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Clinical Genomics: From Research to Reality

INSIDE THIS ISSUE

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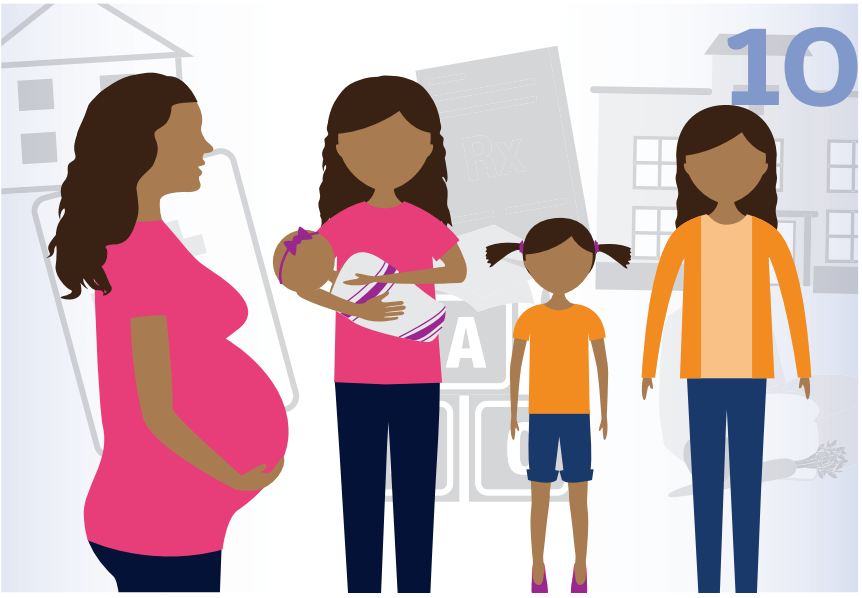
She has Williams syndrome, a rare genetic disorder affecting 1 in 7,500 children. Williams syndrome is the result of a deletion on chromosome 7 that removes 25 to 27 genes including elastin, a connective tissue molecule that enables tissues to stretch and recoil. Nearly everyone with WS has the same missing DNA, but their clinical features can vary broadly. Importantly, their symptoms are so varied they could be cared for in every clinic a children's hospital might have.

Genomics has become an important part of diagnosing and understanding genetic diseases such as Williams syndrome. While genetic tests for Williams syndrome don't necessarily require analyzing a full genome, genomic sequences can help clinicians understand individual risk for common complications of WS such as risk for arterial stenosis and deadly reactions to anesthesia.

Our cover story, which starts on page 18, delves into how genomic testing has evolved and how it is poised to become an important component of clinical diagnostics — not just for children with rare diseases, but for everyone.



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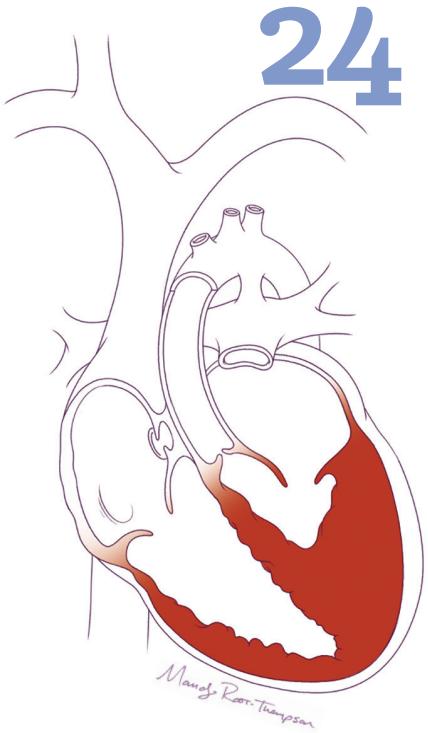


"When you see big studies about children's exposures during pregnancy and childhood around the country, they'll be coming from this database. There are studies we haven't even thought of yet that will be done based on the data we collected."

— Jonathan Slaughter, MD, MPH, neonatologist and principal investigator in the Center for Perinatal Research at Nationwide Children's Hospital

"Single-ventricle disease is a very complicated heart defect, and we all are working at one little piece of the puzzle that alone is nothing. But when you start to put the pieces together, you begin to see the big picture."

— Deqiang Li, MD, PhD, principal investigator in the Center for Cardiovascular Research at Nationwide Children's Hospital

Linaclotide: A New Option For Chronic Pediatric Constipation

A Phase 3 trial shows the safety and efficacy of linaclotide in children aged 6 to 17, informing U.S. Food and Drug Administration (FDA) approval of the medication.

Constipation, a common issue for children, can be a source of prolonged struggle and distress for young patients and their families. Despite many treatments being available, some children continue to battle with this condition for years. There is a lack of high-quality research on medications suitable for treating children with chronic constipation. Carlo Di Lorenzo, MD, led a recent randomized, double-blind, placebo-controlled, multicenter research study published in *The Lancet Gastroenterology & Hepatology*.

"We know that linaclotide is a well-tolerated treatment for chronic constipation in adults with few side effects. We wondered if it would be the same for children," explains Dr. Di Lorenzo. He is the chief of the Division of Pediatric Gastroenterology, Hepatology and Nutrition at Nationwide Children's and professor of Clinical Pediatrics at The Ohio State University College of Medicine.

Conducted at 64 sites in seven countries, the trial enrolled 330 pediatric patients aged 6 to 17 years who met the criteria for functional constipation. Researchers randomized participants to receive either linaclotide or a placebo daily for 12 weeks. The researchers were looking for changes in weekly spontaneous bowel movements and improvements in stool consistency.

By the end of the 12 weeks, patients in the linaclotide group showed a significant increase in bowel movement frequency compared with the placebo group. In addition, stool consistency also improved in the linaclotide group. The most reported adverse side effect of the drug was diarrhea, which was not severe. The study reported no serious side effects or deaths.

"Linaclotide is not systemically absorbed into the bloodstream," Dr. Di Lorenzo explains, "which likely contributes to its favorable side effect profile and minimal adverse effects."

Until now, pediatricians have relied heavily on treatments that, despite widespread use, lack formal FDA approval for children. This large, placebo-controlled trial is the first to provide conclusive evidence of linaclotide's efficacy in children. The medication is readily available in capsule form, which can be broken apart for children to easily swallow.

"This study led to the FDA approval in 2024 of the use of linaclotide in children aged 6 and older," says Dr. Di Lorenzo. "Pediatricians can now consider it a safe and effective treatment option for children and adolescents, hopefully improving their quality of life significantly."

Di Lorenzo C, Khlevner J, Rodriguez-Araujo G, Xie W, Huh SY, Ando M, Hyams JS, Nurko S, Benninga MA, Simon M, Hewson ME, Saps M. Efficacy and safety of linaclotide in treating functional constipation in paediatric patients: A randomised, double-blind, placebo-controlled, multicentre, phase 3 trial. *Lancet Gastroenterology and Hepatology*. 2024;9(3):238-250.

— Pam Georgiana

Postpartum Depression Linked to Increased Use of Acute Infant Care

Study results highlight the importance of primary care in infant and maternal support.

In a recent study published in *Academic Pediatrics*, researchers found a link between postpartum depression in mothers and the infants' use of acute care, which includes emergency department or urgent care visits.

Postpartum depression (PPD) is often unrecognized and undertreated. Frequently mistaken for "baby blues," PPD symptoms are more intense and long-lasting, including extreme sadness or loneliness, irritability and fatigue, frequent crying or severe mood swings.

"We know that postpartum depression is one of the most common complications of childbirth," says Laura Chavez, PhD, MPH, senior author of this study and a principal investigator at the Center for Child Health Equity and Outcomes Research at Nationwide Children's Hospital. "As more pediatric health systems screen for postpartum depression, it offers an opportunity to understand how these screening results are related to the care infants receive. We wanted to understand whether there were differences in receipt of preventative or acute care for infants whose mothers were identified as at risk for postpartum depression."

The study sample consisted of 5,341 infants born between January 1, 2021, and October 29, 2021, whose mothers completed a screening during the child's normal checkup appointment within their first six months of life.

The Edinburgh Postnatal Depression Scale (EPDS), a 10-item screening instrument, was used to identify perinatal depression symptoms. Each question had four response options, ranging 0 to 3 points respectively. There was a possibility of receiving up to 30 points on this screening. The screen was considered positive if the mother scored a 10 or higher.

Although a positive screen does not equal a diagnosis, it can indicate when mothers need additional referrals or monitoring to ensure that depression symptoms don't worsen, says Dr. Chavez.

More than 15% of the mothers screened positive on the EPDS during the first six months, with a mean score of 12.3 total points. Most positive screens were identified before the infant's 1-month checkup with their primary care physician.

More than 62% of mothers who screened positive lived in areas with low childhood opportunity.

The study found a significant increase in the use of acute infant care services among the mothers who screened positive for PPD. There was no connection with preventive care visits.

These results emphasize the importance for primary care physicians to discuss options for families to access same-day primary care appointments or to use primary care for more than just the usual health checkups. Primary care physicians should continue to check in on both the infant and the mother after acute care visits. Their intervention can help mothers suffering from PPD connect with resources they need, says Dr. Chavez.

Tyson DP, Utset LV, Hardy RY, Davenport MA, Barnett KS, Chisolm DJ, Chavez LJ. Postpartum depression screening in pediatric primary care clinics and infant receipt of preventive or acute care. *Academic Pediatrics.* 2025;25(1):102556.

— Alaina Doklovic

Direct Breastfeeding of Mother's Own Milk Benefits Preterm Infants

Despite benefits, new study finds low rates of breastfeeding among preterm infants discharged from the NICU.

Mother's own milk (MOM) and direct breastfeeding (DBF) are associated with numerous health and development advantages, especially for preterm infants. However, the rates of MOM feeding and DBF among infants admitted to neonatal intensive care units (NICUs) are low, says Sudarshan Jadcherla, MD, a principal investigator at the Center for Perinatal Research and medical director of the Neonatal and Infant Feeding Disorders Program at Nationwide Children's Hospital.

"Babies can get nutrition from bottle feeding, but it's not the same as getting mother's own milk through breastfeeding," he says. "Although the field of neonatology knows this, there are many issues resulting in an appallingly low rate of direct breastfeeding in the United States."

In a recent study published in *Breastfeeding Medicine*, Dr. Jadcherla and colleagues examined the role of MOM and DBF in preterm infants with oral feeding difficulties. The researchers retrospectively analyzed data from 237 preterm infants who were referred to Nationwide Children's NICU for evaluation of feeding difficulties and discharged home on full oral feeds.

The analyses showed that 35.4% of these infants received any MOM feeding at discharge. Consistent with other studies, the odds of MOM feeding at discharge were higher with higher maternal age and absence of maternal substance use.

Among the one-third of infants receiving any MOM at discharge, only 4.8% were exclusively breastfed, while 39.3% were partially breastfed. Infants who received DBF had higher birthweight, no incidence of being small for gestational age and lower incidences of respiratory support at birth or intraventricular hemorrhage. These infants also had a younger postmenstrual age at discharge and transitioned from first oral feed to full oral feeds in a shorter time than non-directly breastfed infants.

Dr. Jadcherla, who is also a professor of Pediatrics at The Ohio State University College of Medicine, suggests that "It appears plausible that there is a protective effect of the choice of DBF, even among preterm infants with feeding difficulties."

To encourage more MOM feeding and DBF, breastfeeding education before conception and during early pregnancy may be particularly beneficial for mothers.

"Clinical management and research advocacy must focus on identifying modifiable factors and targeting interventions to the populations at the highest risk of not utilizing MOM, such as younger mothers and mothers who abuse substances," says Dr. Jadcherla.

Educational and support programs to support the use of MOM and DBF should also target NICU staff and other health professionals who tend to sick preterm infants, he says. Hospital systems can take actions to help change perceptions and attitudes towards MOM and DBF for their patients, as well as put practices in place to help mothers provide DBF to their infants.

Bala F, Alshaikh E, Jadcherla SR. Factors associated with mother's own milk feeding and direct breastfeeding at discharge in preterm infants with feeding difficulties: Clinical and research implications. *Breastfeeding Medicine*. 2024 Nov;19(11):827-836.

— Mary Bates, PhD

Transforming Medical Training: Perspectives on Competency-Based Education

The alternative approach would move away from traditional time-based education to a more flexible, competency-focused approach.

Imagine a world where medical education is tailored to each student's pace and learning style, ensuring every graduate is fully competent in real-world clinical settings.

A recent perspective piece, published in *Current Problems in Pediatric and Adolescent Health Care*, dives into the advantages and potential challenges of evaluating medical trainees using Competency-Based Medical Education (CBME) from the perspectives of learners, faculty and program leaders. "Competency-based medical education is a new paradigm of thinking about how we do medical education," says Debra Boyer, MD, MHPE, chief medical education officer, designated institutional official and transplant pulmonologist at Nationwide Children's Hospital and senior author of the publication.

CBME emphasizes the achievement of specific competencies, which are observable and measurable abilities that learners must demonstrate. The goal is to produce physicians who are both knowledgeable and proficient in applying their knowledge in real-world clinical settings.

Currently in the United States, medical training uses a time-based progression standard. Some countries though, such as the Netherlands, have moved more toward competency-based medical education. One pilot study in the U.S., Education and Pediatrics Across the Continuum (EPAC) is using CBME to teach and assess learners, resulting in positive feedback thus far. Pilot studies like this help to develop a stronger growth mindset among medical trainees.

"By getting all of this feedback, the trainees felt like they had really developed that [growth mindset] early on and were comfortable seeking feedback, which is one of the goals of CBME," Dr. Boyer says.

One of the key advantages of CBME is its flexibility. Unlike traditional medical education, which often follows a rigid timeline, CBME allows learners to progress at their own pace. This means that students can advance once they demonstrate mastery of a competency, rather than waiting for a predetermined period to pass.

Implementation of CBME would require a robust assessment system and a strong balance between competency and experience. Dr. Boyer discusses ways to overcome these hurdles, such as giving residents more independence in work duties once deemed competent.

"If you're going to do a competency-based system, things are going to look different," Dr. Boyer says. "I think we have to culturally change that expectation that everything has to be the same and acknowledge that we all require different things."

Dr. Boyer and the pulmonary team are developing and working to implement entrustable professional activities, a component of CMBE, in the residency and fellowship programs at Nationwide Children's, noting that these concepts are much easier for people to understand than the more ambiguous Milestones assessment.

"I think we're doing well, but we could do a lot better. We could develop our learners into even better physicians and help them develop that lifelong learning skill with CBME," Dr. Boyer says.

Card A, Daniels G, Bluth P, Chiel L, Herman B, O'Connor M, Plevinsky J, Boyer D. Competency-based medical education (CBME) in graduate medical education: Perspectives from learners, faculty and program leaders. *Current Problems in Pediatrics and Adolescent Health Care*. 2024;54(10);101677.

— *Madison Storm*

Aligning Aspirations With Workforce Reality in Pediatric Endocrinology

A recent survey reveals a mismatch in career expectations and realities, calling for enhanced mentorship and policy reform.

Pediatric endocrinology, like many pediatric subspecialities, is struggling to sustain an adequate workforce.

When Leena Nahata, MD, served on the Research Affairs Committee of the Pediatric Endocrine Society in 2024, a topic of interest for the upcoming annual conference was understanding the career goals and expectations of current pediatric endocrinology fellows.

"We on the committee had noticed a decreasing interest in research among fellows. So, we wanted to better understand what the current cohort envisions for their future careers," says Dr. Nahata, founding medical director of the Fertility and Reproductive Health Program at Nationwide Children's Hospital, principal investigator in the Center for Biobehavioral Health at Nationwide Children's, and professor of Clinical Pediatrics at The Ohio State University College of Medicine.

The committee conducted a cross-sectional survey study of pediatric endocrinology fellows from the United States and Canada. One hundred twenty-seven fellows completed the survey — nearly a 50% response rate. The results were recently published in *The Journal of Pediatrics*.

Among notable insights from the study was the mismatch between respondents' ideal and actual time spent on patient care. Fellows reported that, on average, they envisioned dedicating 61% of their post-fellowship work time to patient care. However, third- and fourth-year fellows reported accepting job offers with 75% of their time dedicated to patient care.

"This gap suggests that young specialists may quickly discover that clinical obligations supersede time they had hoped to dedicate to research, education and quality improvement. This trend has important implications for career satisfaction, retention and future interest in the field," explains Dr. Nahata.

Equally concerning, only 13% of fellows envisioned spending at least half of their time on research, and 6% of those with job offers had positions with a strong research focus.

"Who will advance the field if we are not cultivating a new generation of physician-scientists?" Dr. Nahata asks.

Early-career roles are often focused on revenue-generating clinical work. Consequently, many talented junior faculty may lack the necessary time and resources to secure funding and become successful physician-scientists.

The study also highlights broader workforce considerations. Nearly one-quarter of respondents noted that visa considerations influenced their job opportunities. Additionally, numerous pediatric endocrinology fellowship positions remain unfilled. This creates a dual crisis: a clinical workforce shortage and a dwindling pipeline of pediatric physician-scientists.

Dr. Nahata advocates for enhanced exposure to pediatric subspecialties, research and structured mentorship during medical training. Advocating for improved compensation for these subspecialties and increasing strategies to make research careers sustainable (such as federal loan repayment and targeted early-career funding) could also help bridge the gap.

Nahata L, Srinivasan S, Roche CI, Leavens KF, Kim MS, Levenson A, Topor LS, Singer K, McCormack S. Measuring up: Do pediatric endocrinology fellows' career expectations align with workforce reality? *Journal of Pediatrics.* 2024;275:114321.

— Pam Georgiana

The Antitumor Potential of CD38-CAR NK Cell Therapy

Investigators created fratricide-resistant and metabolically-enhanced chimeric antigen receptor (CAR) natural killer (NK) and T cells that have cytotoxic effects on many hematologic tumors.

"One of the problems that we usually have with blood cancers is making effective therapies using immune cells, because the immune cells then recognize themselves as a threat and start killing each other," says Meisam Naeimi Kararoudi, DVM, PhD, principal investigator in the Center for Childhood Cancer Research and director of the CRISPR/Gene Editing Core at Nationwide Children's Hospital.

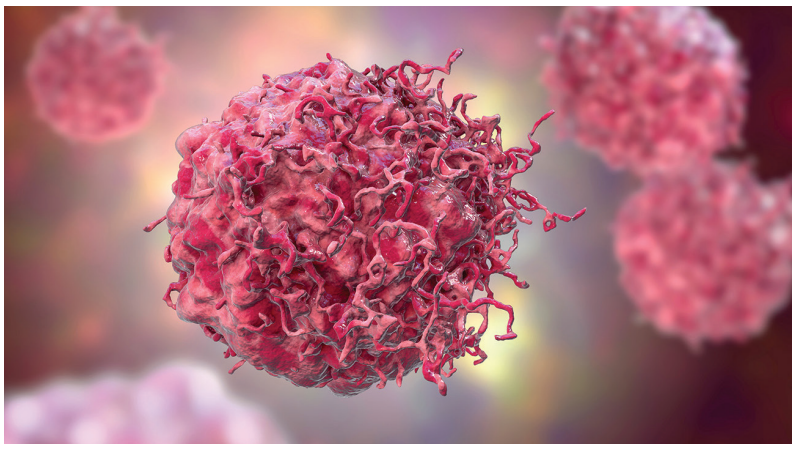
In a study published in *Blood Neoplasia* led by Ella Troy, research assistant in the Center and co-senior authors Dean A. Lee, MD, PhD, director of the Cellular Therapy and Cancer Immunology Program at Nationwide Children's and The Ohio State University Comprehensive Cancer Center, and Dr. Naeimi Kararoudi, the team used the CRISPR-Cas9 platform to edit the genome of NK and T cells from matched pair donors. The cells underwent simultaneous CD38 knock-out (KO) and knock-in using isatuximab-based CD38 fragments. The antitumor activity of the resulting CD38KO/CD38-CAR NK cells was tested using cell lines generated from samples obtained from pediatric patients with acute myeloid leukemia (AML), multiple myeloma (MM) and Burkitt lymphoma (BL).

Compared with wild type (WT) NK cells, the CD-38KO/CD38-CAR NK cells had similar levels of cell expansion over 12 days, suggesting a lack of NK cell fratricide.

"We saw that the CAR itself provides some sort of protection, by kind of covering the gene that we were going after. We still don't know why it happened, but we think that covering, we call it the mocking effect, is the reason that the CAR NK and T cells that we generated — and are supposed to kill each other — didn't kill each other," says Dr. Kararoudi.

In addition, the CD38KO/CD38-CAR NK cells demonstrated more pronounced antitumor effects against AML, MM and BL than WT NK cells.

The antitumor effects of the CD38KO/CD38-CAR



NK cells against AML were enhanced with all-trans retinoic acid (ATRA) combinatorial therapy. Treatment with CD38KO/CD38-CAR NK cells alone resulted in 12% live AML cells, whereas when combined with ATRA resulted in 4.8% live AML cells compared with 31.4% and 32.0% after treatment with WT NK cells alone or combined with ATRA, respectively.

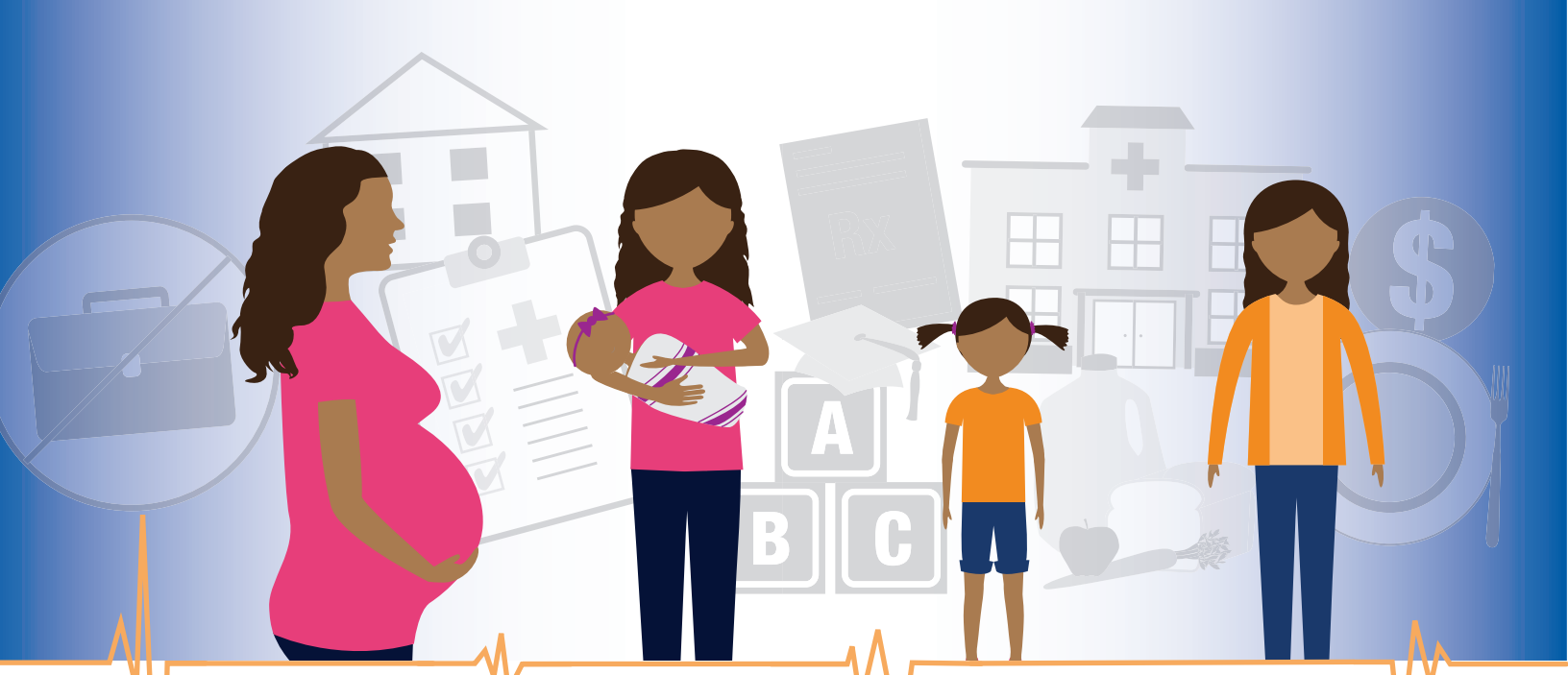
Similar to the CD38KO/CD38-CAR NK cells, the matched donor pair CD38KO/CD38-CAR T cells were found to expand in a similar manner as WT T cells, indicating a lack of fratricide.

The results of this study lead to building a company at Nationwide Children's.

"I used the same target, CD38, and put it into an off-the-shelf CAR T-cell therapy and a different type of CAR T, called Gamma Delta T cells. They are different from the Alpha Beta T cells and NK cells reported in this paper. Gamma Delta T cells are something in between those two and they are a very small population of the immune cells, 1% to 5%. Based on this research, we founded a company called CARTx therapeutics where we generate CD38 CAR Gamma Delta T cells," says Dr. Kararoudi.

Troy E, Caporale J, Sezgin Y, Pereira MSF, Behbehani G, Lyberger J, Lee DA, Kararoudi MN. CD38-CAR human NK cells in combination with ATRA enhance cytotoxicity against CD38-expressing hematologic malignancies. *Blood Neoplasia*. 2024;1(4):100032.

— Jessica Nye, PhD



Studying the Environment's Impact on Pediatric Health Outcomes

A massive population database is expected to inform and transform children's health outcomes.

written by Wendy Margolin

Researchers from Nationwide Children's Hospital and The Ohio State University are focusing on how early exposures might be associated with areas such as neurodevelopment and cardiovascular outcomes as part of a large national study, Environmental influences on Child Health Outcomes (ECHO) Program.

The interdisciplinary team just completed their first year recruiting participants and collecting data to answer crucial questions about how early environmental influences affect child health and development.

"We're just starting to better understand how cardiometabolic risk factors and even social risk factors, like unemployment, insurance, education, health care access and food insecurity during pregnancy, can impact lifelong health outcomes. This study aims to advance that understanding in a novel way," says Kartik Venkatesh, MD, PhD, associate professor of Obstetrics and Gynecology at The Ohio State University College of Medicine.

Dr. Venkatesh is joined by collaborators Sarah Keim, PhD, MA, MS, principal investigator in the Center for Biobehavioral Health at the Abigail Wexner Research Institute (AWRI) at Nationwide Children's; Jonathan

Slaughter, MD, MPH, principal investigator in the Center for Perinatal Research at Nationwide Children's; and Courtney Lynch, PhD, MPH, associate professor of reproductive and perinatal epidemiology at The Ohio State University College of Medicine.

The researchers will follow children from post-conception through age 21 by collecting data from the parents, children and the environment. The goal is to improve and inform children's health for generations. Researchers will collect samples from the parents and the children, including saliva, blood, placenta, hair, stool, clipped nails and even baby teeth.

The Ohio scientists also plan to compare what they learn from patient biospecimen samples and survey questions to geographic data gathered from zip codes, such as air quality and water pollutants.

The research team joins 45 centers from around the country participating in the ECHO Cohort. Nationwide Children's and Ohio State make up the only Ohio center and are funded by a seven-year $17.7 million grant. The data collected in the study is being used to build a national pediatric health database with data from 55,000 children and 20,000 pregnancies enrolled by 2030 — including 850 children from central Ohio.

Nothing of the ECHO study's kind has existed in the United States since the Collaborative Perinatal Project in the 1960s when researchers had access to significantly less data. ECHO's observational and intervention research will inform high-impact programs, policies and practices for years to come.

Scientists at Ohio State began in 2024 enrolling pregnant patients and their partners. Researchers at Nationwide Children's will follow them through age 21.

The Ohio researchers are currently focusing on how the birth parents' cardiometabolic health during pregnancy influence childhood neurodevelopment and behavior. They anticipate conducting additional studies in the future.

The national consortium brings diverse participant populations together into one large ECHO Cohort that scientists can use to address research questions about the effects of early environmental exposures on child health and development — questions that no smaller study can answer alone.

"For a lot of important questions about children's health, we need a large number of children to be able to determine the potential causes and identify ways to prevent disease or promote good health," says Dr. Keim.

As the study continues over the next two decades, researchers will likely investigate questions that no one has anticipated at the study's outset. Additional grants will be offered on an ongoing basis.

Right Time, Right Place

The time is particularly ripe for taking a comprehensive look at the effect of environmental exposures on children's health outcomes. Scientists understand more about genetics and the microbiome than ever before.

And many people are more aware of the impact of social determinants of health.

"We realize that your neighborhood where you grew up, your identity, sexuality, race and ethnicity are really important exposures for your overall experience in life," says Dr. Slaughter, principal investigator on the ECHO study for the Ohio cohort.

Digital technology such as smartwatches, remote digital monitors and telehealth make monitoring study participants easier and less intrusive than ever.

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— Sarah Keim, PhD, MA, MS, principal investigator in the Center for Biobehavioral Health at Nationwide Children's

Ultimately, says Dr. Slaughter, the ECHO cohort will help researchers improve children's lives by understanding what exposures during pregnancy and childhood influence health outcomes.

"When we're making choices about what to focus on as a society, this will be the study that gives us the information we need to help improve children and how they grow in America," he says.

Ohio Cohort Ideal for Diverse Population Study

Central Ohio residents come from urban and rural areas throughout the Midwest and from countries worldwide. The city's steady population growth and diverse communities make Columbus an ideal location for the study.

"Our area's diverse population means we've got participants from Appalachia, the Midwest and from other parts of the world, including Somalia and Nepal. Columbus is a microcosm of the United States," says Dr. Slaughter.

Ohioans in three OSU-Wexner Medical Center clinics representing urban, suburban and rural areas are invited to join the study. Participants need to be less than 20 weeks pregnant to qualify.

Ohio parents have been eager to join the study and exceeded year-one recruitment goals of 75 pregnant individuals.

"There's a growing consensus that what happens during pregnancy can have a profound impact on children, but this is going to another level of breadth and depth of information that will better inform parents on how to give their children the best possible start," says Dennis Durbin, MD, MSCE, president of AWRI at Nationwide Children's.

For the four Ohio investigators and their team, ECHO is a once-in-a-career opportunity to contribute to data that will inform research for decades to come.

"This is a transformative study to understand important pregnancy and early life exposures on later childhood outcomes — something that doesn't currently exist in the United States," says Dr. Venkatesh.

Close, Productive Collaboration

The researchers from Nationwide Children's and Ohio State have a rich history of collaboration, including recruiting patients from pregnancy through birth and studying the same infants and children.

Ohio State features a large infrastructure for recruiting and enrolling pregnant patients, with research assistants actively recruiting and gathering samples from clinics and on the labor and delivery unit 24/7.

"You don't know when someone will show up to deliver, so it could be really hard to capture samples if you don't have someone already there," says Dr. Lynch.

Once patients deliver, they can expect a warm handoff from the Ohio State team to the Nationwide Children's researchers.

"We always like to find research opportunities where we can blend the expertise from Nationwide Children's with the complementary expertise from Ohio State because together, we can always do more impactful work than either one can do alone," says Dr. Durbin.

Into the Unknown

Access to the massive pediatric database can help answer a broad range of questions. For example, there's a constant debate about whether obesity is caused by nature versus nurture.

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— Jonathan Slaughter, MD, MPH, principal investigator in the Center for Perinatal Research at Nationwide Children's

"We don't have a good sense of how much genetics plays into the increasing obesity epidemic. That's something we'll be able to answer at ECHO because we will have the biological data of these individuals, the social and the environmental data," says Dr. Lynch.

Dr. Venkatesh, a high-risk obstetrician and perinatal epidemiologist, says the research questions he and the Ohio team are asking in ECHO are highly relevant.

"I encounter these questions in my conversations with colleagues and patients, and often, it's really hard to get robust, high-quality scientific data," he says.

Dr. Lynch is one of only a handful of reproductive and perinatal epidemiologists studying the impact of stress and mood disorders on reproductive outcomes. She anticipates that having better data on what early exposures mean for the risk of pregnancy loss, preterm birth and a child's future health could help doctors better advise people.

"We hope to provide data that can help pediatricians offer anticipatory guidance to families about how to help keep your family healthy," says Dr. Lynch.

Dr. Keim, who studies how prenatal health impacts children's health outcomes, says, "ECHO fits in well with work I've been doing my whole career because it takes a holistic lifespan view of children's health by not just looking at the child in isolation, but considers their whole family and all kinds of aspects of their environment."

Ultimately, what researchers will study from ECHO remains to be determined. "When you see big studies about children's exposures during pregnancy and childhood around the country, they'll be coming from this database. There are studies we haven't even thought of yet that will be done based on the data we collected," says Dr. Slaughter.

"We have to stay open-minded and follow the science because it would be shortsighted to have all our ideas laid out now while this continues until the children turn 21. The ways we're going to use it are already evolving," says Dr. Keim.

Dr. Keim has worked on a study of children born in the 1960s in her research and now imagines a future where some ECHO babies grow up to become scientists using the massive dataset they helped build.

"Maybe they'll be curious and want to learn about themselves and their friends, and this shows them what science can do to help kids and communities," she says. ■

Setting the Standard for Cloacal Malformation Management

The team in the Center for Colorectal and Pelvic Reconstruction at Nationwide Children's Hospital has transformed the profession's approach to surgical care and follow-up, dramatically altering patient outcomes in the process.

written by Katie Brind'Amour, PhD

To say that cloacal malformation management has been historically understudied may be an understatement.

"At the time we published our surgical protocol, it was the first time in 22 years anyone had suggested a new technique," says Molly Fuchs, MD, pediatric urologist and surgeon for the Center for Colorectal and Pelvic Reconstruction (CCPR) at Nationwide Children's Hospital.

In the past 10 years, the team has introduced a handful of groundbreaking advancements that have transformed cloacal malformation surgical practices internationally and provided a roadmap for ongoing improvement in patient outcomes.

"Cloacal malformation is very rare and is also one of the most complex malformations we come across, so patients have historically had poor outcomes," says Richard Wood, MBChB, FCPS(SA), chief of the CCPR at Nationwide Children's. "We recognized a critical gap in knowledge surrounding the management of these patients and knew we had an opportunity to meaningfully improve their care."

With the support of hospital administration since the opening of the CCPR in 2014, Dr. Wood and colleagues planned and implemented multidisciplinary management and regular data analysis to improve cloacal outcomes. Their first step? Gathering evidence surrounding the best approach to surgical technique for different patients.

A Personalized Approach to Procedures

In cloacal malformations, the urethra, vagina and rectum all share a single tube called the "common channel." The goal of operating is to separate the three channels physically while preserving their unique functions.

For decades, standard practice for surgical management involved measuring the common channel to inform whether attempting the simplest approach, called total

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— Richard Wood, MBChB, FCPS(SA), chief of the Center for Colorectal and Pelvic Reconstruction at Nationwide Children's

urogenital mobilization, could work, or whether a more complex repair, called urogenital separation, would be required. Many surgeons would attempt the easier technique first and, if they found intraoperatively that it would not work, they would switch mid-operation to the other approach. Switching often leads to damage or ultimately loss of the patient's urethra in the process, resulting in a lifetime of catheterization.

The Nationwide Children's team felt that measurement of only the common channel oversimplified patient anatomy and proposed a new algorithm for selecting surgical techniques — one that added in consideration of the length of the patient's urethra. They hypothesized that patients with short urethras would be better candidates for urogenital separation, while those with longer urethras and short common channels would do well with total urogenital mobilization.

The team performed preoperative imaging studies to get common channel and urethra lengths in order to select procedures in advance and published their outcomes, showing that their method resulted in 97% of patients having a viable urethra postoperatively.

"The important thing is that if you choose the right operation in advance and can avoid a switch during the middle of the operation, patients should do fine," says Daniel DaJusta, MD, pediatric urologist and medical director of the CCPR. "That was our first major breakthrough."

Improved urethral function enabled the team to begin looking beyond the basics. For example, after seeing a few cases of urethra-vaginal fistula in patients undergoing urogenital separation, the team implemented the use of interposing tissue as a barrier between urethra repair and vaginal tissue, reducing fistula rates to almost zero. By natural extension, the team's surgical protocol also reduces the need for re-do surgeries and preserves anatomy to allow multiple solutions for future catheterization if full urinary control cannot be achieved.

"Once we figured out what worked best in each operation, it became a matter of following up with patients over time and figuring out their longer-term outcomes," says Dr. DaJusta.

Girls born with cloacal malformations have high rates of bladder dysfunction, kidney damage, incontinence and sexual or reproductive health challenges. The CCPR team wanted to change that.

Cloacal Malformation Procedure Selection Algorithm

Urethra length (UL) and common channel length (CCL)	Surgical procedure	Key steps
UL < 1.5 cm or CCL > 3 cm	Urogenital separation	Urinary and genital tracts are totally separated from each other and the rectum
UL > 1.5 cm and CCL 1-3 cm	Total urogenital mobilization	Urogenital sinus is separated from the rectum while the rest of the urogenital tract is mobilized to the perineum
UL > 1.5 cm and CCL < 1 cm	Posterior sagittal anorectoplasty and introitoplasty	Reconstruction of the vaginal opening through separation of vaginal tissue from surrounding structures, and creation of a functional rectum and anus; the urethra is untouched

"Baseline renal function at the time of surgery is normal for most of these children, suggesting future renal insufficiency must be explained with things happening after surgery over the long term, such as recurring infections or poor bladder emptying. That means renal insufficiency in these patients could be preventable."

— Daniel DaJusta, MD, pediatric urologist and medical director of the Center for Colorectal and Pelvic reconstruction at Nationwide Children's

"We started at the beginning, asking questions about what we don't know about this group of patients, and thinking of the whole picture of how we should be taking care of them," Dr. Fuchs says of the team's comprehensive approach to creating new evidence-based practices for cloacal care.

Bladder Outcomes and Renal Function

According to the literature, about 9 in every 10 girls born with cloacal malformation experience some form of bladder dysfunction, but the exact cause of dysfunction is unclear. Many patients have spinal cord or vertebral abnormalities that can independently cause bladder dysfunction, but surgery to separate the common channels — specifically the total urogenital mobilization approach — has also been suspected of introducing damage.

To determine the effect of surgical technique on bladder function, the CCPR team reviewed 48 cloacal malformation cases with pre- and postoperative urodynamics testing. The children had procedures selected according to the team's algorithm based on the length of both the urethra and the common channel.

In contrast to studies done elsewhere, nearly 80% of the CCPR patients had stable or improved bladder function following surgery. Rather than surgical technique or spine status, the team found that having a common channel measuring 3 cm or longer was the only significant predictor of worsening bladder status, although a higher percentage of patients undergoing urogenital separation (30%) were among those with worsening function compared to those undergoing total urogenital mobilization (9.5%). They published their findings in the *Journal of Pediatric Urology*.

The team has also reported continence outcomes for 152 patients aged 3 years or older, of whom 93 (61.2%) were dry (<1 daytime accident per week): 82% of those using clean intermittent catheterization and 65% of those voiding via urethra. Although the team plans to do further follow-up to better understand the connection between patient anatomy and urinary outcomes, common channel length was not significantly associated with dryness, while spinal cord abnormality was associated with clean intermittent catheterization and normal spine anatomy was associated with the ability to void via urethra and be dry. The team published the results in the *Journal of Pediatric Surgery*.

The team's published cohorts represent some of the largest patient samples in the literature.

"We perform a large number of cloacal surgeries per year," says Dr. Wood of the CCPR team, which performs dozens of procedures annually. "This obviously translates to considerable clinical experience and the ability to answer a lot of research questions that we couldn't do without prospective data collection from so many patients."

Renal protection became the next target for the team, because as many as 50% of all patients born with cloacal malformations end up with kidney problems — many of whom eventually need transplantation or die of renal failure.

"Baseline renal function at the time of surgery is normal for most of these children, suggesting future renal insufficiency must be explained with things happening after surgery over the long term, such as recurring infections or poor bladder emptying," says Dr. DaJusta. "That means renal insufficiency in these patients could be preventable."

The team developed a strict renal protection protocol involving regular laboratory evaluation, personalized surgical procedure selection, proactive imaging for signs of impending kidney damage or urinary retention, and early introduction of catheterization when required.

Over a median follow-up period of 4.2 years, only 2.9% (n=3) of 105 girls progressed from normal kidney function to renal dysfunction. Although 3 additional patients who started with kidney dysfunction progressed as well, none of the cohort with normal kidneys at study initiation required dialysis or transplantation.

The outcomes, also published in the *Journal of Pediatric Urology*, represent a major improvement over the historical renal dysfunction incidence of 50%.

Comprehensive Care and Follow-up

In many institutions, cloacal malformation care sits under the remit of a single specialty. General surgeons perform the primary operation and bid farewell to patients until the need for follow-up or revision surgeries arises. Not so at Nationwide Children's.

"Right from the beginning we saw this as a complex problem with a multispecialty solution," says Dr. Wood, who leads a team of colorectal surgeons, urologists, genitourinary and reproductive health specialists, and specially trained nurses, crafting a robust, collaborative program. "Shared clinics often aren't the most profitable, so we are very fortunate that leadership supported us and knew this was the best way to make a difference for these patients."

Now, preoperative, surgical and follow-up care — including long-term monitoring and counseling — involve experts from multiple teams, as well as dedicated nurse practitioners. Urologists manage bladder, kidney and urethral health while gynecologists consider menstruation, sexual health and childbearing potential at appropriate ages. Colorectal experts work on maximizing fecal continence and addressing behavior-related and functional gastrointestinal issues.

"Getting urology involved early on has been really critical," explains Dr. Fuchs. "Generalists might think that if a baby has wet diapers, they're peeing fine, but we know as urologists that may not be true — they could have a full bladder that is overflowing and causing the kidneys to suffer. Kidney disease is silent at first, so you won't know about it if you're not following patients and looking for it."

As the team's original cohort of patients advances toward adulthood, the team is also preparing a smooth transition to a prepared adult team at The Ohio State University Wexner Medical Center, including Transition Director Alessandra Gasior, DO, who sees patients at both institutions and straddles transitional care for adolescents and young adults.

"All of this is part of a cohesive plan to meeting the needs of this patient population," says Dr. Wood. "We have one of the largest cohorts and some of the best long-term follow-up data out there, and it's only going to get better."

There are many questions about long-term health for these patients that the team hopes to shed light on, especially in their population of patients with procedures selected based on personal anatomy and follow-up with renal protection protocols and ongoing bladder and bowel care.

The team continues to monitor patients for durability of kidney outcomes and continence beyond 5 years, as well as long-term integrity of the surgically created channels. They also share results via publications and consortia dedicated to improving the management of cloacal malformations — the primary drivers of their techniques' adoption globally.

"These kids require a lifetime of care, and we're trying our best to support them on their journey through our research and collaboration," says Dr. Fuchs of the team's ongoing efforts to revolutionize the outcomes of patients with cloacal malformations. "It's rare to see research impact the care of kids so much in such a short period of time, and it's something we are very proud of." ■

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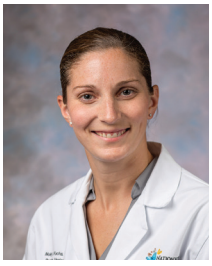

"Getting urology involved early on has been really critical. Generalists might think that if a baby has wet diapers, they're peeing fine, but we know as urologists that may not be true — they could have a full bladder that is overflowing and causing the kidneys to suffer. Kidney disease is silent at first, so you won't know about it if you're not following patients and looking for it."

— Molly Fuchs, MD, pediatric urologist and surgeon in the Center for Colorectal and Pelvic reconstruction at Nationwide Children's

CLINICAL GENOMICS: *From Research to Reality*

written by Abbie Miller, MWC

Without genomic sequencing, many genetic diseases would never be diagnosed.

Genomic testing — whole exome or whole genome sequencing — is vital to reducing the diagnostic odyssey for children with rare, undiagnosed disease. But is genetic analysis only useful in these cases?

Experts across the country have long suggested that genomic testing can be even more useful as a frontline test. An evidence-based clinical guideline from the American College of Medical Genetics and Genomics, led by Kandamurugu Manickam, MD, MPH, FACMG, clinical geneticist and genomicist at Nationwide Children's Hospital, highlights the higher diagnostic yield of genomic testing compared to standard genetic testing, especially for patients with congenital anomalies, developmental delay or intellectual disability. However, issues of cost, scaling and proving the return on investment have stood in the way of making it a reality.

The Human Genome Project was a watershed moment in scientific history when it was completed in 2003. It took 15 years and about $3 billion to accomplish. By 2015, using next generation sequencing (NGS) that same genome took about one day and cost around $2,000. Since then, the process to generate human genome sequencing data has gotten even faster.

MOVING TO THE CLINIC

One of the early, large-scale studies to establish the potential benefits of genomic sequencing for newborns is the BabySeq Project. This ambitious venture sequences both well babies and those admitted to neonatal intensive care units.

Early data published by the BabySeq Project showed that actionable information was found for both seemingly well and more obviously sick infants. Sequencing provided a benefit to both groups, supporting the movement to incorporate genomic testing more broadly in health care.

"The broader application of genomics for both sick and well children represents the next era in genetic and genomic medicine. It is our goal as an institution to lead the way into this new era," says Beth Kozel, MD, PhD, chief of the Division of Genetics and Genomic Medicine and the director of Constitutional Genomics Translational Research in the Steve and Cindy Rasmussen Institute for Genomic Medicine at Nationwide Children's.

Dr. Kozel's vision for the future is one in which genomic information becomes part of the "everyday medical and health care experience."

By utilizing rapid genome sequencing (rGS), which can return results as fast as three days, the clinical and laboratory teams at Nationwide Children's are already making strides on one important goal: the fastest diagnoses for the sickest patients.

RAPID GENOMES: IMPACT IN ACTION

On January 8, 2024, clinical rGS rolled out hospital- wide at Nationwide Children's main campus, and uptake has been higher than expected. Between launch and December 31, 2024, the team has completed more than 220 rapid genome patient samples and nearly 350

> Working with clinicians who have been with us every step of the way enables us to bring the most impactful genomic tests to the clinic. This is possible because of the organization's culture. We're less siloed than a lot of organizations, and that makes us innovative and nimble."
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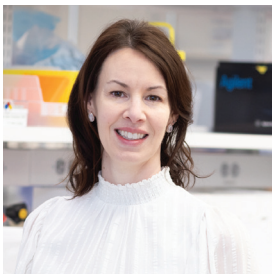
> – *Catherine Cottrell, PhD, FACMG, Section Chief of the Institute for Genomic Medicine Clinical Laboratory at Nationwide Children's*



rapid parent samples, which are used to act as a reference when analyzing patient sequences.

The development of clinical rGS was a significant undertaking and major accomplishment for the Clinical Laboratory within the Institute for Genomic Medicine. Led by Section Chief Catherine Cottrell, PhD, FACMG, a team of highly skilled clinical directors, variant scientists/analysts, and laboratory genetic counselors partnered with Institute for Genomic Medicine managers and supervisors, technologists, technology development specialists, and bioinformaticians to transition this assay from a research test to a clinical offering.

"Working with clinicians who have been with us every step of the way enables us to bring the most impactful genomic tests to the clinic," Dr. Cottrell says. "This is possible because of the organization's culture. We're less siloed than a lot of organizations, and that makes us innovative and nimble."

This clinical testing was developed out of a translational research protocol within the Institute for Genomic Medicine, which was led by Bimal Chaudhari, MD, MPH, a neonatologist, medical geneticist and translational informaticist at Nationwide Children's. Knowledge gained during the research protocol was crucial in honing testing workflows and streamlining analysis. This research experience shaped the transition into a clinical assay and enabled the direct return of genomic results to the patient care team for clinical decision making.

"Remarkably, our teams were able to provide a diagnosis for 28% of rapid cases in 2024," says Dr. Kozel. "This shows that we are testing the right patients and providing life-changing information, hopefully in time for it to impact care and improve outcomes."

Even when testing doesn't find a diagnosis, it can still aid medical decision making — sometimes knowing that a certain diagnosis is not present can be as valuable to the care plan as knowing that it is.

EARLY SUCCESS IN THE NICU

One of the earliest successes is the implementation of rapid genome sequencing in the neonatal intensive care unit (NICU). Historically, about a quarter of neonates who receive early life genetic testing do not get their results back until after discharge. While the information from those tests may help direct their care long term, often the delay represents a missed opportunity for the genomic information to impact care immediately in the NICU.

The Nationwide Children's rGS program aims to change that.

"About 50% of genomic tests happen in the first week in the NICU — this is when it is most cost effective because it has the highest potential to impact care," explains Dr. Chaudhari.

For example, genomic results could influence when or if to do surgery, not just in the NICU but in any ICU situation. However, in these high-acuity areas, decisions can't wait indefinitely.

"That's why we need to test as early as possible when there's an indication there could be benefit to having the genome data," says Dr. Chaudhari.

But how do you know who would be most likely to benefit outside of carefully selected clinical trial populations? When is the right time to order testing? Dr. Chaudhari and his colleagues are actively trying to find out when testing is most likely to offer beneficial outcomes. They recently completed a clinical pathway to support physician decision making in the area.

> It really boils down to two questions. Is the patient sick? Do you know why this is happening?"
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> – *Bimal Chaudhari, MD, MPH, neonatologist, medical geneticist and translational informaticist at Nationwide Children's*

"It really boils down to two questions," says Dr. Chaudhari. "Is the patient sick? Do you know why this is happening?"

If a patient is sick and the treating clinician doesn't know why, a robust body of evidence suggests moving expeditiously to rGS can change the outcome for that child.

Even if a clinician thinks they know why a child is sick, should they consider getting a genomic test? If a newborn is sick enough to be in a Level IV NICU, is a genomic test warranted?

Currently, no research answers these questions, but a collaborative effort between the Neonatology and Medical Genetics teams is in process. Debates in terms of cost, potential benefit, bandwidth of teams, and availability of genetic counselors all factor into just how widespread genomics as a first-line test can become.

BEYOND THE ICU

rGS could apply in some acute care settings, as well, suggests Dr. Chaudhari. Finding those use cases is an increasingly interesting challenge that he looks forward to addressing.

Because the threshold for genomic testing is higher in acute care, the number of patients who receive rGS or non-rapid sequencing in an acute care setting may be smaller than in critical care. For example, a patient who is admitted repeatedly and, as a result, misses clinic appointments where they would be receiving a genomic test may be better served by receiving genomic testing during their acute care stay. This, he suggests, would make a direct impact on the trajectory of care and outcomes for the child, especially if the reason for repeated admission turns out to be genetic.

"But, there are a finite number of genetic counselors, medical geneticists and only 24 hours in a day," he adds. "Scaling is our next frontier."

SETTING A NEW STANDARD FOR PRECISION MEDICINE FOR CANCER

Using genomic data to better understand individual tumors and cancer cases is another area where the impact of genomic testing in the clinical setting is clear.

The National Cancer Institute (NCI) Molecular Characterization Initiative (MCI) is a national project that aims to collect, analyze and report clinical molecular data from children with a primary cancer diagnosis. The MCI is currently enrolling cancer patients from age 0 to 25 being cared for at more than 226 Children's Oncology Group (COG)-affiliated hospitals and clinics. The data from MCI aids the referring clinicians in choosing the best treatment for each child through precision diagnosis.

The MCI is a collaboration among the National Cancer Institute, COG and Nationwide Children's. The Biopathology Center (BPC) at Nationwide Children's processes and stores samples from across the country for the MCI, sending the extracted DNA and RNA for these samples to the Institute for Genomic Medicine for clinical testing. The institute then conducts three separate molecular and genomic tests on the samples, analyzes the data generated and delivers timely, clinically relevant data to the practicing oncologists. Overall, the aim is to return these results within 21 days from the receipt of samples at the BPC.

It is the largest initiative of its kind in the United States and its impact is already astounding.

At about 3 years in, more than 4,300 patients have received MCI testing and more than 90% of patients tested by MCI receive at least one cancer-relevant result that may help define their cancer care or determine their eligibility for a clinical trial. As the types of tumors being analyzed expands, and as the field of molecular characterization continues to evolve, the team looks forward to offering even more valuable information to clinicians as well as fueling future pediatric cancer research. In

Genetic and Genomic Testing in the
INSTITUTE FOR GENOMIC MEDICINE

>18,000
clinical assays in 2024

2,036
MCI patients in 2024 – From 47 U.S. states, Washington D.C., Puerto Rico, Canada, Australia, New Zealand

238
patients received rGS in 2024 with an average time of 3.5 days to provide a preliminary clinical report

>300
faculty, staff and trainees in The Institute for Genomic Medicine in 2024

fact, for every patient receiving MCI testing, the resulting genomic and molecular data are de-identified and submitted to the Childhood Cancer Database Initiative (CCDI). The collective of clinical, genomic, molecular, pathology and outcomes data at CCDI will be accessible to pediatric cancer researchers to investigate and form new hypotheses.

"If you look at other first-world countries — specifically Germany and Australia — they've already done MCI-type programs. And their aggregate results were so compelling that their federal governments agreed to pay for molecular profiling for all children with a cancer diagnosis," says Elaine Mardis, PhD, co-executive director of the Institute for Genomic Medicine and Rasmussen Endowed Chair in Genomic Medicine at Nationwide Children's. She also is a professor of Pediatrics at The Ohio State University College of Medicine and serves as the principal investigator for the MCI project.

The hope of the MCI is that a similar impact will be observed in the United States.

"In three years, we've analyzed more patients than the German and Australian studies combined," says Dr. Mardis. "We are providing actionable results back to providers and informing the cancer care that these kids receive. We hope to amass such compelling data to support the impact of molecular testing that it becomes federally funded and provided for all U.S. children who are diagnosed with cancer."

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> This is the world we're working toward. Where genomic information not only informs diagnosis but also informs routine care, providing the most beneficial impact over a lifespan."
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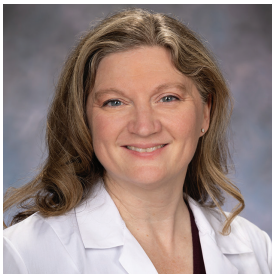

MORE THAN A DIAGNOSTIC TOOL

Dr. Kozel emphasizes the importance of thinking about genomic data beyond initial diagnostics.

As an expert in Williams syndrome, she has conducted extensive research at the National Institutes of Health using genomic data to help predict cardiovascular outcomes and to offer recommendations to improve the clinical care for children with this rare disease.

"While all children with William syndrome have the same deletion and diagnosis, they do not all have the same outcomes," Dr. Kozel explains. "We can use genomic data to understand and predict who will be more likely to have complications during anesthesia, among other outcomes."

Pharmacogenomics — the study of how a person's genetic code influences their response to medications — is an area ripe for developing precision medicine-based approaches for everyone. In a world where genomic information is readily available for disease-specific medications, general anesthesia dosages and protocols and more could be tailored to the needs of the individual patient — not only promoting the best possible outcome but possibly preventing significant harm.

"Pharmacogenomics is just one example of how genomic data adds value to clinical care beyond supporting diagnosis," Dr. Kozel says. "We're ready to go deeper into exploring the impact genomic data can have on clinical care."

Integration of genomic data in the electronic medical record would enable clinicians to be prompted to pursue genetic diagnostics, and, if done, that information could help them make the best recommendations for the patient's care. They could even be alerted when new information about a patient's genetic variants is published in the literature.

"This is the world we're working toward," says Dr. Kozel. "Where genomic information not only informs diagnosis but also informs routine care, providing the most beneficial impact over a lifespan." ■

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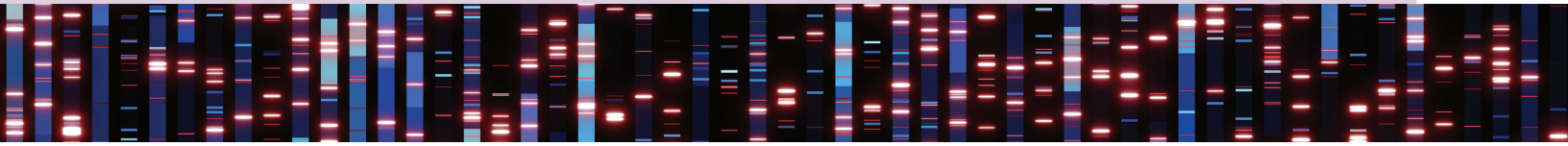
The BabySeq Project. https://www.genomes2people.org/research/babyseq/publications/ Accessed February 21, 2025.

Each genome produces approximately 6 billion data points. How do teams in the Institute for Genomic Medicine sift through the massive quantities of data to provide clinically actionable results? Find out in our special feature online at **PediatricsNationwide.org/GenomicAnalysis.**



From Bench to Bedside:
Collaborations Drive Meaningful Change

The move from a research-first approach to genomic testing to offer more clinically available assays was driven in part by limitations in current clinical testing offerings, as well as by the decreasing cost and turn-around time of genomic sequencing. This environment drove the development of translational protocols.

"Our team works with researchers, clinicians and others outside of our organization to identify testing needs and perform the necessary validations to expand the number of clinical tests available," says Catherine Cottrell, PhD, FACMG, section chief of the Steve and Cindy Rasmussen Institute for Genomic Medicine (IGM) Clinical Laboratory at Nationwide Children's Hospital.

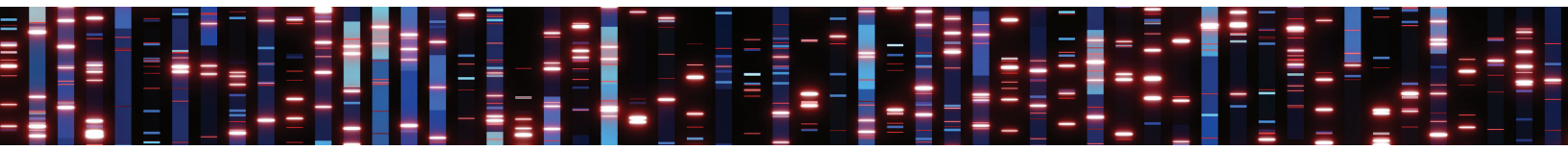
This ability to work directly with clinical providers enhances the efficacy and impact of translational protocols, says Elaine Mardis, PhD, co-executive director of the Institute for Genomic Medicine and Rasmussen Endowed Chair in Genomic Medicine at Nationwide Children's.

"Working with the clinicians who have been with us every step of the way enables us to bring the most impactful genomic tests to the clinic," Dr. Mardis adds. "This is possible because of the organization's One Team vision and culture. We're less siloed and more collaborative, which makes us innovative and nimble. We don't have to convince the clinical lab that a test is worth offering, and this is vital because clinically validating a new test is expensive and time consuming, but if impactful to the practice of medicine, it's very worthwhile."

Few centers across the United States are equipped to drive this level of change and access.

The Institute for Genomic Medicine at Nationwide Children's is a one-of-a-kind enterprise that seamlessly integrates clinical testing and research, with strong ties to pathology and other service lines across the organization.

"Our intentional structure is supported by an ethos of shared purpose," says Dr. Mardis. "We're all working to advance the science and application of genomic studies, but more importantly, we're all here to improve the lives of kids and families."



Single Ventricle, Many Research Angles

An overview of the people and projects behind one of the world's most robust single-ventricle heart disease research hubs

written by Katie Brind'Amour, PhD, MS, CHES

In the field of single-ventricle heart disease (SVHD), there are more questions than answers.

What causes the heart to form with only one ventricle? At what point in fetal development might we intervene to improve its development or function? Which children have the greatest risk for poor outcomes? Can novel surgical approaches normalize a child's expected quality and quantity of life? What promise might medical or gene therapies hold? Can SVHD be cured altogether?

Advances in many other types of congenital heart disease (CHD) have dramatically improved survival for many patients — so much so that it has given rise to a new board-certified field of medical practice, adult CHD. But improvements have been slower in SVHD. It is fatal by the age of 10 in nearly half of children born with hypoplastic left heart syndrome (HLHS), and survival in children with other types of SVHD is not much better. Those who do survive often have major impacts on quality of life, such as limitations on physical activity, increased neurodevelopmental risks and poorer psychosocial health.

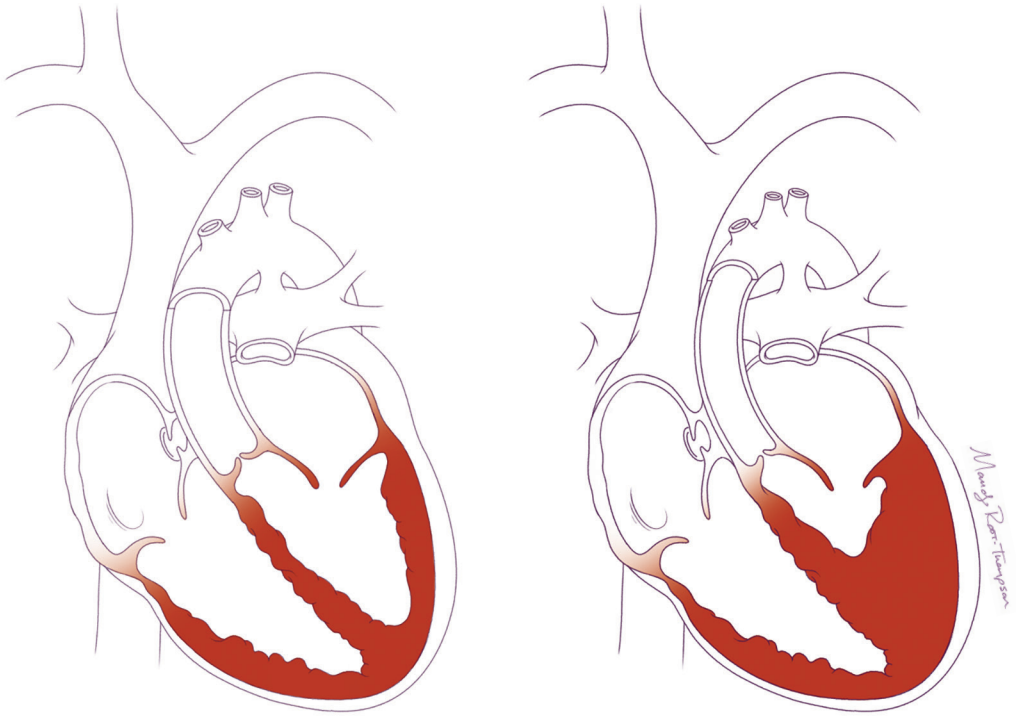
While CHD affects as many as 1% of babies born in the United States, the different forms of SVHD together affect about 1,000 U.S. babies each year.

To complicate matters, SVHD has many possible variations, requiring patient-specific approaches, early intervention and numerous procedures to save the child's life. The Norwood and Glenn surgical approaches first provided life-saving advances for babies with hypoplastic right and left heart syndromes. However, until the development of a surgical procedure called the Fontan — in which surgeons bypass the heart to deliver oxygen-poor blood straight to the lungs without passing through the heart — babies with SVHD remained cyanotic. Even with the advent of the Fontan, long-term outcomes leave much to be desired.

"To an extent, the increasing interest in SVHD is driven by where we are in pediatric cardiology and cardiothoracic surgery," explains Vidu Garg, MD, director of the Center for Cardiovascular Research and co-director of The Heart Center at Nationwide Children's, and a practicing cardiologist. "With some heart defects, surgical closure of a hole is all that is needed and we anticipate that these patients will live a normal, healthy life. But with SVHD, there is still a huge need to improve outcomes. We have a lot to learn."

TISSUE TALENT

Researchers have flocked to Nationwide Children's to join in a growing, diverse community of scientists and clinicians dedicated to improving the outlook for patients with SVHD.



Normal Hypoplastic

In hypoplastic left heart syndrome (HLHS), a form of single-ventricle disease, the left side of the heart is underdeveloped. Patients with HLHS have one pumping chamber that must send blood to both the lungs and the body. This causes both short- and long-term problems, including many open-heart surgeries, catheterization procedures, and, eventually, heart transplantation.

One of the latest arrivals is Daisuke Onohara, MD, PhD, principal investigator in the Center for Regenerative Medicine at the Abigail Wexner Research Institute (AWRI), who recently developed the first successful large animal model for SVHD in lambs.

"There are several good small animal models for HLHS, but there are still many limitations to understanding this disease, which is multigenic and heterogenous," says Dr. Onohara. His model, developed during his time at Emory University School of Medicine, introduces a balloon catheter at 120 days' gestation in fetal lambs to block the mitral valve, after which the reduced flow of blood through the left ventricle induces HLHS.

"That [induction of single-ventricle disease] in a large animal model is powerful on so many different levels," says Christopher Breuer, MD, director of the Center for Regenerative Medicine at AWRI. "It's a model for testing new therapies, it will help us understand how SVHD forms and it will give us insights into better therapeutics that could be curative instead of just palliative."

Dr. Breuer has already initiated a collaboration with Dr. Onohara to study fetal heart valve replacement using tissue-engineered valves.

"There is a theory in the field of 'no flow, no grow,' meaning any sort of anomaly that blocks or reduces flow

through the ventricle can induce hypoplasia and the lack of ventricle formation in the fetus," says Dr. Breuer.

Some interventional cardiologists and perinatologists have conducted fetal valvuloplasty for the past decade or so, which involves opening the valve via angioplasty during the third trimester. Some of those children go from having a single ventricle back to normal biventricular anatomy. Unfortunately, the heart valve remains abnormal and typically requires replacement during the newborn or early childhood period.

Dr. Breuer's goal is to replace the valve *in utero* with a tissue-engineered (TE) valve that will function normally and grow with the child — offering a chance at a cure.

Dr. Breuer and his long-time research partner, Toshiharu Shinoka, MD, PhD, co-director of the Tissue Engineering Program at Nationwide Children's and a principal investigator in the Center for Regenerative Medicine atAWRI, have been developing, improving and studying TE scaffolds for more than 20 years. The idea of TE valves utilizes techniques already supported by a growing body of clinical research on their tissue-engineered vascular graft (TEVG), including the first-ever FDA-approved TEVG trial in children. The scaffold offers a biodegradable replacement vessel seeded with the patient's own cells for patients with SVHD undergoing the Fontan procedure.

Current synthetic conduits used in the Fontan procedure do not grow with the patient and may end up with complications such as thromboembolic events and stenosis, which may eventually require reintervention to place a stent or even another open-heart surgery to replace the graft. TEVG scaffolds, however, enable the patient's body to grow native blood vessel tissue that is vasoreactive and compliant and grows with the patient. Findings to date suggest they could eliminate the need for new grafts as patients age.

HYBRID HEARTS

TEVG is just one research vein targeting improved surgical outcomes for patients with SVHD. Cardiac surgeons in The Heart Center at Nationwide Children's constantly re-evaluate surgical management of HLHS and borderline HLHS. Having spearheaded the development and adoption of the hybrid surgical approach for HLHS, they lead the nation in the number of these operations they perform.

"A few decades ago, it was becoming very clear that improvements with the traditional approach to single-ventricle surgery had plateaued, and people needed to start thinking differently, in a new platform," says Mark Galantowicz, MD, chief of cardiothoracic surgery and co-director of The Heart Center at Nationwide Children's. "That led to the hybrid approach, which has become a paradigm-shifting tool in many centers around the world."

"That [induction of single-ventricle disease] in a large animal model is powerful on so many different levels. It's a model for testing new therapies, it will help us understand how SVHD forms and it will give us insights into better therapeutics that could be curative instead of just palliative."

— *Christopher Breuer, MD, director of the Center for Regenerative Medicine at Nationwide Children's*

LEARN MORE ABOUT THE BREUER LAB

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THE 3 STAGES OF THE HYBRID APPROACH TO SINGLE VENTRICLE CARE

STAGE 1

PALLIATION

performed using cardiac catheterization shortly after birth

STAGE 2

COMPREHENSIVE

performed at age 4-6 months. This complex surgery helps ensure blood flows to all parts of the body

STAGE 3

FONTAN

performed between 2 and 5 years of age

Follow the QR code to watch animations describing each procedure.

The hybrid approach for SVHD minimizes the invasiveness of intervention during the neonatal period, protecting the baby's brain and other vital organs by delaying the more complex, open-heart procedures until they have grown in strength and size. The fact that the initial treatment is easier than the prior standard management of HLHS patients also means that children born at institutions with fewer resources for complex surgeries can now survive; local surgeons can perform the hybrid stage 1 procedure and then transfer the child to a more suitable facility for open-heart surgery when needed.

With more than 20 years of experience in the procedure, hybrid experts at Nationwide Children's have set their sights on the next steps in transforming surgical success for patients with SVHD: understanding variation in the surgical technique's use and outcomes, clarifying best practices, promoting the adoption of hybrid approach guidelines, designating Centers of Excellence and further refining the optimal surgical approach for different single-ventricle anomalies.

"Invariably, these patients are at high risk, and they suffer from this condition for their whole lives," says Can Yerebakan, MD, PhD, associate chief of the Department of Cardiothoracic Surgery and principal investigator in the Center for Cardiovascular Research — and another recent addition to The Heart Center at Nationwide Children's. "If we can have fetal genetic, surgical or combined interventions that can prevent single-ventricle disease from developing, it could be an important way to influence the fate of these patients. Even if we just lessen its severity to a borderline disease, we have effective surgical and interventional approaches for that, and we can really help those patients."

Dr. Yerebakan specializes in the hybrid approach for HLHS and borderline left ventricle disease, in which the left heart is partially underdeveloped but not totally nonfunctional. These patients may benefit from customized adaptations to the hybrid approach to try to stimulate ventricle function and growth rather than undergo primary surgical transition to single-ventricle anatomy. The addition of his expertise further cements the Nationwide Children's team as the most experienced hybrid surgeons in the country.

"Unfortunately, the Fontan will always be a palliative operation and not curative, and TEVG may improve

Can Yerebakan, MD, PhD, associate chief of Cardiothoracic Surgery and principal investigator in the Center for Cardiovascular Research at Nationwide Children's

Daisuke Onohara, MD, PhD, principal investigator in the Center for Regenerative Medicine at the Abigail Wexner Research Institute at Nationwide Children's

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LEARN MORE ABOUT THE ONOHARA LAB
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quality of life and longevity but it also can never fully fix the problem," says Dr. Breuer. "At the end of the day, they still have a single ventricle and abnormal hemodynamics."

That's why numerous teams at Nationwide Children's study the genomic, epigenetic and pathophysiologic aspects of SVHD, using everything from chicks to CRISPR — including Dr. Yerebakan's burgeoning laboratory endeavors at Nationwide Children's, which involve collaboration with Dr. Onohara to identify the optimal time to intervene during fetal development to reverse HLHS. Dr. Yerebakan also studies SVHD development in a chick embryo model to better understand potential biological causes.

Additional endeavors now underway at Nationwide Children's include the use of human induced pluripotent stem cells (iPSCs) to study a host of different aspects of SVHD.

DONATIONS AND DIAGNOSTICS

Human iPSCs from patients with SVHD are easily available to researchers both within and external to Nationwide Children's, courtesy of the research endeavors of Mingtao Zhao, DVM, PhD, principal investigator in the Center for Cardiovascular Research at AWRI, who has recruited more than 200 patients with SVHD and generated more than 70 iPSC lines from their donated blood samples.

While the cells can be used to grow any type of tissue for study — including different heart cell types or brain or liver cells, all of which could reveal valuable information about the impact of SVHD genotypes on different organs — Dr. Zhao uses them for three projects of his own.

The first project, with proof of principle already published in *Circulation Research*, uses cell-free RNA circulating in maternal blood to diagnose SVHD in the fetus. Predicting SVHD early in pregnancy with a simple test could help identify babies earlier who might not otherwise have access to the advanced ultrasound services used to study these defects. Earlier diagnosis means more time to plan appropriate interventions, get the right surgeons identified and — once more fetal therapies are available — a better chance at a cure.

Unfortunately, numbers are a challenge. Because of the rarity of the disease, Dr. Zhao must recruit enough participants to validate his panel in a larger cohort before he seeks approval for the diagnostic test from the U.S. Food and Drug Administration. HLHS affects about 1 in every 4,000 newborns. HRHS affects just 1 in 10,000.

"It is challenging, but we will make every effort to realize this diagnostic as soon as we can," says Dr. Zhao. He is also working to determine whether the cell-free RNA in the mother's blood samples can distinguish between different types of SVHD.

His second project involves the study of HRHS using patient-specific iPSCs. Initial findings were also published in *Circulation*, suggesting HRHS may be caused by the abnormal development of early heart progenitors that give rise to major cell types in the right side of the heart.

Dr. Zhao's other main endeavor involves CRISPR/Cas-9 genome editing, also using the SVHD iPSC lines he established. For this work, he collaborates with colleagues such as Dr. Garg, using CRISPR genome editing to engineer and study the impact of a transcriptional regulator called NOTCH1, known to be involved in many types of CHD. By deleting it in normal iPSC lines, he can study how its absence impacts cardiomyocyte differentiation and proliferation, which he has published in *Circulation Research*. In SVHD iPSC lines, he wants to see how CRISPR/Cas9-based genomic correction of a NOTCH1 mutation affects the phenotype.

"The genetics of SVHD are very complex," Dr. Zhao explains. "NOTCH1 is a contributor, but there are many others — a mutation may collaborate with a few or even a dozen genes to collectively contribute to a phenotype."

NOT JUST NOTCH1

Dr. Garg has been on the NOTCH1 bandwagon since he first identified it in his studies of bicuspid aortic valve, a condition considered genetically related to HLHS. Since then, he has focused on developing mouse models using NOTCH1 as the entry point for studying phenotypes such as aortic valve disease and HLHS. In recent research, Dr. Garg's model combining NOTCH1 and GATA5 mutations results in up to 90% of the mice having an abnormal aortic valve at birth.

"Interestingly, these mice can survive into adulthood, so we can follow them as the valve stenosis gets more severe," says Dr. Garg. "Now we can try to understand why the valve is not forming properly, and also look for novel therapeutics to remodel the valve at birth or slow progression of the stenosis and see if this is an approach worth moving toward the clinic."

The idea behind his work is that by rescuing the aortic valve, blood flow through the valve and ventricle may enable the rest of the heart anatomy to develop properly. Dr. Garg's goal dovetails with other efforts, including the work of Drs. Breuer and Onohara, to prevent SVHD by healing the valve *in utero*.

"Single ventricle disease is truly a syndrome, which makes understanding the genotype and phenotype and the molecular programs at play very important," says Dr. Garg, who also investigates RBFOX2 variation as a key genetic driver of HLHS.

"Now we can try to understand why the valve is not forming properly, and also look for novel therapeutics to remodel the valve at birth or slow progression of the stenosis and see if this is an approach worth moving toward the clinic."

— *Vidu Garg, MD, director of the Center for Cardiovascular Research and co-director of The Heart Center at Nationwide Children's*

LEARN MORE ABOUT THE CENTER FOR CARDIOVASCULAR RESEARCH

NationwideChildrens.org/garg-lab

Mingtao Zhao, DVM, PhD, principal investigator in the Center for Cardiovascular Research at Nationwide Children's

Deqiang Li, MD, PhD, principal investigator in the Center for Cardiovascular Research at Nationwide Children's

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LEARN MORE ABOUT THE LI LAB
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Together with a team of in-house cardiology, neonatology, medical genetics and genomics, data science and translational informatics experts, Dr. Garg is working to expand a genomic sequencing project called COURAGE for Kids from the neonatal intensive care unit to include patients in the cardiac ICU at Nationwide Children's.

Supported by the Steve and Cindy Rasmussen Institute for Genomic Medicine at Nationwide Children's, COURAGE for Kids should provide valuable insights into the presence and potential effects of various mutations in clinical outcomes.

Meanwhile, researchers in the Center for Cardiovascular Research continue to investigate other known genes of interest in CHD.

PUZZLE PIECES

"We need to understand the fundamentals of the problem with more than just one approach before we can go further," says Deqiang Li, MD, PhD, a principal investigator in the Center for Cardiovascular Research at AWRI who worked as a cardiac surgeon before dedicating his career to basic science.

In mouse models, HDAC3 mutations result in smaller, thinner, weaker or missing heart tissue — such as a hole in between heart chambers. Dr. Li and his team want to know why these phenotypes occur, including the pathways, cell communication and changes in function or roles of the gene over time during development.

Recent findings from his lab support a role for HDAC genes and related cellular cross-talk in myocardium development and muscle contractility, which could provide valuable context for SVHD research.

"Single-ventricle disease is a very complicated heart defect, and we all are working at one little piece of the puzzle that alone is nothing," says Dr. Li. "But when you start to put the pieces together, you begin to see the big picture."

The SVHD researchers at Nationwide Children's credit their success to that big-picture vision and practical support from clinical and administrative leadership, which resulted in an advanced vivarium, state-of-the-art hybrid operating suites, genomics and CRISPR/Gene Editing Core resources, the iPSC Core and seed funding for numerous laboratories. The teams are now heavily funded by federal grants and advocacy organizations such as the American Heart Association and Additional Ventures.

"The field is moving forward faster than before, when

funding was scarce and there were fewer parent and patient advocates driving interest," says Dr. Zhao. "Now we've got people using the iPSC lines, small animal models, large animal models and even computational models to study SV disease."

As the researchers make collective progress toward more answers for more patients, they are optimistic about improved therapies and even a cure for SVHD in the next few decades, be it from gene therapy, fetal intervention, TE valves, medical therapy or another approach.

"The overarching goal is improving the quality and quantity of life for these patients — and we've got a first-rate clinical program as well as a robust clinical research arm, animal research and benchtop scientists, and constant translational research," says Dr. Galantowicz. "The stars have aligned here, and I feel that our institution is uniquely capable of expanding the horizon for patients with single-ventricle disease." ■

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— *Mark Galantowicz, MD, chief of Cardiothoracic Surgery and co-director of The Heart Center at Nationwide Children's*

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Who Do You Trust?

Health and science communicators face increasing challenges in a world where misinformation abounds and trust is a coveted commodity.

Abbie Miller, MWC

You might have heard the phrase "post-truth world" used to describe the shifting dynamics of fact, fiction and trusted sources.

With the increase in artificial intelligence (AI) generated content, the end of fact-checking on the world's most influential social media sites, and the bounty of misinformation in every corner of the internet, it is hard to know where to go for information you can trust. But misinformation isn't only happening online. It's happening in face-to-face conversations among friends, families and communities. Often, the spread of misinformation is actually well intentioned.

Misinformation with harmful intent is sometimes called disinformation, which requires a different approach. In health care, both dis- and mis-information are significant problems. However, the well-intentioned spread of health information that is inaccurate, incorrect or dangerous becomes a massive problem in the context of a society that does not trust the traditional keepers of medical and scientific facts and evidence, such as government agencies, academic institutions and health care professionals.

As a scientist, physician or anyone who works in and communicates about health and science, you probably have sources you trust that members of your family or community may consider suspect. And vice versa.

Tracking Trust

The Edelman Trust Barometer is a massive public interest survey conducted by one of the world's largest public relations firms. In 2024, 28 countries and more than 32,000 respondents were represented in the survey, which provides valuable insights for communicators.

In 2024, an ongoing trend of declining trust continued, and where individuals place their trust continued its shift to the private sector. Both the government and media were viewed as less competent and less ethical than nongovernment organizations and businesses. The majority of people (61 to 64%) worry that leaders in government, business and journalism are "purposely trying to mislead people by saying things they know are false or gross exaggerations."

Health care still ranks favorably at 73% trustworthy, but this may be more of an indication of how people feel about direct care for an illness. Health care innovations such as artificial intelligence and gene-based medicine scored neutrally at 50%.

Finding an Opportunity

Trust in people remains strong, and herein lies our opportunity: 77% of respondents said they trust scientists, 74% trust teachers, 63% trust citizens of my country and 62% trust neighbors. As people with a vested interest in science and health communication, we can connect with people in many different ways – as neighbors, community members, scientists and educators.

Connecting in different ways also enables us to take advantage of the "someone like me" effect. When it comes to who respondents believe about new innovations and technologies, scientists and "someone like me" held equal confidence

(74%). If the parent of a newborn trusts the advice of someone "like them" in a parenting social media group just as much as they trust the advice of their pediatrician or a researcher in the field, negative ideas about vaccines or other evidence-based types of care take root and spread rapidly.

Shifting Trust Requires Adjusted Approach

As a health and science communicator, shifts in trust are challenging my long-engrained methods of building confidence and connection with my audience. For example, backing up a recommendation for a healthy behavior or informative statistic by citing the Centers for Disease Control and Prevention (CDC) was once the best way to show that the recommendation or information was trustworthy. But if my audience no longer trusts the CDC, how can I best communicate with them?

If we want to make the biggest impact in health and science communication, we must lean into these areas of trust to connect with our audiences – whether they are peers, patients, families or community members – as people. By focusing on building human connections, we have an opportunity to build bridges in this increasingly divisive era of modern history.

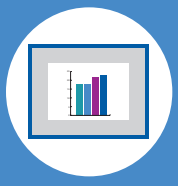
Persuasion, information and connection are the goals of health and science communication, regardless of channel. Whether you are communicating on social media, in person, in print or otherwise, the key skills to building trust with your audience are the same. ■

Edelman Trust Institute. 2025 Edelman Trust Barometer. https://www.edelman.com/trust/2025/trust-barometer. Accessed Feb. 13, 2025.

5 Essential Skills to Improve Communication and Build Trust

- **KNOW YOUR AUDIENCE:** Who needs to know the information you want to share? What are their preferences? Do they have a baseline understanding of the topic or is it all new? Ask yourself questions about the recipient of your communication – whatever the form – to help tailor your message and approach to meet your audience's needs. It's about them – not about you.

- **USE PLAIN LANGUAGE AND UNDERSTAND HOW HEALTH LITERACY AFFECTS YOUR AUDIENCE:** Speaking plainly and using simple words helps people understand new concepts or information when they are tired, stressed and distracted. This applies to peers and patients. But it is important to remember that using plain language should never be about talking down to people. Use your words (written or spoken) to build bridges, not barriers.



- **MAKE IT VISUAL:** A picture can be worth a thousand words, but only if it connects with the audience. Consider whether your audience is comfortable reading charts or graphs, or what labels in an illustration or animation might help clarify content.

- **SHARE YOUR ENTHUSIASM:** People are attracted to people who are passionate about their work. Your enthusiasm and attitude are contagious, whether you are helping a parent understand post-op instructions or presenting your latest research at a national meeting.

- **BE YOURSELF:** Connecting with others on the basis of our humanity allows us to build trust and open doors for conversation.

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Managing the Pain of Medical Procedures With Virtual Reality

Clinicians across departments at Nationwide Children's have piloted a virtual reality (VR) game for pediatric pain management. The latest work moves virtual reality closer to clinical standard practice. Find out how the pilot influenced the use of VR in clinics.

PediatricsNationwide.org/Virtual-Reality-Standard-of-Care

How Accurate Is Pediatric Bipolar Disorder Testing?

Pediatric bipolar disorder affects 1-4% of children, but it is often not diagnosed until adulthood. Diagnosing bipolar disorder remains challenging because its symptoms are nonspecific and often overlap with disorders such as depression and attention-deficit/hyperactivity disorders (ADHD). A recent meta-analysis shows which tests are most accurate in an aim to improve early diagnosis. Find out more about testing children for bipolar disorder.

PediatricsNationwide.org/Pediatric-Bipolar-Testing

Updated Small Baby Care Guidelines Reflect 20 Years of Work Toward Improved Outcomes

As the Small Baby Program at Nationwide Children's Hospital celebrates its 20th anniversary, it is also releasing its latest set of care guidelines for their tiny patients. Divided according to gestational age, care discipline and postnatal time period, the guidelines provide digestible and thorough guidelines for patient management from delivery up through discharge home. Learn more and get the guidelines.

PediatricsNationwide.org/Small-Baby-Guidelines

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