, running and playing — it's like you've given them a new life."
>
> *– Linda Baker, MD, urologist and principal investigator at Nationwide Children's Hospital*

> We want to help drive the conversation to how health systems and their partners can think outside of their facilities to improve lives of children at large."
>
> *– Kelly Kelleher, MD, vice president for Community Health at Nationwide Children's Hospital*

Connecting Well-being to Compassionate Care in Pediatric Residents

A multicenter study identified several well-being factors associated with pediatric residents' confidence in providing calm, compassionate care (CCC) to patients.

Suzanne Reed, MD, has been interested in medical education since her training as a medical student. Captivated by the academic side of education, Dr. Reed has dedicated much of her research and clinical work to medical education, specifically focusing on trainee well-being.

"Much like how we think about research informing clinical care of patients, in the same way, it's important to look at educational processes and learners under the same microscope," says Dr. Reed, a pediatric oncologist and associate program director of the General Pediatrics Residency at Nationwide Children's. "Medical education can affect medical outcomes for trainees, just as it can for patients."

Recently, Dr. Reed published a study in *Patient Education and Counseling* that utilized data from the Pediatric Resident Burnout and Resilience Consortium from 2016-2018, analyzing it with the Calm Compassionate Care Scale and other resident measures of well-being to access the confidence of pediatric residents in delivering that type of care.

Resident with patient

Aligned with findings in related literature, study results indicate factors such as greater mindfulness, self-compassion and empathetic concern are associated with increased confidence in delivering calm, compassionate care. Negative association with confidence in providing calm, compassionate care derived from factors including feelings of decreased personal accomplishment, increased emotional exhaustion and increased depersonalization — a common definition of burnout.

"One marker of burnout often overlooked is sense of personal accomplishment," says Dr. Reed, who is also an associate professor of pediatrics at The Ohio State University. "This is especially important in the trainee population. It's harder sometimes to find a sense of personal accomplishment because trainees are still learning."

In her role with the residency program at Nationwide Children's, Dr. Reed applies the findings of studies like this. The areas of well-being that Nationwide Children's focuses on with residents come directly from residents and evidence-based research to continually improve resident experience in this program.

Today, Dr. Reed is involved in a Nationwide Children's-driven, nationally funded resilience curriculum for residents and pediatric faculty called the Sustaining and Training for Resilience, Engagement and Meaning (STREAM) program. This program aims to develop a curriculum, informed by evidence-based research such as this, to help practitioners build skills to reduce stress and burnout. She's also further investigating the well-being measures of pediatric residents across the training continuum.

Liu A, Ben-Zion S, Schwartz A, Mahan JD, Reed S. Well-being factors associated with confidence in providing calm, compassionate care in pediatric residents. *Patient Education and Counseling*. 2023;115:107906.

— Madison Storm

How Does Thickened Formula Affect Reflux in Infants?

Research suggests the pros and cons of thickened formula require further study.

Infants in the neonatal intensive care unit with suspected gastroesophageal reflux disease (GERD) are often fed formula with added rice cereal or other thickeners, despite limited evidence of its efficacy or long-term consequences. Additionally, the consequences of thickened feeds are not well-studied, says Sudarshan Jadcherla, MD, a principal investigator at the Center for Perinatal Research at Nationwide Children's and the medical director of the Neonatal and Infant Feeding Disorders Program.

"The use of thickeners and thickened feeds comes with short-term and long-term side effects," he says, which may include excessive weight gain, constipation, gastrointestinal dysmotility and necrotizing enterocolitis.

Dr. Jadcherla and colleagues recently conducted a crossover cohort study in 40 infants with suspected GERD at Nationwide Children's. The study is published in the *Journal of Parenteral and Enteral Nutrition*. The team used 24-hour pH-impedance testing to compare the direct effects of rice-thickened formula versus routine feeds on GERD symptom characteristics.

The researchers report that thickened formula had no effect on acid reflux characteristics, other than reducing cough symptoms and the frequency and height of refluxate. All other symptoms were comparable regardless of formula thickness.

Dr. Jadcherla and colleagues also found that the effects of thickened feeds are further modified by the severity of acid reflux index (ARI). Infants with an ARI greater than seven, which is considered abnormal, had longer bolus clearance times after thickened feeds. This suggests that refluxed material remained in the esophagus longer, potentially delaying esophageal clearance amidst greater duration of esophageal exposure to refluxed material.

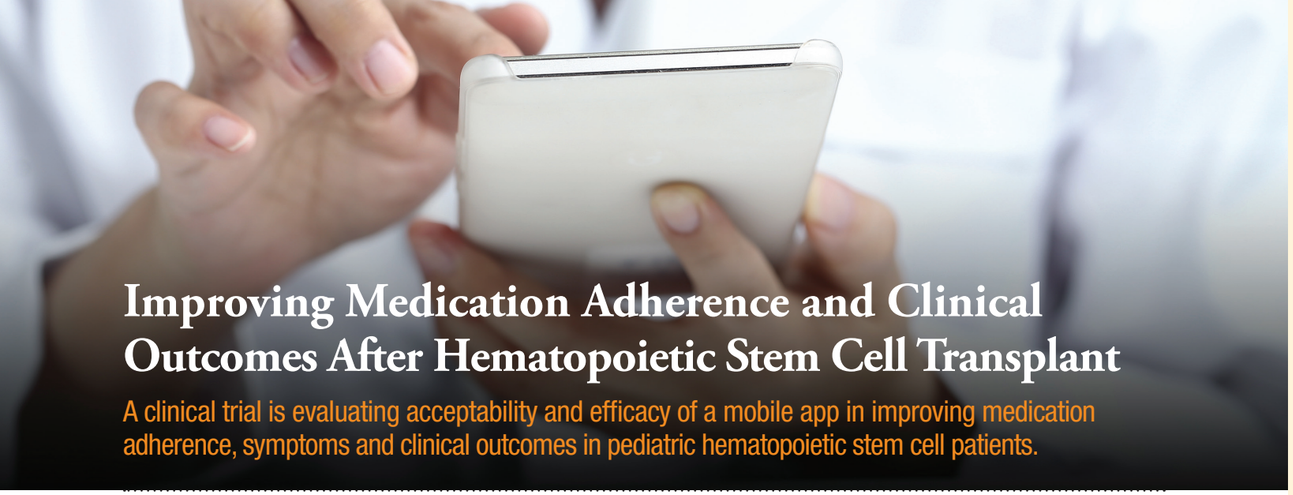
Overall, the researchers say their results suggest there are pros and cons of using thickened feeds: Although thickened feeds may help decrease weakly acidic reflux, they may not alleviate other troublesome GERD symptoms. Plus, all thickeners have associated risks and some negative side effects that necessitate further research.

Dr. Jadcherla says that clinical trials are needed to clarify objective indications and therapeutic use of thickened formula in this population, along with study of their side effects. He and his team have recently been funded by the National Institutes of Health to conduct a clinical trial to test the effects of natural maturation versus acid suppressive medications versus rice-thickened formula on infants with suspected GERD.

"This will be a randomized trial that will, hopefully, be able to answer all of the questions we have about when to use thickened formula," says Dr. Jadcherla, who is also a professor of pediatrics at The Ohio State University College of Medicine. "With this clinical trial, we will determine the short- and long-term side effects, as well as the short- and long-term benefits, of thickened formula for infants with GERD."

Njeh M, Sultana Z, Plumb T, Alshaikh E, Jadcherla SR. Comparison of direct effects of rice-thickened formula vs routine feeds on symptoms and gastroesophageal reflux indices: A crossover cohort study. *Journal of Parenteral and Enteral Nutrition*. 2024 Jan;48(1):64-73.

— Mary Bates, PhD



Improving Medication Adherence and Clinical Outcomes After Hematopoietic Stem Cell Transplant

A clinical trial is evaluating acceptability and efficacy of a mobile app in improving medication adherence, symptoms and clinical outcomes in pediatric hematopoietic stem cell patients.

A research team led by Micah Skeens, PhD, APRN, FAAN, principal investigator in the Center for Biobehavioral Health at the Abigail Wexner Research Institute, assistant professor of pediatrics in The Ohio State University College of Medicine and nurse practitioner with the Division of Hematology, Oncology and Blood and Marrow Transplant at Nationwide Children's Hospital, is conducting a pilot clinical trial using a mobile health app they created — BMT4me© — to monitor medication adherence, symptoms and clinical outcomes of pediatric hematopoietic stem cell transplant (HCT) patients. The National Institutes of Health-funded trial protocol was recently published in *PLoS ONE*.

Medication nonadherence contributes to adverse clinical outcomes and costs the health care industry nearly $100 billion annually. Nonadherence rates are above 50% for pediatric chronic illness patients and adult HCT patients, but little is known about medication nonadherence for pediatric HCT patients.

"It is assumed that pediatric HCT patients will take their medicine because not doing so could be fatal," says Dr. Skeens. "However, a myriad of post-transplant complexities and challenges faced by the patients' caregivers present a significant barrier to medication adherence."

The clinical trial will enroll 50 caregivers of children in the acute phase post-HCT (first 100 days), randomized 1:1 into a standard of care or intervention group.

All caregivers will receive an electronic adherence monitoring device, either a MedyRPM box or MEMS® Cap. Those in the intervention group will have the BMT4me© app downloaded onto their mobile devices and receive instructions on its use. They will log medication doses and information such as symptoms and symptom severity.

Before the clinical trial, the researchers worked extensively with patients, caregivers and providers on the app's user-centered design.

"Working with the families and key stakeholders in the app's development was central to us being able to move forward with the clinical trial," explains Dr. Skeens.

Multiple assessments will be collected until approximately 100 days post-transplant or medication taper completion, including weekly in-person or virtual check-ins and the Pediatric Quality of Life Inventory every three weeks.

Other data to be collected will include weekly Graft vs. Host Disease (GVHD) scores, readmission rates and monthly medication adherence.

A simultaneous multisite clinical trial funded by the National Institute of Minority and Health Disparities with Columbia University will enroll Spanish-speaking pediatric HCT patients and evaluate the app's efficacy in improving post-transplant clinical outcomes in Hispanic children undergoing HCT.

"We believe the app monitors medication adherence and symptoms in real time, allowing us to create personalized interventions to help the caregivers improve post-transplant medication adherence and outcomes," says Dr. Skeens.

Ralph JE, Sezgin E, Stanek CJ, Landier W, Pai ALH, Gerhardt CA, Skeens MA. Improving medication adherence monitoring and clinical outcomes through mHealth: A randomized controlled trial protocol in pediatric stem cell transplant. *PLoS ONE. 2023;* 18(8): e0289987.

— JoAnna Pendergrass, DVM

Personalizing Neurorehabilitation for Children With Batten Disease

While outcome assessment tools are in development, therapy should be tailored to each child's needs.

Batten disease comprises a group of rare, related genetic disorders characterized by progressive neurodegeneration. The disease primarily presents in childhood as seizures, vision loss and developmental regression. Neurorehabilitation services, including physical therapy (PT), occupational therapy (OT) and speech-language pathology therapy (SLP), can delay loss of function and impairment and improve quality of life for these children and their families. However, given the rarity of Batten disease, standardized clinical recommendations and outcome assessments for neurorehabilitation have not yet been established.

"Historically, children with Batten disease would have a shortened lifespan. However, now, with the advent of novel treatments, patients are living longer and need differing levels of neurorehabilitation support," says Emily de los Reyes, MD, attending pediatric neurologist and director of the Nationwide Children's Hospital Batten Disease Center of Excellence.

In a study published in *Pediatric Neurology*, Dr. de los Reyes and colleagues describe the developmental profiles, current dose of neurorehabilitation, and outcome assessments used at Nationwide Children's for children diagnosed with Batten disease.

"We have needed outcome assessment tools developed specifically for this population to capture changes in their developmental trajectory to guide clinical recommendations, and for use in clinical trials," adds first author of the study Rachel Bican, PT, DPT, PhD, assistant professor and principal investigator of the Pediatric FUNctional Mobility (FUN) Lab at Ohio University. "The findings from this study have served as a basis for developing those tools within the Batten Clinic at Nationwide Children's."

The research team, which included a dedicated physician, occupational therapist, physical therapist and speech-language pathologist, reviewed electronic medical records of 70 children with the most common subtypes of Batten disease. On average, patients were 7 years of age.

Children typically received neurorehabilitation services through early education/school, outpatient clinic or a combination of these settings. However, to the surprise of the researchers, 20% of children did not receive any PT or OT services, and 25% of children did not receive SLP services.

The study underscores the need for continued development and validation of new outcome measures for children with Batten disease.

"Each child has different needs at different points in time, and regression occurs at different times. Thus, the therapists need to be able to tailor neurorehabilitation to the needs of each child," says Dr. de los Reyes, who is also a professor of clinical pediatrics and neurology at The Ohio State University College of Medicine. "Although this is a progressive disease, a lot can still be done for each child. The therapists together with the family have to make the decisions about how personalize therapy to each child's needs."

Bican R, Goddard V, Abreu N, Peifer D, Basinger A, Sveda M, Tanner K, de Los Reyes EC. Developmental skills and neurorehabilitation for children with Batten disease: a retrospective chart review of a comprehensive Batten clinic. *Pediatric Neurology* 2024 Mar;152:107-114.

— Lauren Dembeck, PhD

RSS Score May Predict Bronchopulmonary Dysplasia-Associated Pulmonary Hypertension Risk

The RSS score is noninvasive and may be useful for risk stratification in extremely preterm infants.

Elevations in respiratory severity score (RSS) were correlated with an increased risk of bronchopulmonary dysplasia-associated pulmonary hypertension in preterm infants in a new study published in the *Journal of Perinatology*. This study identifies a pragmatic clinical risk score that can be measured noninvasively, which may improve risk stratification for infants born extremely preterm who are evaluated for pulmonary hypertension.

Approximately 20-40% of infants with bronchopulmonary dysplasia (BPD) develop BPD-associated pulmonary hypertension (BPD-PH), a disease of the lung vasculature that increases the risk of both short- and long-term morbidity and mortality.

Echocardiograms are the most frequently used screening assessment for BPD-PH, and consensus guidelines recommend their use at 36 weeks' postmenstrual age. However, echocardiograms are expensive, may lack specificity for BPD-PH and are utilized variably across centers. Additionally, the optimal timing of repeat BPD-PH echocardiography after this age remains unknown.

The RSS is a noninvasive biomarker calculated from the mean airway pressure and the fraction of inspired oxygen. In the study, researchers investigated whether elevations in the RSS, measured concurrently with echocardiography, are associated with an increased risk of BPD-PH in extremely preterm infants. They conducted a retrospective cohort study of more than 200 infants born extremely preterm admitted to the Comprehensive Center for Bronchopulmonary Dysplasia at Nationwide Children's Hospital between 2010 and 2018.

The results indicated that elevations in the RSS were associated with a greater probability of BPD-PH.

"This may be clinically useful because it suggests that a patient with a low RSS who is otherwise doing well is less likely to have BPD-PH and may not require frequent or even repeat echocardiograms," says Matthew Kielt, MD, an attending neonatologist in the BPD center at Nationwide Children's and the study's lead author.

"On the other hand, if a patient has high or increasing RSS scores, that should increase the index of suspicion for BPD-PH and could potentially inform a provider to obtain an echocardiogram more readily."

Researchers say that prospective studies are needed to validate the RSS as a clinical risk biomarker and to identify the optimal timing of echocardiogram assessments for the management of BPD-PH in preterm infants.

"We suspect that early elevations in the RSS may alert a provider to a patient who is at the highest risk of BPD-PH, possibly even before the formal timepoint of BPD diagnosis at 36 weeks postmenstrual age," says Dr. Kielt, who is also an assistant professor of clinical pediatrics at The Ohio State University College of Medicine.

Beer L, Rivera BK, Jama W, Slaughter JL, Backes CH, Conroy S, Kielt MJ. Association of the respiratory severity score with bronchopulmonary dysplasia-associated pulmonary hypertension in infants born extremely preterm. *Journal of Perinatology*. 2023 Oct 18. doi: 10.1038/s41372-023-01798-y. Epub ahead of print.

— Mary Bates, PhD

Clinical Trial Results: AAV Gene Therapy for LGMD 2E/R4

Interim results from a Phase 1/2 trial show safety and improved functional outcomes.

Limb-girdle muscular dystrophy Type 2E/R4 (LGMD2E/R4) is a rare, progressive neuromuscular disorder caused by mutations in the β-sarcoglycan (SGCB) gene. These mutations lead to SGCB protein deficiency, ultimately resulting in muscle loss. Progressive, debilitating weakness and wasting begin in the muscles around the hips and shoulders before moving to the arms and legs.

Researchers from Nationwide Children's Hospital and Sarepta Therapeutics published the interim results of a Phase 1/2 trial evaluating the safety and efficacy of SRP-9003 (bidridistrogene xeboparvovec) for the treatment of LGMD2E/R4 in *Nature Medicine*.

"Children with LGMD typically begin having difficulty running, jumping and climbing stairs before age 10. They then lose the ability to walk in their teen years," says Jerry Mendell, MD, the lead author of the study. "LGMD often leads to significant disability and premature death, and unfortunately, there are currently no approved treatments to alter the course of the disease."

Trial participants aged 4 to 15 years with confirmed SGCB mutation in both alleles received one intravenous infusion of the vector. Participants were split into two cohorts receiving 1.85×10^{13} vg/kg or 7.41×10^{13} vg/kg. Adverse events included vomiting (4/6 patients) and gamma-glutamyl transferase increase (3/6 patients). The adverse events were resolved with standard therapies.

"Overall, the safety profile of the therapy was favorable across both cohorts," says Dr. Mendell, who retired as a principal investigator and attending neurologist at Nationwide Children's in October 2023. He is now a senior advisor in the Center for Gene Therapy at Nationwide Children's and a senior advisor with Sarepta Therapeutics, Inc.

Robust SGCB expression based on immunoblot analysis was observed in patients 60 days after administration: in cohort 1, it was 36% of normal expression and in cohort 2, it was 62% normal expression. Functional outcomes data also showed improvements. Both gene expression and functional improvements were maintained for two years.

"We are pleased to report early results from the Phase 1/2 trial demonstrated significant protein expression in both cohorts at both 60 days and two years after treatment," says Louise Rodino-Klapac, PhD, executive vice president, chief scientific officer and head of research and development at Sarepta Therapeutics. "Additionally, we observed functional benefits including slowed progression of this disease, improved mobility, and enhanced quality of life for individuals living with LGMD2E/R4."

The patients in the Phase 1/2 study will continue to be followed, with a final analysis planned at 5 years post-therapy. Additionally, in January, Sarepta Therapeutics, Inc. announced that screening is underway in SRP-9003-301, a Phase 3, multinational, open-label study of SRP-9003.

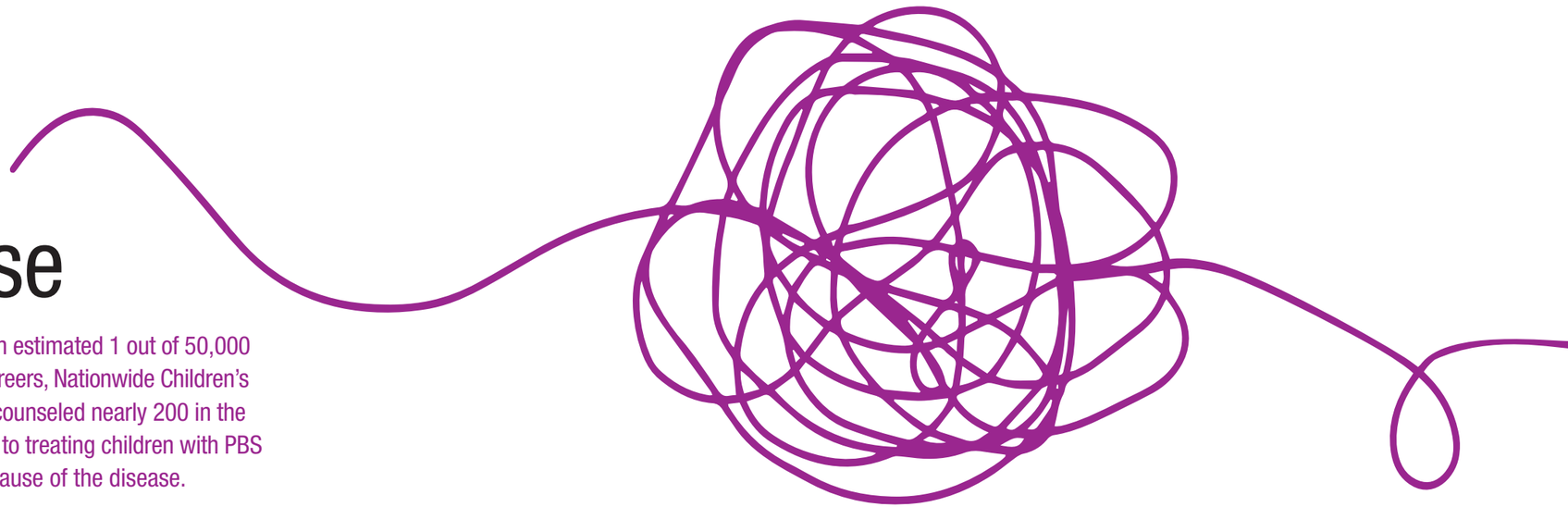
Disclosures: This gene therapy was initially developed by Drs. Rodino-Klapac and Mendell at Nationwide Children's Hospital. It was licensed to Myonexus/Sarepta in 2017.

Mendell JR, Pozsgai ER, Lewis S, Griffin DA, Lowes LP, Alfano LN, Lehman KJ, Church K, Reash NF, Iammarino MA, Sabo B, Potter R, Neuhaus S, Li X, Stevenson H, Rodino-Klapac LR. Gene therapy with bidridistrogene xeboparvovec for limb-girdle muscular dystrophy type 2E/R4: phase 1/2 trial results. *Nature Medicine*. 2024;30(1):199-206.

Sarepta Therapeutics Initiates Screening in EMERGENE, a Phase 3 Clinical Study of SRP-9003 for the Treatment of Limb-Girdle Muscular Dystrophy Type 2E/R4. Sarepta Therapeutics. https://investorrelations.sarepta.com/news-releases/news-release-details/sarepta-therapeutics-initiates-screening-emergene-phase-3?_ga=2.78038679.2022989528.1707178156-1637175906.1705963085. Accessed: Feb. 16, 2024.

— Abbie Miller, MWC

Unraveling the Genetic Mystery Behind a Rare Pediatric Disease



Prune belly syndrome (PBS) is a rare, congenital urologic disease, affecting an estimated 1 out of 50,000 births. While most urologists will see fewer than three cases of PBS in their careers, Nationwide Children's Hospital's Linda Baker, MD, has treated more than 50 patients and met and counseled nearly 200 in the last 15 years. She directs the nation's only multidisciplinary center dedicated to treating children with PBS and heads the only research lab in the United States studying the genetic cause of the disease.

by Wendy Margolin

Linda Baker, MD, loves a good puzzle. That's part of what initially drew her to study one of pediatric urology's rarest disorders, prune belly syndrome. Also known as Eagle-Barrett Syndrome, it affects the abdominal muscles, bladder, urinary tract, kidneys and — in males — testicles. Around 20% of babies with severe PBS don't survive the first two weeks of life. Children with PBS face a lifetime of surgeries and treatment.

This rare disease that proves so difficult for children and their families is a research puzzle Dr. Baker has dedicated 15 years of her career to solving.

A pediatric urologist, principal investigator and co-director of the Kidney and Urinary Tract Center at Nationwide Children's Hospital, Dr. Baker is one of few researchers in the United States working to identify the genetic causes of PBS and the only National Institutes of Health (NIH)-funded investigator studying it. "It's so rewarding to discover something that's never been discovered for a disease. Once we know what genes are at play, how the mutations work and cause the disease, we can develop treatments that might target the mutated genes."

Working closely with PBS patients in the clinic has shown Dr. Baker how her research matters.

"This particular disease takes a huge toll on the whole family — physically, emotionally, financially and socially. If there's anything I can do to help them, that's the big motivator," she says.

Features of Prune Belly Syndrome

Prune belly syndrome gets its name from the wrinkled skin of the abdomen. Children born with PBS have a soft, lax tummy area with partially formed muscles. There's no blood test to diagnose the disease, but its features are apparent at birth.

For those with PBS, the urinary tract muscle is abnormal, which causes a massive, poorly contracting urinary bladder. The ureters are also typically very dilated. These abnormalities can cause reflux, urine blockages and significant kidney problems. For some babies in utero, when the urine doesn't pass out of the bladder and into the amniotic fluid, the lungs don't form properly. While some have two working kidneys, others have damaged kidneys or even kidney failure.

Male children with PBS typically have undescended testicles in the belly, which requires orchiopexy surgery by their first birthday.

During pregnancy, a fetus with PBS will have an enlarged bladder. However, several problems can cause an enlarged bladder full of urine. The most common in males is posterior urethral valves, which is difficult to distinguish from prune belly syndrome *in utero*.

Treatment for PBS

Treating children with PBS takes a multidisciplinary team including urology, pulmonology, cardiology, nephrology, gastroenterology, nutrition, orthopedics and physical therapy. Nationwide Children's is the only children's hospital in the United States with a multidisciplinary PBS clinic.

The treatment pathway outlined in the box below can be complicated by infections that are common for kids with PBS, including urinary tract infections and pneumonia. Abdominoplasty surgery is highly complex. Patients should be treated in the ICU after this surgery to prevent pneumonia or a urinary tract infection and to maximize wound care and nutrition.

"You have to be prepared immediately after the abdominoplasty surgery because PBS patients might

Treatment can be long and challenging. The typical intervention journey for PBS is as follows:

Birth-4 months: Lifesaving and kidney-saving measures and a vesicostomy.

4-12 months: Once medically stable, surgeries can include orchiopexy, abdominoplasty, early-stage urinary tract reconstruction and hip dysplasia repair.

1-5 years: Any of the above surgeries that couldn't be performed earlier, urinary tract reconstruction for urinary continence, GI tract surgery.

5-11 years: Urology and nephrology follow-up every 6-12 months, annual follow-up with other specialists as needed.

11-18 years: Close monitoring of kidney and bladder function through puberty, dialysis/renal transplantation if required, monitor and treat scoliosis.

18+ years: Monitor orthopedic joint complications, yearly renal ultrasounds, dialysis/renal transplantation if required, monitor fertility status.

"When you start with a child who can't stay out of the hospital, and then you get them through a major abdominoplasty and genitourinary surgical reconstruction, and they heal and are chasing their siblings, running and playing — it's like you've given them a new life."

— Linda Baker, MD, pediatric urologist, principal investigator, and co-director of the Kidney and Urinary Tract Center at Nationwide Children's

not always have the smoothest postoperative course," says Dr. Baker.

With proper treatment, children with PBS can function well and live full lives.

"I know of individuals with prune belly syndrome who are PhD scientific researchers and are airplane pilots. Many people can do incredibly well," says Dr. Baker.

Witnessing patients transition from a state of languishing to actively engaging in typical childhood activities is what Dr. Baker finds most rewarding.

"When you start with a child who can't stay out of the hospital, and then you get them through a major abdominoplasty and genitourinary surgical reconstruction, and they heal and are chasing their siblings, running and playing — it's like you've given them a new life," she says.

Researching a Rare Pediatric Disorder

Dr. Baker began studying PBS over a decade ago after advancements in genetic sequencing opened up new research capabilities. That, combined with a penchant for solving difficult puzzles, drew her to the cause.

The first clue indicating the disease could have a genetic cause is that 95% of PBS cases occur in males. Multiplex families with more than one child born with PBS provide additional evidence, supporting the idea that genetics is a likely cause.

"It seemed to me that it was a disease in need of attention and we might be able to understand genetically what causes it," says Dr. Baker, who has an R01 grant from the NIH to investigate mutations and cellular and molecular processes associated with PBS.

But to make progress, Dr. Baker would need access to a lot of patients with PBS. Like any rare disease, finding a significant sample size is challenging. The disease is so rare that some pediatric urologists will never see a patient with PBS in their years of practice. Dr. Baker partners with the Prune Belly Syndrome Network (PBSN) to identify research participants and share research results with families affected by PBS. Today, Dr. Baker has treated over 50 patients with PBS and connected with nearly 200.

Unraveling the Basic Mechanisms Behind Prune Belly Syndrome

No one gene causes PBS, so finding the combination of mutations is like unspooling a knot of threads with multiple ends and directions. To date, three key discoveries have brought Dr. Baker and her lab closer to understanding the genetic changes.

X-linked Filamin A Gene

Dr. Baker and her research team's first DNA mutation findings were in two half-brothers and two unrelated children with PBS. The mutations were in the gene for filamin A — a protein that regulates how cells detect stretching and contraction. This means there's a mechanotransduction problem with the cells.

"That was a fascinating discovery that made a lot of sense because the filamin A gene is on the X chromosome," she says.

With her long-time research partner, Nathalia Amado, PhD, Dr. Baker's lab developed a mouse model with this same mutation. When the pregnant animal experienced low oxygen during pregnancy, the male offspring were born with the PBS phenotype.

"You have in your mind how you believe it will work, but until you test it, you don't know. It's a eureka moment when it comes together."

— Nathalia Amado, PhD, postdoctoral scientist in the Kidney and Urinary Tract Center at Nationwide Children's

"This greatly deepened our understanding of what's wrong in the cells of children with this syndrome and has led to more research," she says.

PIEZO1 Gene

Dr. Baker's lab team found DNA mutations among PBS patients in another gene called PIEZO1, which codes for a protein that acts as a pressure sensor on a cell's surface. PIEZO1 is found throughout the lower urinary tract and is responsible for making a channel that helps the body respond to mechanical forces.

This discovery, published in January 2024 in *Nature Communications*, is providing additional evidence that children with PBS have defects that keep their muscle cells from responding properly to forces, such as the bladder's ability to stretch and contract. Dr. Amado says this discovery was particularly exciting.

"You have in your mind how you believe it will work, but until you test it, you don't know. It's a eureka moment when it comes together," she says.

Myocardin

The other gene Dr. Baker and her team are studying is myocardin — an on-and-off switch for cells to become smooth muscle cells, like in the fetal bladder and ureter. They found five novel myocardin mutations in PBS cases, highlighting the genetic transmission from asymptomatic carriers. These findings support a decade of Nationwide Children's research on myocardin by Ashley Jackson, PhD, principal investigator in the Kidney and Urinary Tract Center, and Kirk McHugh, PhD, director of the Nephrology and Urology Research Affinity Group at Nationwide Children's and professor at The Ohio State University.

"Each discovery at the cellular level showing how these genes and proteins work together is one more piece of the puzzle," says Dr. Baker. "I started working on this hypothesis that the cause is genetic, and we're starting to see evidence of that. It's very rewarding to discover something new."

Beyond Genetics: Improving Care

In addition to studying the genetic and molecular mechanisms behind PBS, Dr. Baker partners with colleagues at Nationwide Children's to support treating children with the disease. In one study, psychologist Canice Crerand, PhD, a principal investigator in the Center for Biobehavioral Health, works with kids who have body image concerns to help them manage their quality of life and improve their mental health.

Linda Lowes, PT, PhD, and Melissa Smith, PT, DPT, principal investigators in the Center for Gene Therapy at Nationwide Children's, specialize in neurodevelopmental pediatrics and study the physical function of individuals with PBS. As physical therapists and researchers, they seek to understand how well the muscles of babies, children and adults with PBS work to improve development.

Children with prune belly syndrome have a floppy abdominal wall that causes a different gait, making stairs and sports challenging. Kirsten Tulchin-Francis, PhD, director of the Honda Center for Gait Analysis and Mobility Enhancement at Nationwide Children's and a gait expert, can analyze PBS patients' gait to make adjustments and prevent the progression of scoliosis, arthritis and joint problems.

From Bench to Bedside

Researching the basic science behind PBS has the

potential to improve kids' lives. Dr. Baker and her growing research team have made progress in uncovering the genetic causes of PBS, but there's still a long way to go. They hope to have some therapies and treatments in clinical trials within 5-10 years.

Working one-on-one with patients keeps Dr. Baker focused on why she's dedicated to finding a treatment.

"All you have to do is look at some of these kids and talk to these families, and your motivation always stays high. They're the whole reason I do this," she says.

To develop a treatment, they'll need to know more about the genetic causes of PBS.

"It bothers me that I still don't have the answer for what causes prune belly syndrome in the majority of kids, even though I've already spent 10 years of my life trying to answer that question," she says. "So long as I don't have the answer, I'll keep asking questions."

The PBS studies are still recruiting research participants. Contact prunebellysyndrome@NationwideChildrens.org for more information. ■

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The First Three Years With PBS: *Bryson's Story*

The first time Andrea Williams met her new baby was four days after his birth. Baby Bryson was born with the rare congenital disorder, prune belly syndrome (PBS), and was rushed to the Nationwide Children's Hospital NICU immediately after birth. His enlarged belly meant he was delivered by C-section at 37 weeks, and it wasn't until his mother was discharged that she could meet her new baby.

They've been inseparable ever since.

"I said 'hi, Bryson,' and he looked around because he knew my voice. I'm tearing up just thinking about it," says Williams.

It was a bittersweet beginning for Bryson's challenging first year.

Preparing for a New Baby With Prune Belly Syndrome

Williams first found out her baby likely had PBS at a 13-week ultrasound. Bryson had an enlarged bladder overly full of urine that maternal-fetal medicine physicians suspected was PBS. Williams underwent a vesicocentesis to extract fetal urine and decompress his massive bladder and tummy.

Throughout her pregnancy, Williams underwent bimonthly ultrasounds. She got a comprehensive genetic panel so that she and her doctors could prepare as much as possible for the uncertainties of her baby's condition. The team closely watched her amniotic fluid levels because some mothers of babies with PBS run low. It turns out that Bryson had another anomaly, patent urachus, that caused some urine to leak at the site of his umbilicus during the pregnancy. This allowed him to empty urine, preventing the depletion of amniotic fluid.

Infancy and Toddlerhood With PBS

Children with PBS undergo multiple surgeries throughout childhood, especially in the first few years. Bryson's first surgery was at only 13 days old to decrease his ureter reflux. He remained in the NICU for 22 days.

That first year, Bryson got repeated urinary tract infections that would send him back to the hospital. His ureters and renal pelvis were not draining urine properly into the bladder. Ultimately, the team at Nationwide Children's performed pyelostomy and ureterstomy surgeries to drain urine, making more stomas with low pressure to decrease urinary tract infections and prevent kidney damage.

One of the biggest unexpected challenges for Williams was purely technical — how to keep her son dry and comfortable with multiple stomas draining urine. There was a period where Bryson needed a diaper in front for his leaking belly button, one in back for his right kidney stoma (pyelostomy), and a third one around his bottom. Williams was determined to keep her son comfortable and dry without looking bulky. She needed him to be able to move around like a typical toddler and for friends and family to hold him without worrying about leaks. She found a way to use abdominal binders to keep the diapers in place and allow her son to play and feel confident.

Through it all, there are moments when Williams forgets Bryson has PBS. When he's busy playing, running or demanding to do everything himself, she can just enjoy being a first-time mom to an active toddler.

Bryson received physical therapy in his first year and hit his developmental milestones on time or within range. Undeveloped abdominal muscles can make those milestones challenging for some kids with PBS.

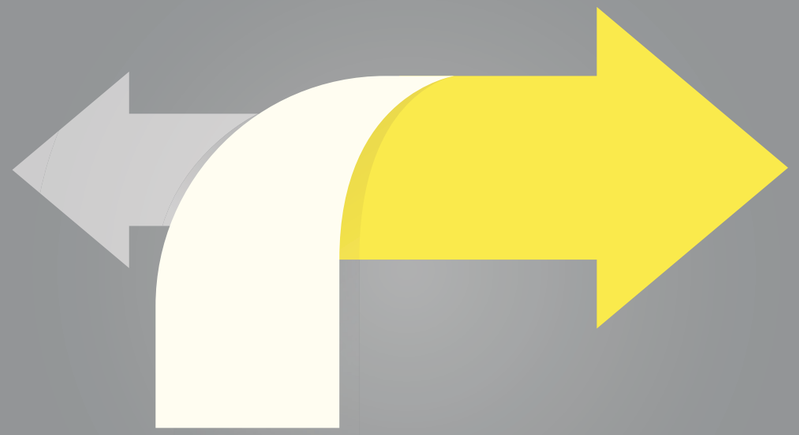
At 2.5 years old, Bryson underwent an 11-hour surgery co-led by Linda Baker, MD, and Daryl McLeod, MD, MPH, pediatric urologist at Nationwide Children's, to close his urostomy and bring his undescended testicles down to his scrotum.

This spring, he's expected to undergo abdominoplasty, which is an intense, multidisciplinary surgery with a long recovery. He'll also get his flared rib repaired and pyelostomy closed.

Williams can't anticipate all the twists and turns ahead for her son with PBS. But she does know from experience that he's a tough little warrior.

"I didn't know what to expect before he was born and what he would need," she says. "But he's a fighter, and he doesn't let a lot bother him."

Williams doesn't know anyone else in Columbus with PBS, but she's connected with families online and attended the 2023 Prune Belly Syndrome Network conference, which was in Columbus for the first time this past summer. She is excited that future annual Prune Belly Syndrome Network conferences will continue in Columbus and hopes other PBS families will attend.



Turning Complications Into Fuel for a New Approach to Better Outcomes

A new web application enhances Morbidity and Mortality data storage and actively improves patient care.

by Alaina Doklovic

Morbidity and Mortality (M&M) Conferences are mandated meetings that occur regularly at all academic medical centers and are powerful opportunities for learning and reflection. These conferences have been around for decades and provide opportunities to learn from medical errors, complications and unanticipated outcomes that may occur both individually and systemically. The goal is to continuously strive to improve performance and clinical outcomes.

"Complications are inevitable, and we are never going to totally eliminate them," says Gail Besner, MD, chief of Pediatric Surgery at Nationwide Children's Hospital. "But our surgical team at Nationwide Children's is truly invested in making sure that we do absolutely everything possible to prevent the same complication from happening to another child. To do that, we need to transparently present every complication in an open, multidisciplinary forum to discuss errors that occurred to improve patient care in the future."

Ten years ago, Dr. Besner's team at Nationwide Children's developed a quality improvement (QI)-based M&M Conference to prioritize the discussion of individual and system failures and develop "action items" for tangible ways to implement the improvements discussed during the conferences. In 2017, they published the results of that work in the *Journal of the American College of Surgeons*.

However, because of a reliance on individual documents to store M&M data, a more effective method needed to be put into place to better assess results and reduce system errors.

In 2018, Dr. Besner worked with Joshua Hampl, now lead business intelligence developer in the Department of Information Services at Nationwide Children's, to develop a secure electronic health record (EHR)-integrated web application (web app). This application would not only store all M&M data electronically in one place but also create a method of assigning and monitoring the completion of action items along the way.

How It Works

During an M&M Conference, multiple medical personnel and trainees gather to identify and discuss complications that occurred. The group decides which complications are treatable and assigns changes to prevent the error from happening again. These changes are called "action items."

Action items could include initiating a new policy or procedure, fixing one that is already in place, or removing barriers in place for medical personnel. With all data now stored in the web application, the QI Team has continual access to the plans needed to remedy the error. As each action item is created, a person will be assigned to make sure these changes are actually implemented. The database will automatically send out bi-weekly emails to remind the owner of the action item deadline, keeping every error type on track and monitored.

In their most recent study currently under review in the *Journal of Pediatric Surgery*, Dr. Besner and her team report that this method of storing M&M data with the web app dramatically improved the review of M&M data, leading to a 67% decrease of the most common system complications and failures. The QI initiative also significantly reduced the number of open action items per month, and the time to closure of action items. This web app not only enhanced the storage and tracking of M&M data but had a real and tangible impact on improving the quality of patient care.

Moving Forward

With the team's initial success, they hope to expand the application's usage beyond the walls of Nationwide Children's and into hospitals and academic institutions throughout the United States.

"Each year, multiple hospitals across the United States ask about our process. We are taking steps to make it sharable for those who want to implement it in their institutions. It has been incredibly gratifying to see the improvements for children here, and to see that expand beyond our walls will be just wonderful," says Dr. Besner.

In 2024, Dr. Besner and her team plan to start testing their application at select hospitals throughout the United States. Hampl recently obtained a grant from the Office of Technology Commercialization at Nationwide Children's to transfer the application to an architecture suitable for external deployment.

"It's rewarding to see the operational impact that our application has facilitated over the past 4 years — action items result in changes to policy and protocol, trends in failure modes are identified and escalated to secondary or tertiary review, and individuals are able to easily search and find what they need. This kind of improvement for patients throughout the United States will be extraordinary," says Hampl. ■

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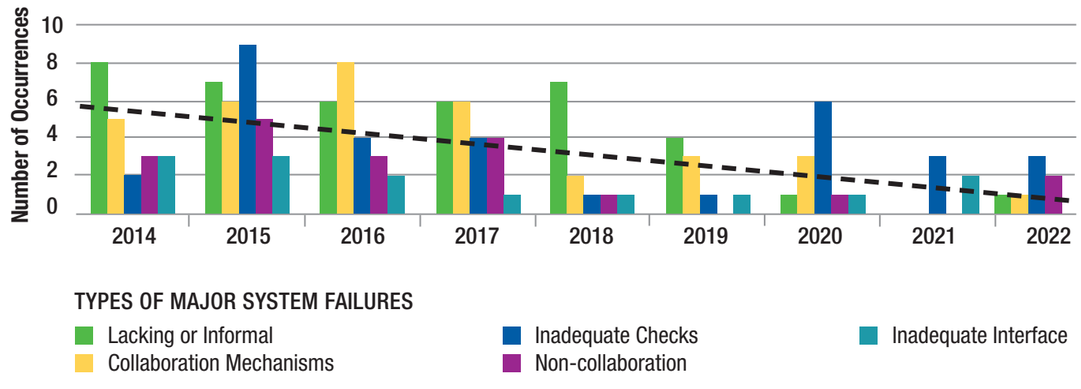
MAJOR SYSTEM FAILURES DECREASE WITH M&M APP

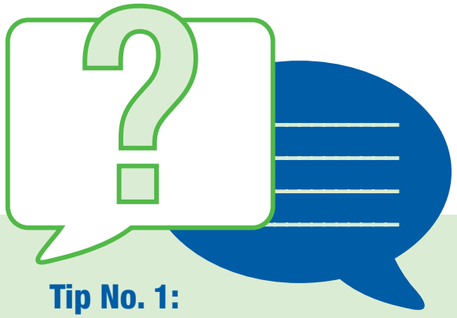


Practical Advice for Investigator-Initiated Trials

by Lauren Dembeck, PhD

Investigator-initiated trials play a crucial role in advancing medical research and contributing to evidence-based medicine. These trials are initiated, designed and conducted by researchers, often physicians or scientists, rather than by pharmaceutical or biotechnology companies. They allow researchers to explore specific hypotheses, novel interventions or unique patient populations that may not be addressed in industry-sponsored trials.

"The field of investigator-initiated studies is growing, and it is a beautiful opportunity to engage study participants with clinical research in a meaningful way," says Samantha Sharpe, CCRP, clinical research project manager at Nationwide Children's Hospital.



Tip No. 1:
Make a Detailed Schedule

When writing the study schedule of events, think through every single step, considering the smallest of logistical details. This can be achieved by imagining a mock run of what it would take to implement all the visits of the study.

During this planning phase, special consideration should be given to recruitment and retention of study participants. When the estimated sample size target is not met, researchers can be challenged to draw valid conclusions or discern differences between treatment groups, compromising the scientific validity of the study.

To aid participant recruitment and retention, study protocols should be designed with a patient-centric approach, incorporating the needs and concerns of the participants and, in the case of pediatric studies, their parents or caregivers. For example, in pediatrics, will the study require the children to miss school and the parents to miss work? How will siblings be accommodated during visits? How long will each follow-up visit last?

"We have to be intentionally mindful, taking a holistic view when considering participant recruitment. The needs of the participants can get missed in the desire to capture large amounts of study data. There has to be a balance," says Sharpe.

Another area that deserves special consideration is regulatory and compliance requirements and local guidelines. While some institutions have dedicated regulatory departments or teams, investigators without those resources can hire regulatory specialists to help them conduct their study in a compliant manner and develop consent and assent forms.

Investigator-initiated trials present a multitude of challenges for the investigator. Over the last decade, Sharpe has refined her expertise in clinical research management. She has presented internationally on best practices for developing investigator-initiated trials since 2018.

"When we're talking about investigator-initiated studies, it is like building a house from the ground up — all planning and operation is directed by the investigator," explains Sharpe. "It requires them to think comprehensively about all aspects of the study, checking all the 'blind spots' that are often overlooked and can hinder swift execution of study deliverables and scientific progress."

Investigators also need to think backward about the possible outcomes of the study and what data will be needed to draw those conclusions.

"Truly successful studies are built on detailed planning before implementation," says Sharpe. "While deadlines often make investigators feel the need to rush, it is important to be thoughtful at the beginning of the planning process. Those initial weeks of planning increase the probability of success throughout the rest of the study."

INSTITUTIONAL SUPPORT FOR INVESTIGATOR-INITIATED TRIALS

Institutional support is vital for investigator-initiated trials. At Nationwide Children's, this is reflected in the strategic plan of integrating clinical care and research, building new facilities and augmenting infrastructure capabilities, investing in both new and ongoing research areas, and funding investigators via an intramural funding program.

"Our goal is to continue to build infrastructure that expedites clinical trials and catalyzes discoveries, so we can offer cutting-edge innovations and treatments to our patients faster," says Cynthia Gerhardt, PhD, chief clinical research officer at Nationwide Children's. "It's very important that the institution supports investigators by providing resources, training, and funding for their trials under development."

Dr. Gerhardt also highlights the importance of collaborations with other institutions via multicenter and decentralized trials. Both allow for increased numbers of participants, enabling investigators to draw more robust conclusions. These are particularly important in pediatrics research because many pediatric conditions are rare, making it difficult for a single center to recruit enough patients to trials.

"The future of clinical trials is about collaborating with providers in the community," says Dr. Gerhardt. ■

"Truly successful studies are built on detailed planning before implementation. While deadlines often make investigators feel the need to rush, it is important to be thoughtful at the beginning of the planning process. Those initial weeks of planning increase the probability of success throughout the rest of the study."

– *Samantha Sharpe, CCRP, clinical research project manager at Nationwide Children's*

"Our goal is to continue to build infrastructure that expedites clinical trials and catalyzes discoveries, so we can offer cutting-edge innovations and treatments to our patients faster."

– *Cynthia Gerhardt, PhD, chief clinical research officer at Nationwide Children's*

Tip No. 2:
Make a Manual of Operations

"The study protocol is the scientific idea, and the manual of operations is essentially the directions of how to have that idea realized," explains Sharpe.

A manual of operations should include how each step of the study will be carried out — moving ideas to implementation. This process includes engaging with potential team members and discussing the study (e.g., finance, regulatory and clinical research teams). The feedback gained during this process not only solidifies the manual of operations but can also help the investigator refine the study protocol, potentially avoiding any changes that can impact study completion. For example, if collecting peripheral blood samples is indicated in the protocol, the manual of operations should address where the collection tubes can be obtained; who will collect the samples; whether the blood draw is happening as part of routine care, and how samples will be transported and processed.

Tip No. 3:
Don't Forget Your Budget

For an investigator-initiated study, the investigator is also in charge of detailing all costs of the study. This includes appropriately compensating any staff members performing duties outside of their usual clinical care requirements and determining how much to compensate participants for their time. Study costs can also include support services, specimen processing, research procedures and numerous other operational fees. In the example above, it is important to define clearly if the study is paying for the time and supplies for the blood draw. ■

Optimizing Prenatal and Neonatal Care for Infants With Treatable Rare Diseases

As new treatments emerge and diagnostics improve, earlier interventions offer infants with rare metabolic and neurogenerative conditions a future wildly different than ever before.

by Katie Brind'Amour, PhD, MS, CHES

Not long ago, a diagnosis of molybdenum cofactor deficiency (MoCD) type A meant death before kindergarten.

Since the FDA approval of NULIBRY® (fosdenopterin) in 2021, however, children diagnosed with MoCD type A — an inherited metabolic disorder that results in severe developmental delay and neurological damage due to the accumulation of sulfites and S-sulfocysteine (SSC) in the brain — have hope for a significantly longer life.

If this intravenous (IV) drug is administered prior to serious brain injury, they may avoid significant intellectual and physical disability.

The trick? Getting the diagnosis and beginning treatment before significant damage has been done.

A Sibling's Silver Lining

In 2018, Jeyad Asfour was born to parents Hanan and Mohammed. Within days of birth, he suffered seizures and went on to experience profound developmental delays.

After years of being told his symptoms were due to hypoxic ischemic encephalopathy (HIE) during childbirth, Jeyad's family moved to central Ohio. During an appointment at

"We explored the options, including whether we could get permission from the FDA for emergency use or set up a research study to try to give the fetus the drug in utero, but those all involved unknown risks, and there was no established way to give this drug before birth."

— *Bimal Chaudhari, MD, MPH, neonatologist and genetics and genomic medicine specialist at Nationwide Children's*

a Nationwide Children's Hospital, Hanan insisted that the typical events leading to HIE had never happened when her son was born. She also mentioned that a niece had been diagnosed with a rare genetic condition that could cause symptoms like her son's.

"A neurologist sent the family to me — I have a reputation for doing evaluations of babies in the NICU who have diseases that look like HIE," says Bimal Chaudhari, MD, MPH, a neonatologist and genetics and genomic medicine specialist at Nationwide Children's. "I took a look at the child's records and said, 'I'm sorry you've been told this, there's no way your child has HIE,' and we did genetic testing and got him the right diagnosis."

The test revealed Jeyad had MoCD type A. Although there had been no treatment available for the condition when he was born, fosdenopterin had been approved by the time of his diagnosis. Finally, the family had an answer, a treatment and a way to prevent further neurodegenerative progression for Jeyad.

Fast-forward 2 years, and Hanan found out she was expecting another child. She was eager to proactively identify expectations for her new child's health and contacted Jeyad's geneticist to discuss a game plan.

The genetics and maternal-fetal medicine teams at Nationwide Children's collaborated with Hanan's obstetric experts at a local hospital system, Ohio Health, who confirmed that this sibling, another son, also had MoCD type A.

The news was devastating, but the early knowledge offered the family hope — and an opportunity to intervene before significant brain injury had begun.

Pioneering Management

Observable brain injury in cases of MoCD type A occurs during the third trimester, though from published literature it is unclear at exactly what gestational age the injury first emerges. For any given child, it is uncertain how significant the damage will be by the time of a full-term delivery.

The family's growing care team within the Fetal Center at Nationwide Children's — now comprised of maternal-fetal medicine, obstetrics, genetics, neurology, palliative care, a medical ethicist and neonatology specialists — discussed possible interventions.

"We explored the options, including whether we could get permission from the FDA for emergency use or set up a research study to try to give the fetus the drug *in utero*," says Dr. Chaudhari. "But those all involved unknown risks, and there was no established way to give this drug before birth."

Fosdenopterin requires daily IV treatments, rather than a one-time or periodic intervention, complicating things considerably. With fetal drug administration not being a viable option, the team explored the next-best opportunity to prevent significant brain injury.

"The best option available was to offer elective preterm delivery to reduce the time of exposure to toxicity in the brain, and provide the baby really early treatment," says Adolfo Etchegaray, MD, chief of fetal medicine at Nationwide Children's, who consulted on the case and explored opportunities for prenatal management.

The family and team thought long and hard about the risks and benefits of elective premature delivery, which — if done too early — can be fraught with health threats to multiple organs, especially the lungs.

"We had a few multidisciplinary meetings to talk about at what point the risks of prematurity would be fairly low and when we might expect to see some injury occurring due to MoCD, since the family and the care team all wanted to deliver prior to any visible injury," says Darrah Haffner, MD, MHS, an attending pediatric neurologist at Nationwide Children's.

Based on her research, the literature suggested that damage could typically be visible on standard prenatal ultrasound — meaning it had already become significant, chronic cystic injury — by 35 weeks' gestation.

"We knew we needed to precede that 35-week cut-off by at least a couple weeks to avoid that extensive injury," says Dr. Haffner, "so we did serial MRIs in utero to track his development."

The initial MRI, done at 22 weeks 5 days gestation, suggested fairly normal brain development. By 28 weeks 5 days, however, the team felt growing space behind the cerebellum was cause for concern. The images indicated potential mega cisterna magna, which is not specific to MoCD but is present in many cases of neurometabolic disorders.

"We know the earlier a child is born, the more likely they are to face lung immaturity, problems in the intestines and other complications of prematurity," says Amy Schlegel, MD, director of the Perinatal Palliative Care Program and medical director of the NICU at Nationwide Children's main campus. "We made every effort to choose that inflection point wisely, when we would be able to most positively impact the child's neurologic outcome and still minimize the risks of prematurity. We settled on around 32 weeks knowing that at this gestational age, the risks of severe lung disease are lower, and babies are often large enough to tolerate feeding, EEGs and the medications they are likely to need."

The team planned for a C-section at 32 weeks 6 days, with the procedure scheduled at Nationwide Children's to allow the fastest administration of fosdenopterin and ongoing care in the NICU.

When Hanan came in a day early with concerns about reduced fetal movement, the operation began just ahead of schedule.

Making MoCD History

Baby Ghaith was born via an uncomplicated C-section on March 29, 2023. He received his first IV dose of fosdenopterin before he was 10 minutes old.

This administration within minutes of delivery is the earliest treatment of MoCD known to the Nationwide Children's team.

"The one pharmacy in the country that stocks fosdenopterin isn't in the habit of dispensing drugs to people who haven't been born yet," says Dr. Chaudhari. "It actually required an inordinate coordination of effort between pharmacy services, neonatal services, and fetal medicine to ensure the drug was available as soon after delivery as possible."

Fosdenopterin works to reduce the toxic build-up of SSC in the brain by providing the missing component MoCD children need (cyclic pyranopterin monophosphate) to make molybdenum cofactor, which breaks down the sulfites and SSC. Theoretically, if it is administered before toxic accumulation, it should prevent acute injury to the brain. The sooner it is in a child's system, the better the chance a child has to prevent new damage — and its related seizures and symptoms — from occurring.

Ghaith experienced seizures starting about 12 hours after delivery, consistent with MoCD. By 36 hours after fosdenopterin administration, however, the seizures had ceased — something that rarely occurs even with appropriate seizure management in children with MoCD who do not receive fosdenopterin.

"Even doing all of these things, the baby still has some low level of brain injury, but it is worlds different than in kids without access to early treatment — such as his brother — and he was a little premature, after all," says Dr. Chaudhari. "If you talk to Hanan and Mohammed, they'll readily endorse the differences they see at this age for Ghaith compared to his older brother."

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Time will tell how effective the drug is over the long term, but initial follow-up suggests it is a game changer when delivered prior to widespread brain injury.

Teasing Out the Impact

Ghaith's initial postnatal MRI, done at 5 days of age, revealed that acute brain injury had indeed occurred following his 28 weeks 5 days gestational age MRI; the basal ganglia demonstrated new damage compared to his prenatal scans.

Injury to this area of the brain is frequently associated with muscle or motor skill delays. Sure enough, Ghaith displayed muscle tone abnormalities during his time at the NICU, and has since been diagnosed with cerebral palsy.

By about 5 weeks of age, however, just before his discharge from the NICU, Ghaith's repeat MRI revealed astonishing news — unheard of for children with untreated MoCD.

"We could see where he had developed permanent cystic change from the prior injuries to the basal ganglia," says Dr. Haffner, "but there was no new acute, ongoing injury. That's real success, the fact that we were able to stop the injury where it was and it didn't spread to the back parts of his brain, and all over — that's a really good thing."

Provided the drug continues to work so well, the team expects to have halted the neurometabolic effects of Ghaith's MoCD. This means early delivery and drug administration may have prevented debilitating developmental delays and even premature death for this little boy.

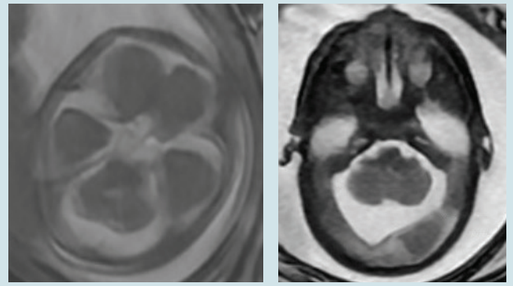
"I would be cautiously optimistic about what this case represents, in that I see this as an example of what an innovative team can do for a family in a difficult situation," says Dr. Chaudhari.

As of one year of age, his cerebral palsy remains Ghaith's only noticeable delay.

While the drug has not existed long enough to study its long-term impact, data from other recipients suggest varying degrees of helpfulness — most likely due to varying degrees of existing brain damage prior to treatment. The Nationwide Children's team is optimistic that early intervention changed the trajectory of Ghaith's life.

Serial Prenatal MRIs

The initial MRI (22 weeks' gestation) showed largely normal development. Follow up at 28 weeks revealed potential mega cisterna magnum, or increased space behind the cerebellum. Although the volume was not worrisome yet, it is a common feature of MoCD. The care team believed it suggested emerging injury.



Postnatal MRI at 33 weeks 3 Days Gestational Age Equivalent (day 5 postnatally)

Postnatal MRI revealed acute injury to the basal ganglia (white areas in the top images) occurred between 28 weeks' gestation and birth.

"When he went home from the NICU, we could already potentially predict some motor differences down the road for him," says Dr. Schlegel. "But I also suspect that, had we allowed another 2 months *in utero*, that injury would have been much more significant. I know we did something to change Ghaith's outcome, and we are going to continue to support healthy outcomes for him through nutrition, medicine, and occupational and physical therapy for a long time to come."

A Brighter Outlook for Children With Rare Neurometabolic Diseases

As the damage had not noticeably progressed on his follow-up MRI, and there have been no clinical indications of new MoCD-related symptoms, Ghaith's ongoing care will consist only of physical and occupational therapy, daily at-home fosdenopterin, and periodic neurologic and genetic follow-up visits at Nationwide Children's.

"This has become one of my favorite patient stories because of how collaborative we were with the family and our teams in making recommendations, how carefully we pulled in specialists with expertise in ethics, obstetrics, palliative care and neurology throughout the case," says Dr. Schlegel. "I know we did the right things for this baby and thoughtfully came together to change the outlook for him."

At Nationwide Children's, this type of early identification and bespoke intervention is par for the course. Although prenatal identification of rare genetic disorders often occurs only among cases such as Ghaith's, where a prior sibling or family member has already undergone a diagnostic odyssey or the mother has elected to undergo prenatal testing, the technology available for rapid, early diagnosis is dramatically more advanced — and rapid — than in years past.

"We've reduced the time it takes to get a diagnosis by about 90% or more in the last decade, so much so that we can make a diagnosis on a research basis in just 30 hours or so if there is a sick baby," says Dr. Chaudhari. "When neonatologists hear that, suddenly they are willing to pursue early diagnostics. And if those diagnostics happen, suddenly treatments become viable."

As diagnosis begins to precede irreversible brain damage, treatments begin to have the opportunity to prevent injury, making the entire cycle of testing and intervention more worthwhile.

"If we can diagnose early," explains Dr. Chaudhari, "a lot of things that used to be untreatable suddenly become treatable."

Dr. Chaudhari and Dr. Haffner both specialize in identifying alternative explanations for delays and disabilities experienced by babies who spent time in a NICU. Such children often receive the label of HIE with little formal investigation into the possibility of other conditions that can mimic that pattern of brain injury.

"It's the bread and butter of what I do," says Dr. Haffner. "We can't automatically say it's hypoxic ischemic injury, and I'm very passionate about that. When the case is subtle or questionable, we have to look at other things that could be mimicking those symptoms, especially now that we have therapies for things like MoCD — we could treat and change the course of these diseases."

For diseases with effective new therapies, it may even make sense to extend screening beyond families with a known history of a disease to the broader population via newborn screening or prenatal genetic testing.

"We need to improve opportunities for prenatal testing to identify conditions," says Oluyinka Olutoye, MD, surgeon-in-chief and a world-renowned neonatal and fetal surgeon at Nationwide Children's. "Now that there is ever-growing potential to intervene medically before a child is born, it expands the utility of prenatal testing. When a diagnosis is made earlier, we can find ways to intervene earlier to improve outcomes."

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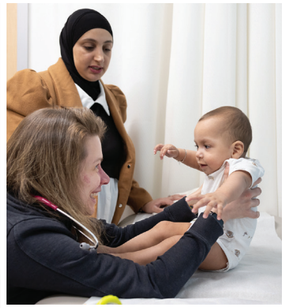


Visit PediatricsNationwide.org/MOCD to watch Ghaith's story

Reimagining the Future of Genetic Disease Therapies

Better still than early identification with immediate postnatal treatment, as in Ghaith's case, would be therapy while a patient is still *in utero*.

"As great as is to be able to treat the baby, the world really needs to start thinking fetal," says Dr. Chaudhari. "We need to get better at translating neonatal interventions into fetal interventions so that we aren't delivering prematurely. It was the best we could do for their family in that moment, but it's not what we should be striving for long-term."

While this was not available for Ghaith, it may become possible for others with a wide variety of genetic disorders and other rare conditions.

"The speed of genomics is starting to give us opportunities to intervene earlier and earlier both postnatally and prenatally," says Dr. Etchegaray. "We have that capability, and it's certainly an advantage being at a place where many of the new gene therapies are actually being developed — we see genetics not only as a way of understanding a diagnosis, but as a potential tool to correct that problem."

"This case is a harbinger of what's possible," says Dr. Olutoye. "It shows what can be done to change the trajectory of health for our patients, to improve outcomes for infants and children."

The Fetal Center team at Nationwide Children's already intervenes before birth for a whole host of complicated diagnoses, including structural heart anomalies and spina bifida. These prenatal interventions allow the tiny patients life-altering and potentially life-saving changes in their health conditions early, to reduce the risk for ongoing development.

"I'm really excited regarding what is to come in maternal-fetal medicine," says Dr. Etchegaray. "We can open our menu of interventions for thousands of conditions for which we would be able to provide really personalized medicine, treat exactly one gene, protein or pathway with a customized recipe instead of treating at the level of the entire target organ."

This ideal is something the broader teams at work behind the scenes of Ghaith's care hope to achieve for a growing number of rare diseases and complicated diagnoses. Dr. Olutoye expects to see more successes like Ghaith's as Nationwide Children's and other leading institutions fine-tune early diagnosis, treatment development and proactive, personalized intervention plans for children with rare diseases. ■

This case has been submitted for publication.

New National "**Vital Signs**" to Measure Population-wide Pediatric Health

by Jeb Phillips

In 2017, an opinion piece in *JAMA Pediatrics* started this way: "We call for a national effort to develop a parsimonious set of quality and outcome measures for (all) children." And now, for perhaps the first time in American pediatrics, that "parsimonious set" has been laid out to guide communities and health systems across the United States.

A series of publications in the National Academy of Medicine's *NAM Perspectives* has put forward four "Vital Signs for Pediatric Health" that can be used to track overall well-being across the entire span of childhood in United States, the way a vital sign like blood pressure can help measure health for an individual.

The signs are elegantly simple, but they are also proxy measures pointing to the most complex issues in childhood:

- Infant Mortality
- School Readiness
- Chronic Absenteeism in Middle School
- High School Graduation

"Without these kinds of population health measures, hospitals can build wonderful facilities that have magic inside of them, but the communities at large can decay," says Kelly Kelleher, MD, MPH, vice president for Community Health at Nationwide Children's Hospital. Dr. Kelleher is both one of the authors of that original call in 2017 and one of the lead authors of the recent group of "Vital Signs for Pediatric Health" publications.

"We want to help drive the conversation to how health systems and their partners can think outside of their facilities to improve lives of children at large," he says.

Nationwide Children's has previously instituted its own set of Pediatric Vital Signs, showing the promise, and the challenge, of such a large initiative. Now other health care organizations have a national roadmap — if they choose to follow it.

DEVELOPING THE VITAL SIGNS FOR PEDIATRIC HEALTH

The original idea for the pediatric vital signs was embedded in a larger group of overall core health metrics proposed by the National Academy of Medicine in 2015. Also called "Vital Signs," the 15 metrics named issues from individual spending burden (the amount a person must spend on health care) to overall life expectancy. Those metrics focused on adults.

A series of pediatric-focused meetings followed, first through Nationwide Children's, Children's Hospital Association and the American Academy of Pediatrics, and then through the National Academies of Sciences, Engineering and Medicine's Forum for Children's Well-Being.

The discussions took a while.

"With kids, you have so much changing all the time, the mental, the emotional, the behavioral, the physical health, that we had to make the argument cogently and often that kids are different," says Kimberly Eaton Hoagwood, PhD, Cathy and Stephen Graham Professor of Child and Adolescent Psychiatry at New York University' Grossman School of Medicine. Dr. Hoagwood is the lead author of the recent vital sign publication about high school graduation, and she is a co-author of two of the other papers.

The child metrics were carefully selected to encompass different stages of child growth, capturing a small number of meaningful metrics which had at least some available data at state and/or local levels, says Jennifer Kaminski, PhD, lead health scientist, Policy Analysis and Engagement Office, Office of Policy, Performance, and Evaluation at the Centers for Disease Control and Prevention. Dr. Kaminski is lead author of the recent vital sign publication about school readiness, and a co-author of the other papers.

With funding from the CDC, the convening power of the NASEM and the contributions from experts across childhood health, four core metrics were proposed.

THE VITAL SIGNS

The signs are separated by age and developmental stage. For a group of metrics developed by people in pediatric health care, they can seem more focused on education than health. But that's where much of the available data on children and adolescents are, says Dr. Kaminski. Biology, education, parent income level, geography, race, access to health care and many more elements can all play a role in child health and development.

Infant Mortality Rate

The rate of child death before 1 year of age may be the most widely used measure of overall child health in the United States, according to the authors. It's a possible indicator of, and it is driven by, maternal health, gaps in community care systems, socioeconomic inequity and other population health-level elements.

It is, perhaps, the most obvious vital sign to use.

Infant mortality varies widely by geography and demographics; in 2020, some states had double the rates of others, and for most of the last 60 years, Black infants died at over two times the rate of White infants.

Importantly, communities that have positively affected infant mortality rates have developed collaborations across sectors, potentially promoting better coordination among and between child and maternal health systems, according to the authors. Infant mortality rate is an indicator, but its improvement can also be a spur to broader community improvement.

VITAL SIGN	PAPER AUTHORS
Infant Mortality	Kelly Kelleher, MD, Nationwide Children's; Kimberly Hoagwood, PhD, New York University; Deborah Klein Walker, EdD, Global Alliance for Behavioral Health and Social Justice; Jennifer Kaminski, PhD, CDC; William Gardner, PhD, Children's Hospital of Eastern Ontario; Erin G. Fox, MPH, The Ohio State University
School Readiness	Kaminski; Sandra Barrueco, PhD, University of Maryland Baltimore County; Kelleher; Hoagwood; Anne Edwards, MD, American Academy of Pediatrics; Fox
Chronic Absenteeism	Sara Johnson, PhD, Johns Hopkins School of Medicine; Edwards; Tina Cheng, MD, Cincinnati Children's Hospital Medical Center; Kelleher; Kaminski; Fox
High School Graduation	Hoagwood; Walker; Edwards; Kaminski; Kelleher; Julia Spandorfer, BA, NYU, Fox

"We want to help drive the conversation to how health systems and their partners can think outside of their facilities to improve lives of children at large."

— Kelly Kelleher, MD, vice president for Community Health at Nationwide Children's Hospital

"There are a lot of people who are paying attention to data, and to the suffering that children and young people are experiencing. There are some emerging youth leaders who have been through this and who have new ideas about ways to create opportunities to engage in meaningful work. Those embers are there. We need to blow on them to help them ignite."

— Kimberly Eaton Hoagwood, PhD, Cathy and Stephen Graham Professor of Child and Adolescent Psychiatry at New York University's Grossman School of Medicine

School Readiness

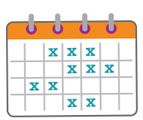
Readiness for kindergarten can serve as a lens to gauge the early development of children across a variety of domains, the authors argue. Measuring readiness, however, is not simple.

A full accounting of readiness considers physical well-being and sensory motor development; social and emotional development; approaches to learning; language development; and general knowledge and cognition, such as literacy and math skills. The measures used across districts and states can vary widely.

Only 42.5% of children 3-5 years of age were considered "healthy and ready to learn" in 2019 according to the National Survey of Children's Health, and significant readiness disparities exist among demographic categories. In addition, not all states and jurisdictions measure school readiness.

One of the major challenges of using school readiness and any other education-related metric is the traditional disconnect between education systems and health care, and the additional consent needed for sharing data. Still, school readiness may be the most comprehensive overall look at well-being in early childhood, the authors write.

Chronic Absenteeism in Middle School



Absenteeism as a metric can be used at any schooling age, but with proposed metrics at other developmental stages, the authors suggest it made most sense to use it as a vital sign for children who are approximately 10-15 years old.

The U.S. Department of Education defines "chronic absenteeism" as missing 10% or more of enrolled school days. Approximately 14% of middle school students are chronically absent in a given year, again with large disparities by income, geography, race and other demographics.

Most drivers of absenteeism are "external" to education — health, economic stability, parental resources — and the metric could be especially illuminating in 2024.

"Chronic absenteeism may take on a renewed importance as a vital sign as the U.S. works to recover from the health, economic social and education impact of the prolonged COVID-19 pandemic," the authors write.

High School Graduation

Like infant mortality, high school graduation has become a signal measure of population health over the last several decades. It is seen as not only a snapshot of the way things are, but as one predictor of adult outcomes. Nearly 80% of men in prison, for example, have not graduated from high school according to one study, and lifetime earnings are significantly less for people without a high school degree.

The authors chose the U.S. Department of Education's Adjusted Cohort Graduation Rate as the most representative way to look at the statistics. In 2018-2019, the national rate was 86%, an improvement over the 79% rate in 2010-2011. The kinds of disparities that exist with the other proposed vital signs exist in high school graduation as well.

And as with the other signs, there are potential benefits far beyond education that may come with focusing on high school graduation rate and trying to improve it, the authors say. Precursors to dropping out of high school include issues from early chronic absenteeism to teenage pregnancy. A strategy to positively impact those precursors could also impact graduation.

JUST THE START

Identifying these vital signs is just the beginning of a challenging, continual process to support health systems in promoting pediatric growth and development. The experience at Nationwide Children's may be illustrative.

Nationwide Children's developed its own group of eight "Pediatric Vital Signs" to measure the health of children in Franklin County, Ohio in 2018: infant mortality kindergarten readiness, high school graduation, obesity, teenage pregnancy, suicide, all-cause child mortality, and a hybrid measure called "preventive services delivery." Dozens of members of the Nationwide Children's staff are involved improving well-being through those metrics, with community public health, education, health care and other partners.

Certain metrics, such as infant mortality, showed real improvement before COVID-19. Promising strategies were developed and implemented in the other metrics. Then the pandemic came.

"In many cases, we're now trying to get back to our pre-COVID baseline," says Dr. Kelleher.

The Nationwide Children's Pediatric Vital Signs, however, have helped provide a specific analysis of the pandemic's impact on child well-being. They point to particular areas of stress in social areas, and the team at Nationwide Children's is adjusting their strategies to make a difference.

What the most recent proposed metrics provide is a place for other pediatric health systems to start, says Dr. Kaminski. Those systems may decide that other metrics make sense in their regions, or that strategies different from the ones suggested in the *NAM Perspectives* publications make sense.

"I have realistic optimism about the project," she says.

"Even a great set of papers does not alone change the world. What I think this will do, is where there is already interest or investment in moving population health forward, you can point to these and say, 'here's a set of metrics. Look, the NASEM and CDC and Nationwide Children's have shown evidence for these.' It's a long game, but public health is a long game."

Dr. Hoagwood feels similar optimism because of her discussions with young people and young adult peer leaders. She also thinks of these publications as a starting place, and that many of the best strategies for improving metrics like infant mortality and high school graduation rates are going to come from communities themselves.

"There are a lot of people who are paying attention to data, and to the suffering that children and young people are experiencing," she says. "There are some emerging youth leaders who have been through this and who have new ideas about ways to create opportunities to engage in meaningful work. Those embers are there. We need to blow on them to help them ignite." ■

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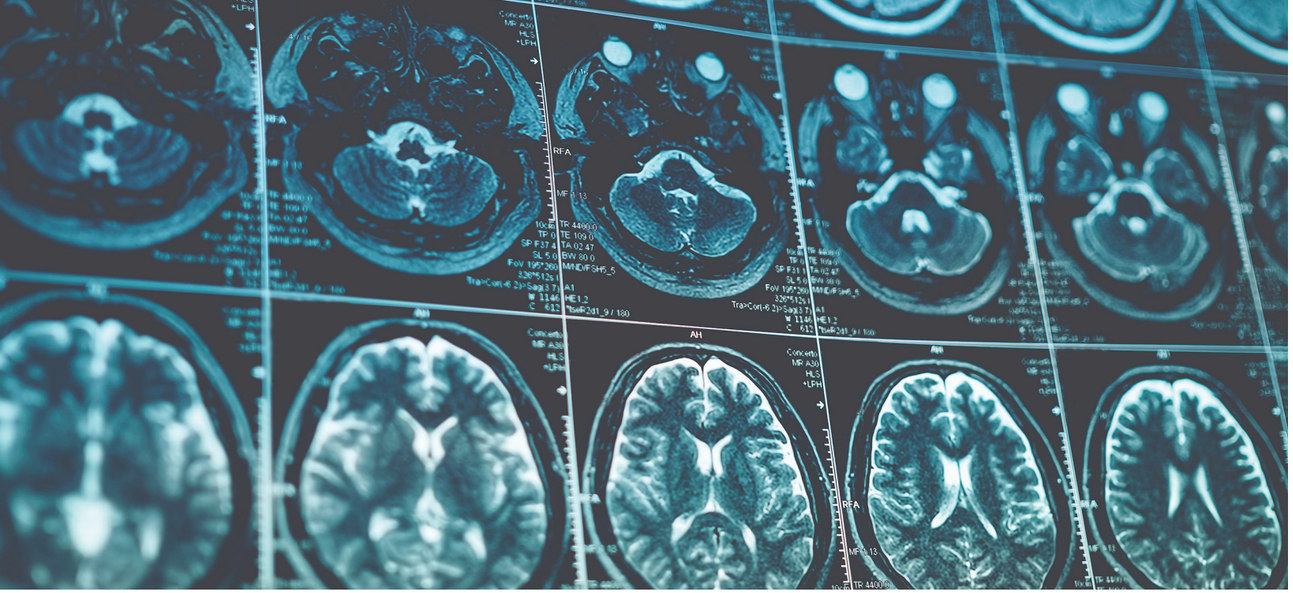


Accelerating Advances in Epilepsy Surgery

One program is bringing together clinical care, surgery and research to create a brighter future for children with intractable epilepsy.

by Abbie Miller, MWC

Childhood onset epilepsy affects 1% of children worldwide.

Up to a third of patients with epilepsy will have medically refractory epilepsy, continuing to have seizures despite using two or more antiseizure medications.

Options for this group include intercranial epilepsy surgery, Vagus nerve stimulator (VNS) insertion, ketogenic diet and drug trials. It is increasingly recognized that epilepsy surgery can dramatically improve the quality of life for children with intractable epilepsy. In some cases, it is the only potentially curative option.

The Epilepsy Surgery Program at Nationwide Children's is among the first group of programs to earn Germain Family Accelerator Program funding. The Accelerator Program was established by the Germain Family Foundation and is managed by Nationwide Children's research administration.

"Accelerator funding is awarded to established programs with successful track records in clinical care and research," says Dennis Durbin, MD, MSCE, president of the Abigail Wexner Research Institute at Nationwide Children's. "The Accelerator designation was created through a generous gift from the Germain Family Foundation, and we are proud to see our programs take advantage of this opportunity."

Practical Improvements for Access

Research suggests that early surgical intervention can boost developmental outcomes and even cure young children with intractable epilepsy, but low referral rates and other barriers result in limited access for some.

In 2022, the Epilepsy Surgery Program at Nationwide Children's had eight beds in the Epilepsy Monitoring Unit, limiting the number of children who could be tested. In 2023, the addition of just two more beds increased the capacity. In the past year, they were able to increase testing from 103 in 2022 to 140 patients.

"Increasing capacity to test children who may benefit from epilepsy surgery is the first step to closing the treatment gap for children with intractable epilepsy," says Adam Ostendorf, MD, medical director of the Epilepsy Surgery Program and associate division chief for research at Nationwide Children's. "Getting to 10 beds is just the first step. We are already planning how our capacity can continue to grow."

In addition to creating space for increased testing, the team is developing research to understand differences in surgical access based on social determinants of health.

"On average, patients wait 22 years for epilepsy surgery," says Ammar Shaikhouni, MD, PhD, pediatric neurosurgeon at Nationwide Children's. "And non-white children are four times less likely to receive surgery. We need to find out why this is. We know that testing is similar across race and ethnicity, so we're partnering with others to do focus group research to find out why there's such a difference among people who get epilepsy surgery."

Research to Understand Causes of Epilepsy

"The causes of epilepsy are incredibly diverse and remain a mystery in more than half of people with epilepsy," says Dr. Ostendorf.

Neurologists and neurosurgeons are collaborating with experts in the Steve and Cindy Rasmussen Institute for Genomic Medicine to identify mutations that cause epilepsy. The research, supported by more than $3 million in National Institutes of Health funding, has already led to five publications and the discovery of a novel way some seizure-causing mutations are inherited, detailed in *Nature Genetics*.

"We were motivated to study the genetic causes of drug-resistant epilepsy so future research might be able to develop more effective treatments," says Tracy Bedrosian, PhD, senior author of the *Nature Genetics* paper, principal investigator in the Institute for Genomic Medicine and co-leader of the Epilepsy Surgery Accelerator Program at Nationwide Children's.

The study was based on samples collected during surgery at Nationwide Children's. Now, the team is establishing a multicenter protocol in the existing Pediatric Epilepsy Research Consortium. Through the expansion efforts, they've sequenced more than 100 patients to date.

"Every surgery is an opportunity to identify mutations that cause epilepsy," says Dr. Shaikhouni, who is also an assistant professor of neurological surgery at The Ohio State University College of Medicine. "Collaboration with other epilepsy centers is critical to take our research further. More patients mean more data for faster discovery."

Future of Epilepsy Surgery

In addition to learning from every surgery and every sample, the team has established a study utilizing massive amounts of electroencephalogram (EEG) data to identify children who may benefit most from epilepsy surgery.

In collaboration with the newly established Office of Data Science at Nationwide Children's, Dr. Shaikhouni and his collaborators are unleashing the power of data science on more than a terabyte of EEG recording data. This work, presented at at the American Epilepsy Society meeting in 2023 and the American Society for Pediatric Neurosurgery meeting in 2024 makes potentially curative epilepsy surgery more than a last resort.

"So often, we go through years of trial and error with medications, testing and frustration for families, only to arrive at surgery," says Dr. Shaikhouni. "But the reality is, for many of these children, that surgery is curative. How much better could they be served if we could identify the ones most likely to benefit the most from surgery and fast track them to a potentially curative solution." ■

> "Every surgery is an opportunity to identify mutations that cause epilepsy. Collaboration with other epilepsy centers is critical to take our research further. More patients mean more data for faster discovery."
>
> — Ammar Shaikhouni, MD, PhD, pediatric neurosurgeon at Nationwide Children's

New Frontiers for Data Science in Pediatric Research

Peter White, PhD, chief data sciences officer at Nationwide Children's Hospital

Data science has always been an important part of research, but novel technologies are creating opportunities for a new frontier of data-driven science.

From discovery science to population health, researchers generate masses of data that hold immense potential to transform pediatric research, diagnostics, treatments and even guide disease prevention strategies. To make sense of this data deluge, we've been harnessing the power of cloud computing and cutting-edge data science techniques, such as artificial intelligence (AI), machine learning (ML) and big data analytics.

And that's why the Abigail Wexner Research Institute at Nationwide Children's Hospital has taken the bold step of creating the Office of Data Sciences. As the first chief data sciences officer, I'm proud to be leading this important initiative that will enable our research community to learn more from our data than ever before. Throughout my career here, I've had the opportunity to empower our research community with cutting-edge capabilities in genomics, data analysis and interpretation.

Organizational Support for the Data Sciences

In our quest to empower our researchers with the tools for innovation and excellence in their fields, we dedicated the past six months to a comprehensive analysis of our extensive clinical and research data ecosystem. This deep dive revealed critical insights: as our capacity for data generation and storage has expanded rapidly, we've encountered challenges with siloed datasets that hinder seamless integration. Furthermore, while our research community has a palpable enthusiasm to leverage data science methodologies, several obstacles have emerged. High data transaction costs, the intricate nature of big data analytics, and the scarcity of skilled personnel have significantly constrained our ability to harness the full potential of our data resources.

The outcome of our planning has led to the establishment of the Office of Data Sciences, marking a new chapter of excellence within our research institute. This initiative embodies our strategic vision to fully unlock the capabilities of biomedical data sciences throughout our research endeavors. By leveraging our robust foundation in EPIC, data sciences, genomics and cloud technologies, along with a collective ambition to enhance data literacy and embrace cutting-edge technologies, our office is perfectly positioned to utilize AI and sophisticated data science techniques. Our aim is to propel research forward by making the most of our extensive clinical data ecosystem.

To guide our efforts, we have pinpointed four critical areas of focus for the new office: data lake, data intelligence, data translation and data mastery.

All four strategic initiatives share an aspect of the application of AI, which holds remarkable promise for transforming the health care sector and offers innovative solutions to complex challenges. Technologies such as ChatGPT exemplify the potential of AI to enhance our understanding and management of health conditions, promising a future where data-driven insights lead to better patient outcomes. As we stand on the brink of this technological revolution, it's crucial to invest in research and development to fully realize AI's capabilities in clinical settings.

However, integrating AI into health care is not without its challenges. Current AI technologies, including advanced large language models like ChatGPT, exhibit limitations that necessitate cautious optimism. One notable concern is their lack of determinism; the same query can yield varying responses, complicating their reliability in clinical decision-making. Moreover, these systems can "hallucinate," generating responses that seem plausible yet lack factual grounding. Such issues underscore the importance of ongoing research and validation to ensure AI's safe and effective application in health care environments.

Applying Data Science: The First Two Projects

Two pivotal translational initiatives will help us synergize data within the Office of Data Sciences data lake and assess emerging data science technologies.

Four Critical Areas of Focus

To guide our efforts, we have pinpointed four critical areas of focus for the new office:

1. Data Lake: We aim to revolutionize how diverse data sources are integrated, employing AI-enhanced technologies within a centralized data lake. This initiative will facilitate access to advanced data analytics and ML platforms via cloud computing technologies, enabling groundbreaking research possibilities.

2. Data Intelligence: By spearheading innovative AI projects, we intend to lead advancements in child health. This involves formulating a strategic approach to AI application in research and fostering a robust community of data science expertise.

3. Data Translation: Our objective is to accelerate the transformation of data science research into tangible insights and practical applications. We will achieve this through strategic translational initiatives and the deployment of advanced data science technologies, including AI and ML. This approach is designed to bridge the gap between theoretical research and its real-world impact, ensuring that scientific discoveries are promptly translated into benefits for patient outcomes.

4. Data Mastery: Our commitment extends to broadening the data science talent pool and making data science knowledge universally accessible. To realize this, we are launching education initiatives specifically designed to cultivate data science expertise among groups presently underrepresented in the field. Coupled with the creation of innovative software and the integration of AI technologies, these efforts are set to significantly elevate our research capabilities.

A GENiUS Idea for Newborns

The first is a collaboration named GENiUS: GENomic analysis with enhanced AI for Understanding and Swift diagnosis. This project unites ODS with the Steve and Cindy Rasmussen Institute for Genomic Medicine, the Division of Clinical Genetics and Genomics, and the Division of Neonatology. With GENiUS, we hope to integrate electronic medical record (EMR) data with our comprehensive genomic sequencing data, optimizing genetic testing's efficacy for our most vulnerable neonatal intensive care unit patients.

GENiUS is poised to tackle two significant challenges. The first focuses on utilizing large language models (LLMs) and ML to identify neonates requiring genomic testing by detecting signs of genomic diseases — signs that might elude clinicians. The second is dedicated to the automation of genomic data analysis, ensuring genomic data from patients who initially test negative are continuously re-analyzed and updated. Such updates are crucial as new disease mechanisms are uncovered and as the patient's clinical condition evolves, guaranteeing the most accurate and timely diagnosis for ongoing care.

Data Science for Suicide Prevention

The second translational initiative is a pioneering partnership with the Center for Suicide Prevention and Research, aptly named DREAM: Data Review and Evaluation Assistant for Medicaid Data Chatbot. This initiative leverages a comprehensive Medicaid claims database to develop a Chatbot powered by advanced LLMs. This innovative tool is designed to empower researchers at the Center for Suicide Prevention and Research by enabling rapid evaluation of new ideas and hypotheses. It also facilitates their navigation through the complex queries required to distill meaningful insights from this extensive dataset.

By incorporating behavioral health data into the data lake and developing sophisticated AI tools for data extraction and analysis, DREAM aims to foster the creation of groundbreaking biobehavioral health promotion strategies. This initiative exemplifies our commitment to leveraging AI for enhancing research and underscores our dedication to critical areas of public health, such as suicide prevention.

We believe LLMs have significant potential to extract valuable insights from unstructured text, such as clinical notes, and assist in interpreting genomic data. Our approach is to rigorously assess LLM technology with research data to ensure its application is responsible and free from potential harm. We are dedicated to understanding its biases and are making careful recommendations to ensure ethical AI use, aiming to prevent health inequities.

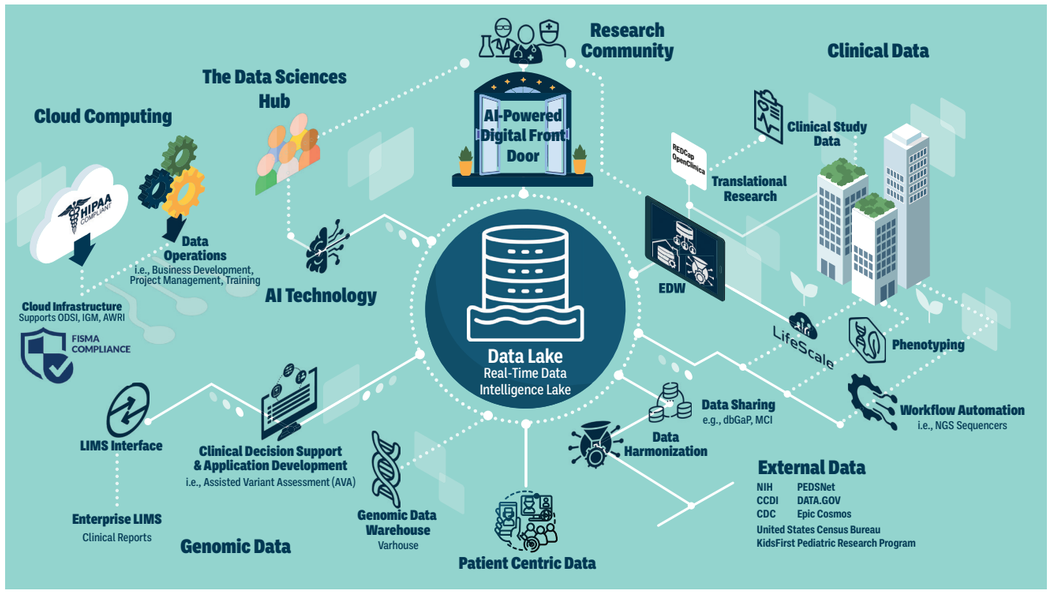
Bright Future Ahead

Reflecting on my journey, I am reminded of the palpable excitement I felt 15 years ago when I started working with genomics and next-generation sequencing. Just as genomics has proven to be a revolutionary force in medicine and biomedical research over the past decade, I envision data science as the next catalyst for transformative discovery and advancements.

I am mindful of the challenges that lie ahead. The path to integrating data science deeply and effectively within biomedical research is fraught with complexity. Challenges such as ensuring data privacy, data interoperability, navigating the intricacies of AI and ML applications in health care, and fostering a culture of continuous learning and adaptation among our team are but a few of the obstacles we must overcome.

This is not going to be easy, but we have the right ingredients to be successful — an innovative spirit, a collaborative research community and a relentless pursuit of excellence. More importantly, we are guided by a shared vision and an unwavering commitment to improving patient outcomes through the power of data science. ■

This graphic visualizes the diverse data sources that make up the Data Lake. The Data Lake initiative will facilitate access to advanced data analytics and ML platforms via cloud computing technologies. Ultimately, it will enable new research possibilities.



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Unleash the full potential of the biomedical data sciences and transformative AI to drive innovative health research, fuel development of groundbreaking diagnostics and treatments, inform disease prevention and health promotion strategies, and ensure equitable health outcomes for all people.

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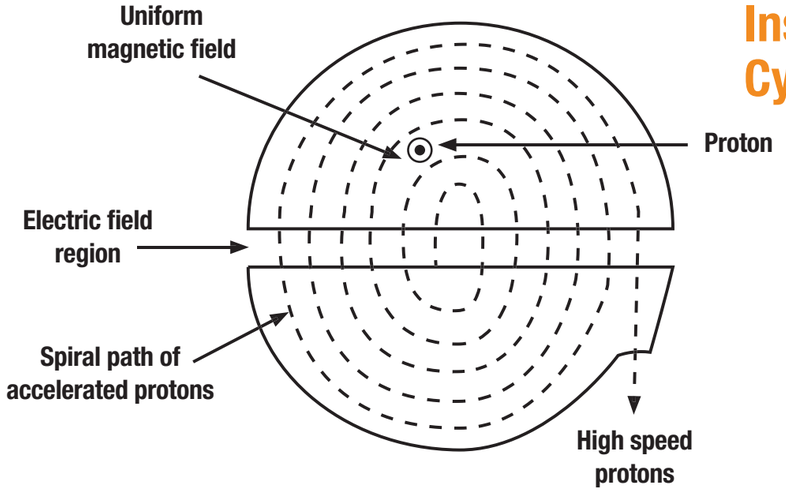
Proton Therapy – A New Era of Cancer Therapy for Children

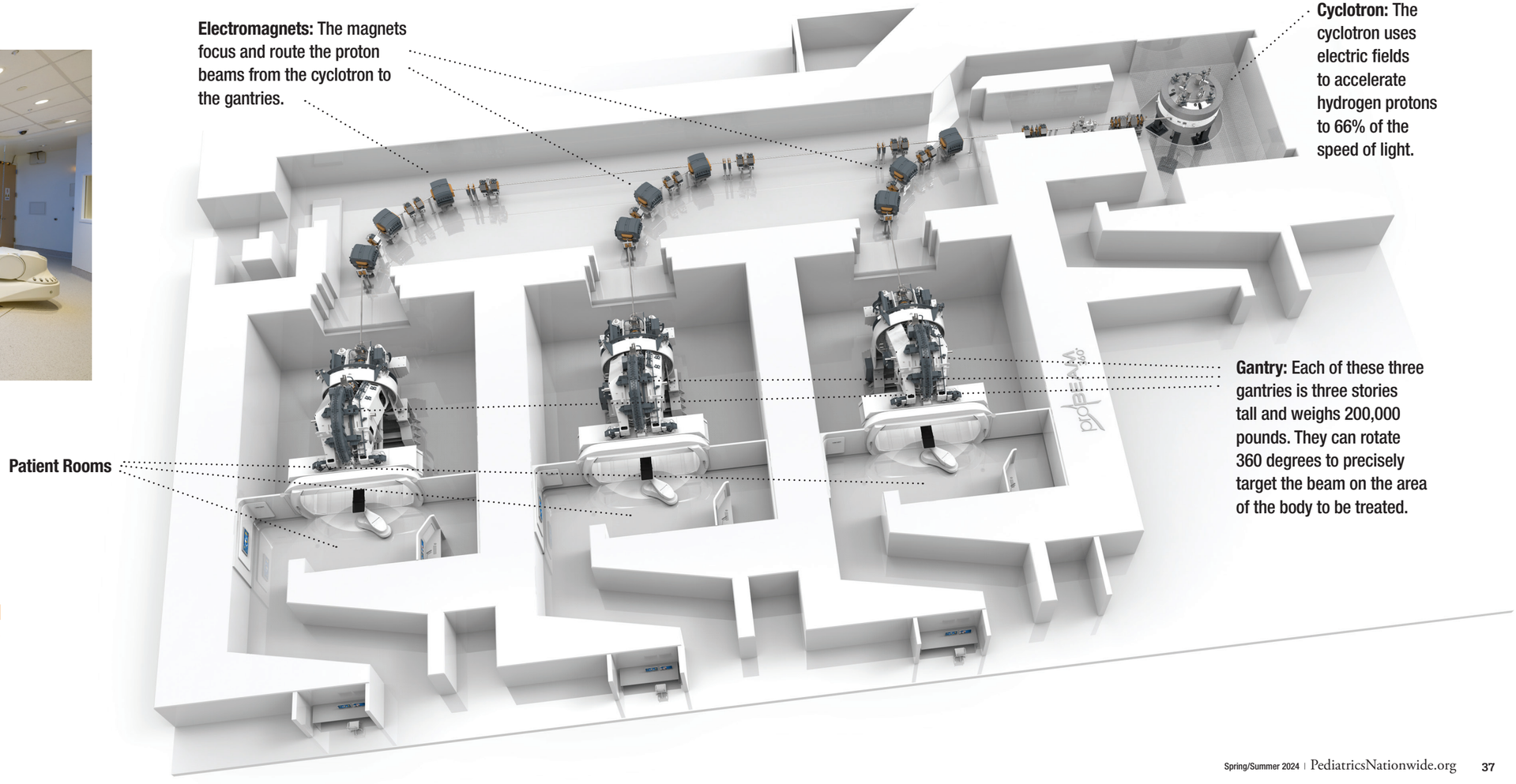
Proton therapy offers benefits over traditional photon radiation therapy. Using proton therapy, doctors can give more specific, concentrated doses of radiation with less risk and damage to the surrounding tissue.

The patient room shown above features customizable lighting to aid in patient relaxation. The gantry and bed are both movable to support the treatment of specific areas on the body, minimizing radiation exposure to healthy tissue.

Learn more about the Nationwide Children's and The Ohio State University Proton Therapy Center at PediatricsNationwide.org/Proton-Therapy

Inside the Cyclotron





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FEATURED ONLINE EXCLUSIVES:

Results of a Phase I Trial With Haploidentical NK Cells for AML

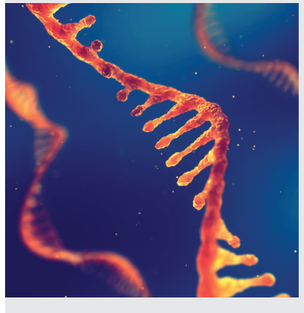
Natural killer (NK) cells are a component of the innate immune system that have shown promising anti-tumor effects, but it has remained unclear if they are effective against relapsed acute myeloid leukemia (AML). In this phase one trial, 12 adult patients were treated with *ex vivo* expanded NK cells.

PediatricsNationwide.org/NK-for-AML

Adolescents Need More Cognitive Activity and Less Screen Time After Concussions

A new study shows limiting screen time and returning to school early following a concussion may hasten recovery timelines. In a study published in the *British Journal of Sports Medicine*, researchers evaluated the intensity and duration of daily cognitive activity reported by adolescents (ages 11-17 years) following concussion and examined the associations between these daily cognitive activities and post-concussion symptom duration.

PediatricsNationwide.org/Postconcussion-Cognitive-Activity



Gene Therapy for the Masses?

Long-lived financial and logistical hurdles make bringing new gene therapy products to market a major challenge. To help bring more of these medical miracles to fruition, experts across industry, regulatory review, science and medicine have begun to problem-solve together.

PediatricsNationwide.org/Gene-Therapy-Masses

Help us advance the conversation on child health.

Follow *Pediatrics Nationwide* on Instagram @NCHforDocs

to stay up to date on pediatric research, clinical advances, practice tools, case studies, patient education and posts from professional conferences. Join the community of physicians, researchers and health care experts dedicated to advancing the conversation on child health.

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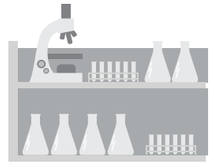

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