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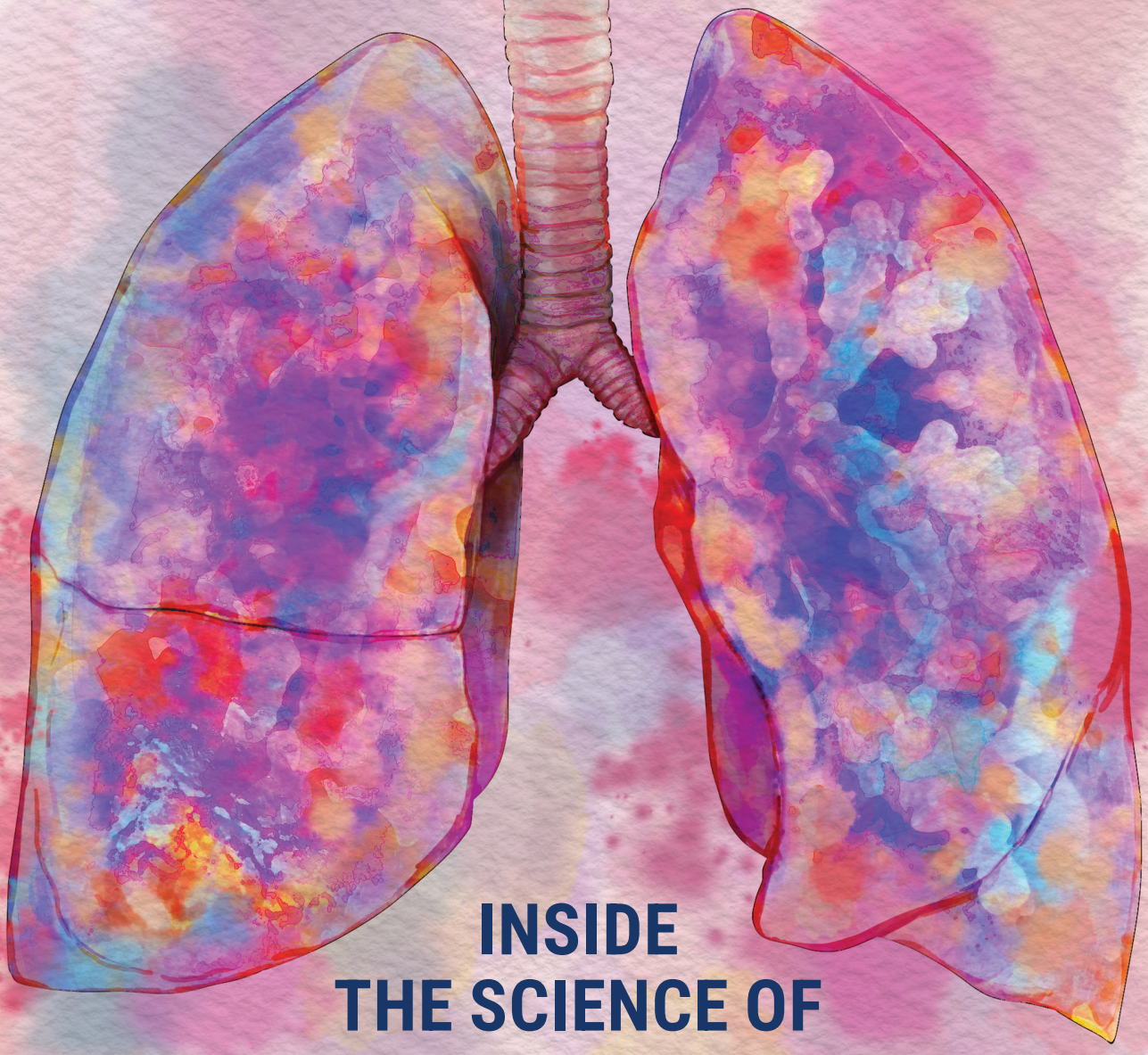


INSIDE THE SCIENCE OF PEDIATRIC LUNG DISEASE

INSIDE THIS ISSUE

A publication of Nationwide Children's Hospital

INSIDE THE SCIENCE OF PEDIATRIC LUNG DISEASE

Table of Contents

A NOTE FROM THE EDITOR

Our breath connects us with the moment, grounds us and has the power to calm our minds and bodies. But for millions of children, an easy breath is not guaranteed.

Lung disease accounts for about a third of admissions to children's hospitals. From the common culprits, such as asthma, to rare lung diseases, such as cystic fibrosis and sickle cell lung disease, our researchers are working to understand mechanisms of disease, recovery and prevention through basic science studies and landmark clinical trials.

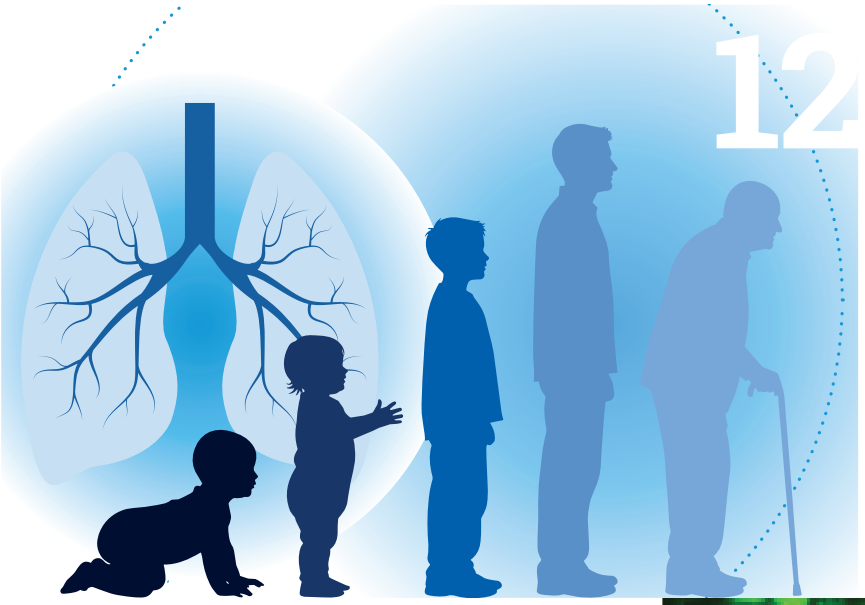
In a unique culture of collaboration, researchers from across the organization, including those in the Center for Perinatal Research, Center for Clinical and Translational Research and Center for Microbe and Immunity Research, are working with colleagues in Critical Care Medicine, Pulmonology and Allergy and Asthma in novel ways to connect the dots on lifelong lung health.

Bronchopulmonary dysplasia (BPD) is the most common chronic lung disease in infants born preterm. Nationwide Children's Hospital has long been recognized as a leader in clinical care for these vulnerable patients, with a dedicated BPD Unit housed within the Neonatal Intensive Care Unit (NICU). Now, researchers are building a novel study to understand BPD in ways we haven't even been able to attempt before.

In the articles in this special section, you'll dive into some of the projects and programs at Nationwide Children's that are poised to improve our understanding of lung disease to drive better outcomes for children everywhere.

I hope you enjoy them as much as I have.

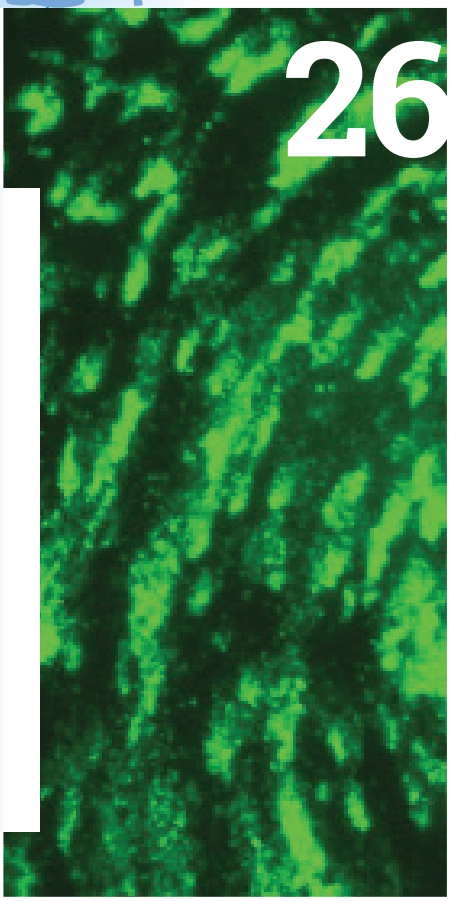
– Abbie Miller, MS, MWC



DEPARTMENTS

FEATURES

INSIDE THE SCIENCE OF PEDIATRIC LUNG DISEASE



"We've discovered that Notch ligands are not just activating the receptor. Our data suggests that ligand processing regulates whether that cell will change its fate. It's a novel sub-mechanism, and we're excited about it."

— Susan Reynolds, PhD, principal investigator, Center for Perinatal Research at Nationwide Children's

How Diabetes Rewires the Heart's Smallest Vessels

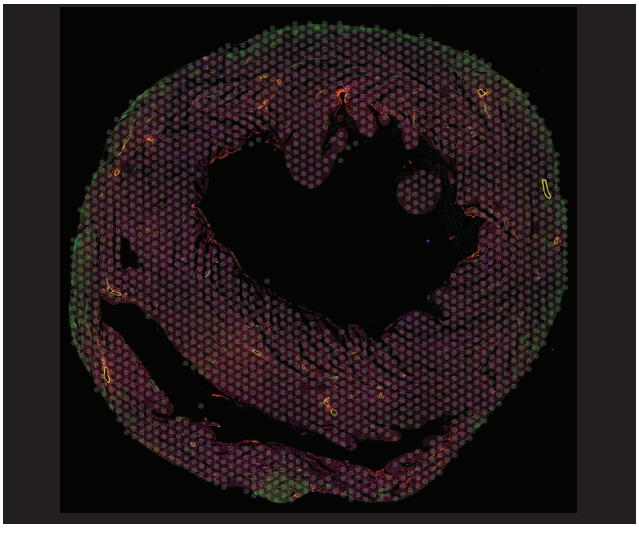
A landmark study uncovers how diabetes alters the heart at the cellular level.

Cardiovascular disease is the leading cause of death in type 2 diabetes. While its effects on large arteries are well recognized, growing evidence suggests the earliest cardiovascular injury occurs in the heart's smallest vessels. Coronary microvascular disease (CMD), marked by impaired endothelial and smooth muscle function, adverse remodeling and reduced blood flow, can appear long before symptoms of heart failure. Yet the cellular mechanisms that drive this process have remained unclear.

A new study led by investigators at Nationwide Children's Hospital offers the most detailed look to date at how diabetes alters the coronary microcirculation. Using single-cell RNA sequencing and spatial transcriptomics, the team mapped nearly 20,000 cells in diabetic and non-diabetic mouse hearts to understand how each cell type changes and where those changes occur.

Aaron Trask, PhD, FAHA, FCVS, principal investigator in the Center for Cardiovascular Research, led the work, which is published in *Basic Research in Cardiology*.

"We now have patients as young as five years old with type 2 diabetes," Dr. Trask says. "The microcirculation is one of the first tissues to show signs of disease, so understanding what's happening there is critical."



Immunohistochemical staining of the vessel's cellular components, which guided the selection of subregions for analysis

Both the single-cell and spatial analyses revealed a consistent pattern: diabetes induces broad metabolic reprogramming across the microvasculature.

"We saw strong enrichment of pathways like oxidative phosphorylation and fatty acid metabolism across many cell types," he says. "That wasn't surprising in cardiomyocytes, but seeing that shift in vascular cells was somewhat unexpected."

Adipogenesis-related genes were also elevated, even though true adipocytes were rare.

"Almost all the cell types were expressing adipogenic markers," Dr. Trask notes. "That has really opened a new area of investigation for us."

Spatial transcriptomics confirmed that these changes were concentrated in and around coronary resistance microvessels, which regulate coronary blood flow to the heart tissue. This approach also revealed altered communication networks among neighboring cells.

"We expected endothelial and smooth muscle cells to dominate vascular signaling, but fibroblasts emerged as major communicators," he says. "That was surprising and suggests we may underappreciate their role."

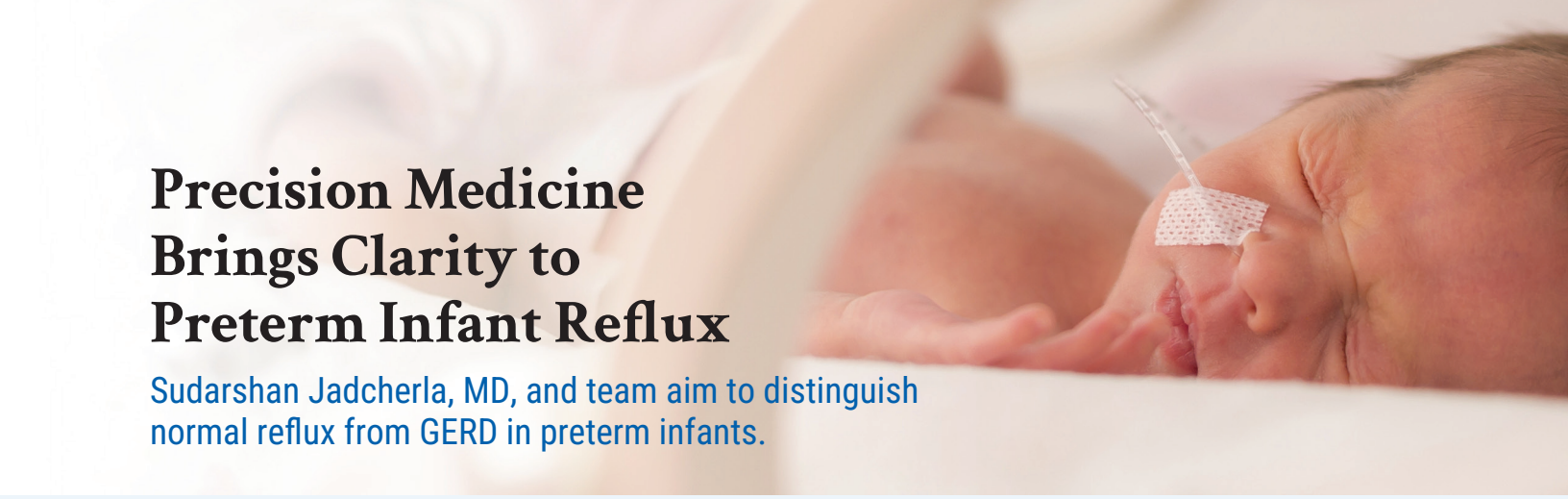
The team validated several of the most altered pathways using proteomic analysis of isolated coronary microvessels, strengthening confidence that the transcriptomic changes reflect true biological shifts.

The findings provide a new framework for understanding how CMD develops at the earliest stages of diabetes, insights that may guide future therapies.

"If a pediatric patient has type 2 diabetes, they likely already have underlying microvascular disease," Dr. Trask emphasizes. "We need to think about ways to treat early and prevent progression to heart failure."

McCallinhart PE, Strawser CH, Garfinkle EAR, Navarro JB, McAllister C, Vetter TA, Lucchesi PA, Mardis ER, Mezache L, Veeraraghavan R, Miller KE, Trask AJ. Single cell and spatial transcriptomic profiling of the type 2 diabetic coronary microcirculation and myocardium. *Basic Research in Cardiology*. 2025 Dec;120(6):1109-1129.

— Lauren Dembeck, PhD



Precision Medicine Brings Clarity to Preterm Infant Reflux

Sudarshan Jadcherla, MD, and team aim to distinguish normal reflux from GERD in preterm infants.

Gastroesophageal reflux (GER) is common in preterm infants regardless of whether they are being fed formula or breast milk, often presenting as irritability, coughing or feeding difficulties. These symptoms often lead clinicians to suspect gastroesophageal reflux disease (GERD), prompting interventions that sometimes include stopping breast milk. But is this always necessary?

Researchers at Nationwide Children's Hospital, guided by Sudarshan Jadcherla, MD, aim to address a critical gap in diagnosis of GERD in babies in the NICU: distinguishing normal reflux from pathological GERD.

"About 45% of babies diagnosed with GERD do not actually have the disease," says Dr. Jadcherla, principal investigator in the Center for Perinatal Research at Nationwide Children's. "They have symptoms, but they do not actually have the disease. We need to be able to distinguish between what is abnormal and what is normal. Using precision medicine approaches allows us to do just that."

The team utilized a type of technology called pH impedance testing, a tool used at Nationwide Children's that is not widely available and allows clinicians to precisely characterize reflux events. This precision allows physicians to determine whether reflux is abnormal or simply part of normal physiology.

Using pH impedance testing, they measured acidity and whether reflux was liquid, gas or mixed, correlating these findings with real-time symptoms. Abnormal symptoms were associated with missed feeding milestones.

The study, published in *Journal of Perinatology*, also revealed that breast milk-fed infants exhibited more acid reflux events than formula-fed infants, likely due to breast milk's natural acidity and lower viscosity. These events sometimes extended higher into the esophagus and lasted longer. However, symptoms and discharge outcomes were similar between groups. Importantly, developmental assessments over two years showed superior receptive and fine motor skills in breast milk-fed infants compared to formula-fed infants.

"Despite its acidic nature and association with reflux episodes, our research upholds the principle that breast milk remains the gold standard for preterm infant nutrition," says Dr. Jadcherla. "Its unique properties support growth, healing and neurodevelopment — benefits that far outweigh concerns about reflux when managed appropriately."

Determining whether GER is abnormal or normal allows clinicians to create personalized plans for preterm infants with reflux symptoms. The goal is to maximize the use of breastfeeding for nutrition benefits.

To further improve care, Dr. Jadcherla and his team are conducting the GIFT Trial (GERD Infants in Feeding and Therapeutics), an NIH-funded study evaluating targeted strategies for infants with pathological GERD. Through this clinical study, they hope to identify who needs treated, how to treat them, and for how long.

"Incorporating precision medicine approaches in a carefully tested, randomized, controlled trial manner will lead to better strategies in the future. Without support from health care providers and parents, we can't advance treatment," says Dr. Jadcherla.

Osborn EK, Sultana Z, Bala F, Alshaikh E, Jadcherla SR. Distinct gastroesophageal reflux characteristics in preterm-born infants fed human milk versus formula: insights for clinical practice on outcomes. *Journal of Perinatology*. 2025;45(12):1765-1771.

Learn more and refer eligible patients for this trial at ClinicalTrials.gov/study/NCT06114836.

Effectiveness and Adoption of a Mental Health Crisis App

Youth who used a statewide mental health crisis app in Utah reported significant declines in the intensity of their presenting concerns and were generally satisfied with the app.

Youth who used SafeUT, a statewide crisis app in Utah, reported experiencing significant decreases in the intensity of their presenting concerns, according to a study led by Mindy Westlund Schreiner, PhD, psychologist and clinical scholar in behavioral health at Nationwide Children's Hospital.

SafeUT was created in 2016 for youth to address suicide as the leading cause of death among 10- to 24-year-olds in Utah. Among several benefits, SafeUT uses licensed clinicians and is integrated with Utah's schools.

Dr. Westlund Schreiner and her research team examined the characteristics of 210 youth who used the SafeUT app between August 2021 and October 2022. Study participants completed surveys covering several areas, including satisfaction with the app and barriers to accessing mental health services.

Results were published in the *Journal of the American Academy of Child and Adolescent Psychiatry.*

Fewer than half of the participants reported currently using mental health services at the time of survey completion. Additionally, only 45% reported accessing these services before using SafeUT.

More than 25% of the youth reported a gender identity other than cisgender male or female. These youth, compared to cisgender youth, were significantly more likely to have reported a suicide attempt in the 2 weeks before survey completion.

Parent- and guardian-related barriers were the most frequently reported barriers to accessing mental health services.

"Although families (may) want to do everything they can to help, youth often do not want to burden their parents with their mental health concerns, known as 'perceived burdonsomenesss,'" Dr. Westlund Schreiner says.

She emphasizes the critical need to reduce this barrier, such as by helping youth identify a trusted adult who can help facilitate conversations about mental health with the child's parents. Policy-level changes are also necessary, given the legal requirement of parental or guardian consent for youth to access mental health services in many states.

A troubling study observation was that nearly 20% of participants reported a suicide attempt in the 2 weeks before completing the survey.

"This rings a lot of alarms," Dr. Westlund Schreiner says, noting that there are likely more unreported suicide attempts captured in epidemiological studies, as opposed to the present study, because they do not present to emergency departments.

"Preliminary results demonstrate that there are differences in the barriers that youth encounter in accessing mental health services, depending on whether they live in rural or urban areas," Dr. Westlund Schreiner says.

Approximately 87% of participants reported feeling somewhat supported or very supported by their licensed SafeUT clinician. About 84% reported feeling somewhat satisfied or very satisfied with the app. Importantly, the intensity of presenting concerns decreased significantly following their chat in the SafeUT app.

Schreiner MW, Farstead BW, Pazdera M, Bakian AV, Kious BM, Manotas K, Crowell SE, Kaufman EA, Langenecker SA. Characteristics of youth crisis app users: Mental health service access and barriers and perceptions of helpfulness. *JAACAP Open.* 2024 Aug 28;3(3):421-430.

— JoAnna Pendergrass, DVM

Lowering Thrombin Levels Offers a Double Benefit in Glomerular Disease Model

Preclinical studies suggest that reducing levels of the clotting enzyme may simultaneously reduce kidney damage and lower risk of blood clots.

Preclinical research in an *in vivo* model now confirms what Bryce Kerlin, MD, and his team first proposed in a publication 8 years ago: excess thrombin directly injures podocytes, and high levels in the blood and urine promote proteinuria, hypercoagulation and kidney damage.

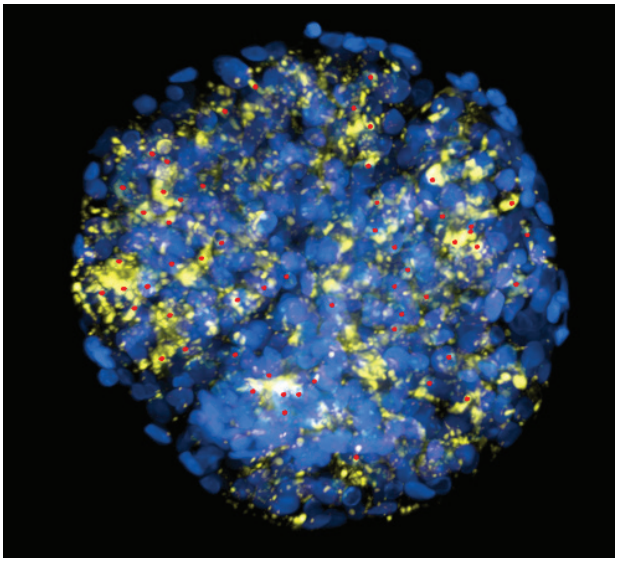
"It took a very complicated set of experiments to test the hypothesis in podocytes and glomeruli in living kidney, instead of just cultured cells in a petri dish," says Dr. Kerlin, hematologist and principal investigator in the Center for Clinical and Translational Research at Nationwide Children's Hospital.

The latest of his team's related publications became the July 2025 cover story for the *Journal of the American Society of Nephrology*, which shared a new way to count podocytes (see image at right) and the details of *in vivo* rat models to study the impact of thrombin. The team provoked glomerular disease in the model, then administered intravenous prothrombin protein to some of the rats and an anti-prothrombin therapy (antisense oligonucleotides) to others. They used healthy controls as well as rats with glomerular disease but no prothrombin-related treatments for comparison.

After 10 days, they examined a wide variety of kidney health markers. Rats that received the anti-prothrombin therapy had less prothrombin colocalized with podocytes, less tubular injury and podocyte foot process effacement, less podocytopathy and proteinuria, better plasma albumin levels and improved podocytopenia compared to rats given extra prothrombin.

"Extra prothrombin exacerbated kidney disease, while knocking it down significantly rescued the disease," says Dr. Kerlin.

If thrombin functions similarly in humans with glomerular disease, inhibiting thrombin production could hold tremendous potential for simultaneously ameliorating kidney damage — slowing or preventing the progression to chronic kidney disease — and reducing the risk of deadly blood clots that represent a major risk to such patients. High-quality clinical trials will be required to determine what effect prophylactic anticoagulant therapies may have on disease remission and venous thromboembolism risk.



The many steps required to translate these findings to the clinic are already in Dr. Kerlin's long-term plans, but he cautions that even using FDA-approved anticoagulants, enough data to justify practice changes could be a decade away — or more.

"Every scientist's dream is to get something beneficial to patients into the clinic," says Dr. Kerlin, who hopes this vein of study may be a significant opportunity to improve kidney health for millions of patients. "Getting over that hump is difficult. We have a lot of work to do."

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— Katie Brind'Amour , PhD

Speeding Up Science With Patient-Derived Xenografts

A perfect storm of advanced technologies and scientific collaboration opens doors to rapid progress in pediatric oncology research.

written by Katie Brind'Amour, PhD

The world of pediatric cancer research faces the challenges of small patient numbers, increased ethical considerations, limited funding and poorly classified diseases. In some ways, these challenges reflect the field's successes over the past half century, which have driven overall 10-year survival rates from just under 59% to nearly 83%, with even higher cure rates in some cancers.

The remaining patients, however, have rare or aggressive diagnoses, and the limited number of scattered cases make traditional clinical trials a logistical ordeal — even if investigators can find the funding.

"Gone are the days where we could take a bunch of models, treat them with a drug and say 'It cured tumors in mice, let's bring it to the clinic!' We don't have that luxury in pediatric cancer," explains Filemon Dela Cruz, MD, principal investigator in the Pediatric Research in Oncology Xenografting Consortium (PROXC) and a pediatric hematologist-oncologist at Memorial Sloan Kettering Cancer Center, where PROXC is hosted. "To be able to answer the questions, you need numbers. We're fortunate that these difficult patients are a small proportion of the patients we treat, but it means we have to be even more selective about what agents we nominate to develop further in the clinic."

A Meeting of the Minds

PROXC began as a group of clinician-scientists interested in optimizing and standardizing protocols for their own development of patient-derived tumor xenograft models. These models maintain the unique biology and complex, living-tumor heterogeneity of the original patients from whom they were obtained.

At Nationwide Children's Hospital, these samples are collected through the Bio-KIDS program, a universal patient consent that allows donation of leftover tissue from a clinically indicated surgery or biopsy. Each tumor receives its indicated clinical workup from pathologists, which often includes genomic sequencing. Tissue samples that remain are then placed into specialized mouse models, where they grow into patient-derived tumors and are cataloged according to tumor characteristics, preserving those living tissues for future research.

"For a long time, the standard lab research model has involved cell lines that were generated 20 years ago and passaged over and over in cell culture. So it's uncertain how much the cell cultures used today actually look like the tumors that originally came from those patients," says Ryan Roberts, MD, PhD, physician for the Division of Hematology, Oncology and Blood and Marrow Transplant and principal investigator for the Center for Childhood Cancer Research at the Abigail Wexner Research Institute at Nationwide Children's. "That is why we have done so much work to try to generate laboratory models that look more like our patients' cancers, and that represent the heterogeneity of our patients."

As a result of efforts such as these, researchers have begun to understand that not all osteosarcomas are alike, nor are all rhabdomyosarcomas or other tumor types. Even within a single patient, tumors are not homogenous. As scientists amass data in different diagnoses, cancers have begun to shift from a single classification, such as medulloblastoma, to subtypes of disease with distinct prognoses and treatments.

"All of these pediatric diseases are going through this process, and having good models helps us figure out which patients could benefit from which drugs," says Dr. Roberts, who is also one of PROXC's seven principal investigators, together with researchers at Dana-Farber, St. Jude Children's Research Hospital, Texas Children's Hospital and University of California San Francisco. "Things are transforming already and will continue to change over the next decade. We are getting much more sophisticated and personalized in prescribing therapy as we learn to use existing drugs more intelligently and develop new drugs for specific biologies."

After the PROXC constituents developed their protocols for patient-derived xenograft (PDX) creation, they chose to keep their partnership going. They realized that by pooling the unique models they had each developed, they could establish one of the largest PDX repositories in the world.

The group also knew that the consortium could function as a tremendous platform for preclinical research, enabling pediatric oncology studies the likes of which the scientific community had never seen. They all signed a sweeping data- and model-sharing agreement to enable easy exchange of their PDX collections, genomic sequencing data and basic science findings. Then they put their idea to the test.

PDX Progress

Nationwide Children's alone houses more than 200 models, many of which the entire consortium can now access — some of which are the only models in the world of rare tumor types. Together with contributions from the other member institutions, consortium researchers now have access to more than 700 PDX models.

When someone wishes to study a particular cancer or genotype, they can go to the PROXC "library" to identify all of the group's relevant models to advance therapy to explore, the team has the ability to conduct a multi-site trial with tumor models from numerous patients, using the group's uniform protocols.

Members even conduct standardized, blinded experiments with drug distribution from a central site. This novel method of preclinical research effectively tests a therapy on tumors from multiple patients, and when done in a blinded fashion, approximates a clinical trial in the most advanced way possible — without involving real patients.

"The gold standard for preclinical work is now patient-derived xenografts," says Dr. Dela Cruz. "The fact that we can do it in a standardized way across multiple sites and models is unprecedented."

He and a colleague at Memorial Sloane Kettering had seen initial success in cell lines and cell-line-derived xenografts using a repurposed therapy to treat desmoplastic small round cell tumors (DSRCT), an ultra-rare and almost universally fatal type of sarcoma. It wasn't until they saw the same anti-tumor effect in multiple PDX models of the tumor that they allowed themselves to get excited, though.

PDX By the Numbers

>700 PDX Models
>400 Ped Sarcoma PDXs
>140 Osteosarcoma PDXs
>50 Ewing Sarcoma PDXs
>100 Rhabdomyosarcoma PDXs
>60 Neuroblastoma PDXs
>60 Wilms Tumor PDXs
>13 Tumor Types
~50 Tumor Histologies

> Without patient-derived xenografts and similar resources, we're really stuck just studying one patient's cells. That's like trying to describe the universe of apples if all you have is a Granny Smith. These models let us appreciate the nuance of what happens in real patients — why some respond and some don't to a particular drug. Understanding that is hugely important, and we couldn't do it without these models."
>
> *– Ryan Roberts, MD, PhD, physician for the Division of Hematology, Oncology and Blood and Marrow Transplant and principal investigator for the Center for Childhood Cancer Research at Nationwide Children's*

"The PDX studies suggested there would be a positive effect, and there was biologic rationale to say this class or type of drug would have activity in this type of tumor," says Dr. Dela Cruz. "It made sense to move it into a pediatric trial."

Despite running out of the finite drug supply before the trial could finish accrual, the study had positive results that aligned with preclinical PDX findings — a promising step toward better therapies for DSRCT.

In another PROXC-facilitated success story, Dr. Roberts and his team made inroads into the primary focus of his research: lung-based metastases of osteosarcoma tumors. His findings, reported in *Cancer Research*, revealed a population of cells that travel to and interact with lung tissue, triggering sustained fibrosis and creating a suitable environment for the growth of new tumors.

Preliminary research in both PDXs and cell-line models suggests that targeting the IL1 signaling from osteosarcoma tumors significantly inhibits metastatic progression. Nintedanib, a drug approved to treat certain types of chronic lung fibrosis and non-small cell lung cancer, showed success in preventing metastasis by inhibiting fibrosis in multiple preclinical investigations.

This preliminary success, sped up considerably by single-cell RNA sequencing and the ability to rapidly and affordably study multiple living tumor models, now faces the same barrier as Dr. Dela Cruz's: access to the drug for patient trials.

"This is a common issue we run into," says Dr. Dela Cruz. "We can discover these things, but funding and drug supply are issues that need to be addressed at multiple levels."

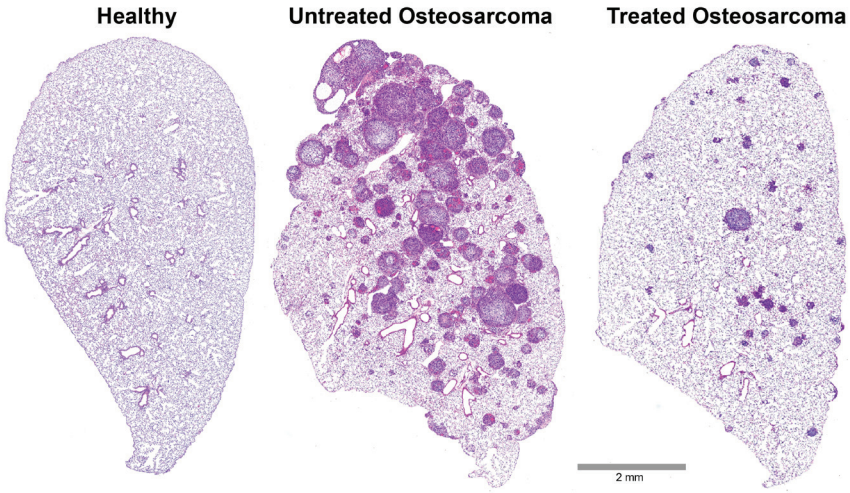
Paving the Way Forward

The PROXC investigators have not let these all-too-common barriers deter them from continued progress in pediatric cancer research, and their determination continues to pay dividends.

In a recent Children's Oncology Group trial, the drug trastuzumab deruxtecan failed in pediatric osteosarcoma. However, because of PDX research (published in *Molecular Cancer Therapeutics*) suggesting potential efficacy in a different subset of patients, the trial was able to redefine the target population — emphasizing tumors with PDX-demonstrated sensitivity regardless of HER2 status, including cases of DSRTC and renal tumors — and redirect the indication to one better informed by tumor biology. Now repositioned, trial enrolment begins again in 2026.

"Without patient-derived xenografts and similar resources, we're really stuck just studying one patient's cells. That's like trying to describe the universe of apples if all you have is a Granny Smith," says Dr. Roberts. "These models let us appreciate the nuance of what happens in real patients — why some respond and some don't to a particular drug. Understanding that is hugely important, and we couldn't do it without these models."

The world of single-cell sequencing has further opened the world of rare tumors to investigators, shining a



Microscope images of lung from mice with healthy lungs, mice with osteosarcoma bone tumors metastasized to the lungs, and mice with osteosarcoma that were treated with a drug that prevents scar formation in the lung. By blocking the scar-forming reaction, researchers prevented most metastatic lesions from forming. Those that did emerge grew much more slowly. This is the first proof-of-principle step toward a treatment that could save the lives of children and young adults affected by this aggressive disease.

light on minority cell populations, mutation similarities across cancers, tumor heterogeneity over time and treatment, and potential weaknesses to exploit with new or existing therapies.

"With single-cell sequencing, I can do an experiment in one week that gives me a body of data that would have taken me 5-6 years to generate less than a decade ago," says Dr. Roberts. "It's pretty incredible what these new techniques can do."

The complexity of these technologies demands expertise in multiple scientific disciplines to bear fruit. At Nationwide Children's, the Roberts lab relies heavily on the Steve and Cindy Rasmussen Institute for Genomic Medicine for sequencing, the High-Performance Computing Core for data management, the Biopathology Center for overflow storage, the Bio-KIDS program for continued source material, multiple clinical divisions for patient recruitment, the Clinical Trials Office for study logistics and the Animal Tumor Core for help with models. Coupled with a Germain Family Accelerator Grant for sarcoma research and the resources of the full PROXC team, Dr. Roberts is optimistic about what lies ahead for the field of pediatric oncology.

"We can now take all of the cells in a tumor, including the complex networks that form a metastatic lesion, and pick apart all the genes expressed in each individual cell, showing what happens when they are treated with a specific drug," says Dr. Roberts. "We are trying to use it to design specific solutions that may differ from patient to patient, to pick the best drug for each person and truly deliver precision medicine."

His team is currently diligently mapping the responses of each enzyme in each cell type for osteosarcoma lung metastases, genome-wide. Once they know which pathways are activated abnormally, they can select or develop drugs that target those pathways.

"We've been talking about moving the needle for a long time, but I think we're at an inflection point because of this unprecedented insight into tumor heterogeneity," says Dr. Dela Cruz, who believes that computational tools will soon help identify potential sensitivities of rare and resistant tumor types, which can then be reprogrammed or treated to push tumors into a sensitive state.

"This is where PROXC is uniquely equipped to address the remaining challenges in this field," says Dr. Dela Cruz. "When you have one of the largest PDX collections in the world, you can ask questions no one else can answer." ■

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From Bronchopulmonary Dysplasia to Chronic Obstructive Pulmonary Disease: A Developmental Continuum

A growing understanding of BPD and COPD suggests shared mechanistic roots.

Yan Hu, PhD, principal investigator in the Center for Perinatal Research at Nationwide Children's

A Prolonged Window of Vulnerability

Lung development is a highly orchestrated process that begins early in gestation and continues well into postnatal life. Following airway branching during the embryonic and pseudoglandular stages, distal lung maturation, including small airway and alveolar formation, extends through infancy and early childhood. This prolonged developmental window renders the lung particularly vulnerable to environmental and inflammatory insults, with lasting consequences for respiratory health.

Premature Birth and the Origins of BPD

Preterm birth abruptly disrupts this finely tuned program. Exposure of the immature lung to mechanical ventilation, hyperoxia and inflammation occurs during critical windows of epithelial and mesenchymal differentiation, often resulting in bronchopulmonary dysplasia (BPD).

Since its initial description by William H. Northway, Jr., MD, and colleagues in 1967, the clinical phenotype and outcomes of BPD has evolved substantially. Advances in neonatal care, such as antenatal corticosteroids, surfactant replacement and noninvasive ventilation, have dramatically improved survival among extremely preterm infants, including those born before 28 weeks of gestation. However, these successes have shifted the clinical burden from early mortality to long-term respiratory morbidity driven by impaired lung development and regenerative capacity.

A Precursor to Adult Chronic Lung Disease

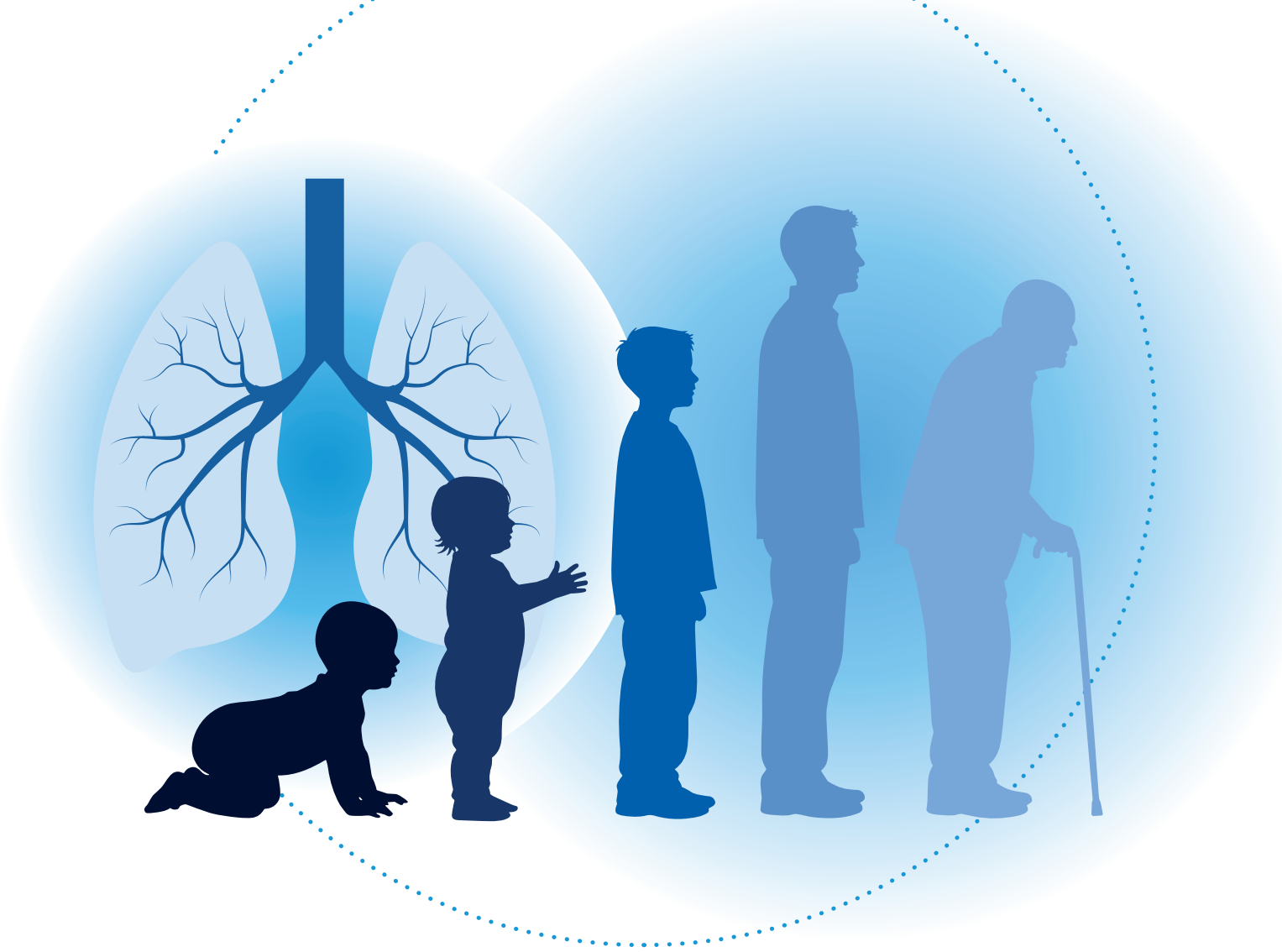
Increasing evidence now supports the concept that BPD confers increased risk for chronic respiratory morbidity in adulthood, including the development of chronic obstructive pulmonary disease (COPD). Survivors of preterm birth, particularly those with a history of BPD, exhibit persistent airflow limitation, altered architecture and reduced lung function.

These observations challenge the traditional view of COPD as solely an age- or exposure-related disorder and instead position it along a developmental continuum initiated by early-life injury. Shared pathological features, including alveolar simplification, small airway remodeling, chronic inflammation and extracellular matrix dysregulation, suggest common mechanistic roots between BPD and COPD.

Notably, no current therapies effectively promote lung regeneration in either condition, underscoring a critical unmet clinical need.

Regenerative Pathways Across the Lifespan

Building on our work in lung epithelial stem cell dysfunction in COPD, my lab's research extends



beyond a singular focus on alveolar type II cells to investigate a broader spectrum of epithelial progenitor populations, including airway secretory cells capable of contributing to alveolar repair following injury. We leverage high-throughput approaches, including high-resolution spatial transcriptomics and single-cell RNA sequencing, across transgenic animal models and human lung tissues to define molecular programs that govern epithelial cell fate, plasticity and regenerative capacity in health and disease. To functionally interrogate these pathways, we integrate mouse, ferret and human-derived precision-cut lung slices (PCLS), which preserve native tissue architecture and multicellular interactions, alongside lung organoid systems. Together, these complementary platforms enable mechanistic testing of hypotheses generated from transcriptomic analyses and facilitate the identification of targetable pathways that promote effective lung regeneration.

Bridging Developmental Biology and Disease Mechanisms

Despite growing recognition of the developmental origins of chronic lung disease, the biological mechanisms linking early-life injury to adult pathology remain poorly defined. Clinically, the long-term burden of preterm birth and BPD is difficult to quantify due to limited longitudinal follow-up into adulthood.

Addressing this gap requires experimental systems that capture both early developmental disruption and long-term regenerative capacity. By integrating models of impaired lung development with subsequent adult injury, and combining these with PCLS and organoid platforms, we aim to better reflect the trajectory from neonatal lung injury to chronic respiratory disease and move toward a precision medicine approach for lifelong lung health. ■

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Bronchopulmonary Dysplasia Research: Innovating on All Fronts

From understanding the disease at a molecular level to improving strategies for oxygen support after discharge, researchers are tackling bronchopulmonary dysplasia from all angles.

written by JoAnna Pendergrass, DVM

The doctors in the Neonatal Intensive Care Unit at Nationwide Children's Hospital care for more babies with bronchopulmonary dysplasia (BPD) than any other institution in the country. Their Comprehensive Center for Bronchopulmonary Dysplasia brings together experience and research to guide evidence-based care and is now a model for other institutions.

BPD, a chronic lung condition that affects premature infants, has no cure and treatments are sometimes challenging to manage. Premature infants often require oxygen and ventilator support to survive. However, this support can damage their underdeveloped and already fragile lungs, increasing their risk of developing BPD, which often results in poor growth and development.

"BPD is the most common complication of prematurity, and the number of infants with BPD is increasing as we improve care for ever-tinier premature infants," says Edward Shepherd, MD, a neonatologist and director of the Comprehensive Center for Bronchopulmonary Dysplasia at Nationwide Children's.

The center, which is the only one of its kind in the world, welcomes infants with severe BPD to receive treatment, and its team is closely integrated with the Center for Perinatal Research at Nationwide Children's. This integration of clinical care and research sets the stage for programs that are poised to drive changes in outcomes.

In the following, we share a glimpse into two projects devoted to that mission: a clinical trial for home oxygen and the BPD 'Omics project.

PediatricsNationwide.org/CCBPD

"BPD is the most common complication of prematurity, and the number of infants with BPD is increasing as we improve care for ever-tinier premature infants."

– *Edward Shepherd, MD, neonatologist and director of the Comprehensive Center for Bronchopulmonary Dysplasia at Nationwide Children's*

Oxygen Support After Discharge: A Clinical Trial

Babies with severe BPD often have long hospital stays. Sometimes, infants and their parents celebrate first birthdays in the BPD unit. After the twists and turns of a long hospital stay with a life-threatening condition, going home is a relief. But it's not without its challenges.

"When infants suffer from BPD, they are often discharged with home oxygen, which is administered 24/7," Dr. Shepherd explains, adding that "this oxygen administration is burdensome to the family and significantly increases follow-up needs and expenses."

Dr. Shepherd recently served as a site investigator on a 5-year clinical trial evaluating the implementation of a recorded home oximetry program (RHO) for infants with BPD.

Given the burden of at-home oxygen administration, the clinical trial researchers investigated whether an RHO program could shorten the time infants take to safely fully wean from oxygen supplementation after hospital discharge, by sending twice weekly oximetry readings to the health care team. They also sought to determine if the program's success at one institution could be generalized nationwide.

"Such reductions in oxygen support would represent a substantial improvement in quality of life for families and would potentially save significant health care resources," Dr. Shepherd says.

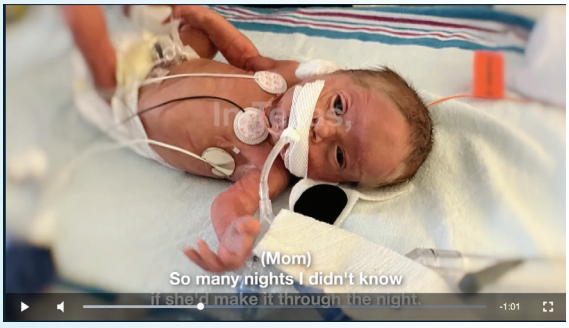
The clinical trial was based at the University of Massachusetts and involved 14 institutions.

Eligible study participants, Dr. Shepherd notes, were generally any premature infants with the diagnosis of BPD who were to be discharged on home oxygen therapy at any of the participating sites. Of 525 eligible infants, 391 participated in the trial.

"As the site investigator at Nationwide Children's, I was responsible for ensuring that our BPD clinic was capable of implementing the RHO program, had the infrastructure to support it and had the means to communicate with and manage each of our patients,"

Hadley's life began with a fight to breathe. Hadley's lungs were those of an infant born at just 22 weeks, and she depended on intensive respiratory support from her first moments. With Hadley's life on the line, her family made the journey to Ohio — so Hadley could receive care in the nation's only BPD-specific unit.

Watch Hadley's story and learn more: PediatricsNationwide.org/BPD-Hadley



"This study would not be possible in most NICUs, because they don't have the patient volume nor can they perform the innovative omics-based research."

– Patrick Gallagher, MD, director of the Center for Perinatal Research at Nationwide Children's

Dr. Shepherd says, adding that Nationwide Children's contributed many of the study's participants.

At hospital discharge, the participating patients were sent home with a pulse oximeter that continuously recorded oxygen saturation, Dr. Shepherd says. These recordings were uploaded twice weekly to the University of Massachusetts location.

"Twice-weekly uploads meant that patients could wean much faster than historically, when weans occurred only with monthly visits," Dr. Shepherd notes.

The reports were interpreted as 'wean' if oxygen saturation levels were consistently high; 'maintain' if the levels were high but not consistently; and 'increase oxygen administration' if levels were less than adequate.

A manuscript of the clinical trial is currently in development.

The Science Behind BPD: The BPD 'Omics Project

While the clinicians and clinical researchers at Nationwide Children's are improving clinical care for infants with severe BPD, some researchers in the Center for Perinatal Research are aiming higher — by looking smaller. They've launched the BPD 'Omics Project, which is taking a biology-based approach to finding new ways to manage, or even prevent, BPD in premature infants.

The "omics" being evaluated for this project are genomics, transcriptomics, proteomics and metagenomics.

"BPD is a developmental, heterogeneous lung injury syndrome," says Matthew Kielt, MD, neonatologist and principal investigator in the Center for Perinatal Research at Nationwide Children's. "Its biologic mechanisms that contribute to the observed clinical heterogeneity — flaring nostrils, grunting, rapid breathing, etc. — remain incompletely understood due to a lack of study of this vulnerable and growing population of babies with this condition."

Given the many unknowns about the origins of BPD, the goal of the BPD 'Omics project, explains Dr. Kielt, is to elucidate the biological mechanisms and causes of the most severe forms of BPD to develop personalized therapies for affected infants. By identifying BPD-specific biomarkers and 'omic signatures, he says, clinical trials can be designed to evaluate precision medicine that is geared toward specific therapeutic targets.

"This study would not be possible in most NICUs, because they don't have the patient volume nor can they perform the innovative omics-based research," adds Patrick Gallagher, MD, director of the Center for Perinatal Research at Nationwide Children's.

"The use of 'omics technologies has been made possible by advances in biomedical technologies," says Dr. Gallagher. "Integration of clinical features of BPD with longitudinal multi-omics data has the ability to provide a comprehensive understanding of the nature, function and significance of changes contributing to disease progression, prognosis and response to treatment."

In addition to leading the Center for Perinatal Research, Dr. Gallagher works with investigators to operationalize the BPD 'Omics studies, including coordinating sample procurement through the Ohio Perinatal Research Network. His laboratory group performs bioinformatic analyses of the single-cell sequencing samples of tracheal aspirates of babies with BPD.

"Discovery drives innovation. While Nationwide Children's is a national leader in BPD patient outcomes, we are humbled by how much remains unknown about this complex disease."

– *Thomas Lynch, PhD, principal investigator in the Center for Perinatal Research at Nationwide Children's*

Thomas Lynch, PhD, a principal investigator in the Center for Perinatal Research at Nationwide Children's, is contributing to the BPD 'Omics project with preclinical research focused on a novel animal model. He is also conducting the single-cell RNA sequencing using tracheal aspirate samples from multiple patients at various time points, which generates bioinformatics data for Dr. Gallagher's work.

"We would like to use our initial findings to help refine patient subgroups or critical events to develop relevant preclinical animal models," Dr. Lynch says.

The use of animal models, he notes, is critical to understanding underlying disease mechanisms, allowing researchers to "crack open discoveries and help streamline the development of safe and effective treatments for in-human clinical trials."

The 'omics project is ongoing. Dr. Kielt explains that the project is integrated into the daily operations of the Comprehensive Center for BPD, with the project's researchers frequently interacting with the multidisciplinary team of providers, which includes advanced practice care providers, respiratory therapists and nutritionists.

Eye of the Future

Through clinical and preclinical approaches, the teams behind the clinical trial and BPD 'Omics project are closing the knowledge gap about BPD to achieve their ultimate goal of providing high-quality inpatient and outpatient care for infants with this condition.

The clinical applications from these and other studies led by the Center for Perinatal Research will not only inform a more personalized approach to BPD management but also identify solutions to reduce the burden on families and health care resources.

"Discovery drives innovation," Dr. Lynch says. "While Nationwide Children's is a national leader in BPD patient outcomes, we are humbled by how much remains unknown about this complex disease." ■

Sickle Cell Lung Disease: Opportunities to Advance Care and Research

A series of studies aims to close gaps by integrating immunology, microbiology and environmental health into clinical research.

written by Pam Georgiana

For children with sickle cell disease, lung complications remain among the most serious and least predictable drivers of morbidity and mortality. Despite advances in supportive care and disease-modifying therapies, clinicians still lack reliable tools to predict which patients will develop severe pulmonary complications such as acute chest syndrome, how acute events progress to chronic lung injury, or who will benefit most from targeted interventions. At Nationwide Children's Hospital, a new series of studies aims to close those gaps by integrating immunology, microbiology and environmental health into longitudinal clinical studies.

That effort will be led by Benjamin Kopp, MD, MPH, ATSF, FAAP, who returned to Nationwide Children's in March 2026 as chief of the Division of Pulmonary, Sleep Medicine and Cystic Fibrosis. Dr. Kopp completed his pediatric residency, fellowship training and early faculty work at Nationwide Children's before spending four years at Emory University, where he expanded a nationally recognized research program in sickle cell and other lung diseases.

"Many of the questions we are asking now came from my time as a fellow and junior faculty member," Dr. Kopp says. "What has changed is our ability to measure biology and environment together in ways that can directly inform clinical care."

From Clinic Observations to Longitudinal Science

In 2014, Dr. Kopp helped establish one of the nation's early multidisciplinary sickle cell clinics at Nationwide Children's, integrating pulmonology into routine sickle cell care. Outcomes from that clinic informed early pilot studies that formed the foundation of a multi-site longitudinal study that began at Emory and will continue at Nationwide Children's in partnership with Emory and St. Jude Children's Research Hospital.

The study follows children with sickle cell disease for at least five years and compares them with age- and race-matched siblings without the disease. During routine clinic visits and hospitalizations, investigators collect blood and airway samples, along with detailed clinical data. The team will deploy advanced bioinformatics and single-cell immune profiling to understand how immune pathways, microbes and environmental exposures interact over time.

"We do not have good predictors for complications like acute chest syndrome," Dr. Kopp explains. "Treatment is largely reactive and often nonspecific. Most children receive antibiotics, even though many episodes may not be infectious."

The "Exposome" Meets the Microbiome

A defining feature of the program is the use of a public health exposome framework, developed by environmental health researchers at The Ohio State University, including Darryl B. Hood, PhD. The exposome refers to the full range of environmental and social exposures a person experiences over time and how those exposures influence health. In this research, the goal is to understand how factors such as air quality, housing conditions and broader social environments shape immune responses and drive lung disease progression.

"The immune system does not operate in isolation," Dr. Kopp says. "It is shaped by both microbes and by the environments children live in. Studying those interactions together allows us to identify modifiable

"There is still so much we do not understand. But by committing to long-term, community-informed research, we can begin to close the gap between what we see in the clinic and what we can actually change for children living with chronic lung disease."

– *Benjamin Kopp, MD, MPH, ATSF, FAAP, chief of the Division of Pulmonary, Sleep Medicine and Cystic Fibrosis at Nationwide Children's*

factors and biomarkers that can guide prevention and treatment."

Initial analyses focus on protein and metabolite signatures associated with acute chest syndrome and chronic lung injury. Environmental factors such as air pollution and microplastics are being examined in parallel, though these components remain in the early stages of investigation.

Supporting Life-Long Health

Michelle Gillespie, MD, focuses on the high-risk transition from pediatric to adult care for patients with sickle cell lung disease, building directly on the biologic insights generated through Dr. Kopp's research. Dr. Gillespie's work applies research findings to a critical clinical period when patients are at heightened risk for worsening outcomes.

"Transition is a particularly vulnerable time," Dr. Gillespie says. "Many patients who grow up with lung disease may not understand their disease. For example, they may become accustomed to symptoms like shortness of breath and not realize that it could signal serious complications."

Unlike cystic fibrosis and many other chronic conditions, sickle cell disease lacks standardized transition guidelines and educational tools. Dr. Gillespie is beginning her research by assessing what patients and providers know, as well as identifying the specific information they want and need. Based on those findings, she plans to develop educational resources and clinical guidance for patients and providers as they move toward adult care.

Her research will also incorporate biomarkers identified through Dr. Kopp's longitudinal study to identify adolescents and young adults at higher risk for poor pulmonary outcomes and inform earlier, more targeted interventions.

Importance of Community Involvement

Both investigators emphasize that families and caregivers are essential partners in this work. Community input will help shape study design, recruitment and long-term sustainability, particularly in a field that has historically received limited research funding.

"There is still so much we do not understand," Dr. Kopp says. "But by committing to long-term, community-informed research, we can begin to close the gap between what we see in the clinic and what we can actually change for children living with chronic lung disease." ■

Parallels Between Two Lung Diseases

Dr. Kopp's research intentionally spans both sickle cell disease and cystic fibrosis, examining shared and distinct drivers of chronic lung injury. While cystic fibrosis has benefited from transformative therapies, chronic inflammation and limited global access remain significant challenges. In sickle cell disease, therapeutic options are far more constrained.

"In cystic fibrosis, the new therapies are not appropriate or available for every patient," Dr. Kopp says. "In sickle cell disease, therapy options are even more limited. Studying these conditions side by side helps us identify pathways that may overlap and those that differ, which could lead to safer and more accessible therapies."

His long-term goal is to advance personalized, immune-based treatment strategies that reduce hospitalizations, preserve lung function and extend life expectancy for patients with both conditions.

Beyond Modulators: Ensuring All Patients With Cystic Fibrosis Benefit From the Next Wave of Therapy

written by Lauren Dembeck , PhD

Before CFTR modulators transformed care, cystic fibrosis (CF) was defined by relentless daily treatment and progressive lung disease. Children grew up with thick airway secretions, chronic cough, recurrent pulmonary infections, and frequent hospitalizations. Maintaining weight was a constant struggle, and lung function typically declined year after year despite aggressive airway clearance, antibiotics and nutritional support. For many families, the clinical course of CF followed a largely predictable trajectory, one that included shortened life expectancy and limited therapeutic options beyond symptom management.

"The impact of the Cystic Fibrosis Foundation cannot be overstated," says Karen McCoy, MD. "When it was founded in 1955, children with CF rarely survived beyond early childhood. Through standardized care, research investment and multidisciplinary centers, life expectancy had increased to the mid-30s or early 40s by the early 2010s before CFTR modulators even entered the picture. This increase in life expectancy was the result of many hours of daily care and multiple interventions throughout each day."

Dr. McCoy is a pediatric pulmonologist at Nationwide Children's Hospital, where she served as chief of the Division of Pulmonary Medicine through February 2026. She has been a principal investigator on many trials and studies that have advanced cystic fibrosis care, including the trial that led to the approval of CFTR modulators.

When CFTR (cystic fibrosis transmembrane conductance regulator) modulators entered clinical care more than a decade ago, they began reshaping the natural history of CF. For most children and adolescents, daily symptoms eased, lung function stabilized and quality of life improved in ways clinicians had never seen.

"For a large proportion of patients, the difference was nothing short of dramatic," says Dr. McCoy. "We saw children who once struggled to gain weight suddenly thrive. We saw families recalibrate their expectations for the future in really profound ways."

Modulators such as Trikafta® (elexacaftor/tezacaftor/ivacaftor) and Alyftrek™ (vanzacaftor/tezacaftor/deutivacaftor) have significantly improved patient outcomes, with life expectancy reaching up to 65 years.

At the same time, modulators remain ineffective for approximately 10% of individuals with CF.

Modulators work by stabilizing or enhancing the function of partially formed CFTR proteins. When no protein is produced due to mutations that terminate synthesis of the CFTR protein prematurely, the shorter protein does not function, and the modulators have no target.

"For a large proportion of patients, the difference was nothing short of dramatic. We saw children who once struggled to gain weight suddenly thrive. We saw families recalibrate their expectations for the future in really profound ways."

– Karen McCoy, MD, pediatric pulmonologist at Nationwide Children's

"There's simply nothing for the modulator to bind to or improve," explains Brodie Ranzau, PhD, postdoctoral fellow in the Vaidyanathan laboratory at Nationwide Children's. "Additionally, CFTR modulators are designed to target specific CFTR variants, so patients with other variants may not benefit from these therapies."

Sriram Vaidyanathan, PhD, principal investigator in the Jerry R. Mendell Center for Gene Therapy at the Abigail Wexner Research Institute, adds that the global picture is even more complex.

"About 90% of patients in the United States can benefit from modulators. But when you look at different ancestral populations, the proportion is much lower, and there are more than 2,000 different mutations reported in CFTR," he says. "There are regions of the world where patients have little to no access to modulators, or where other variants are more common."

Across Nationwide Children's and collaborating sites at The Ohio State University, researchers are developing next-generation approaches to ensure that every individual with CF can benefit from advances in therapy.

Gene-Edited Cellular Therapy for Durable Airway Repair

For patients whose CFTR variants do not respond to modulators, researchers are pursuing mutation-independent strategies designed to restore CFTR function regardless of the underlying mutation. One of the most promising approaches is a gene-edited cellular transplant therapy being developed by Dr. Vaidyanathan and collaborators.

The strategy centers on the airway's own regenerative capacity. Basal stem cells are harvested from a patient's airway, corrected *ex vivo* using gene editing to insert a functional CFTR gene, expanded in culture, and then reintroduced with the goal of regenerating airway epithelium capable of producing functional CFTR.

"What sets this apart is durability," Dr. Vaidyanathan says. "If you correct the basal cells, the cells that continually regenerate the airway lining, you have the potential for a long-lasting, possibly permanent treatment."

This approach addresses key limitations that have hindered earlier genetic therapies for CF. Strategies that use a virus to deliver the CFTR gene or messenger RNA that can be translated into the CFTR protein could provide CFTR temporarily but target mature airway cells that naturally turn over and cannot provide a permanent fix. As a result, any therapeutic benefit is transient. By contrast, correcting the mutant CFTR gene in the basal stem cell population is permanent and preserves native regulation of CFTR expression, allowing corrected cells to persist as the airway epithelium renews over time.

Dr. Ranzau's work further strengthens this strategy by addressing a practical challenge: how many cells must be corrected to achieve clinical benefit. Using patient-derived airway cultures, he is testing enhanced CFTR variants with improved folding or channel activity to lower that threshold.

"Historically, the assumption was that you needed to replace about 70% of airway cells," Dr. Ranzau explains. "Our data suggest that with more efficient CFTR variants, you may only need to correct 25% to 30% of cells to reach near-normal function."

Those findings are based on laboratory assays that mirror those used to establish the efficacy for CFTR modulators before they entered clinical trials, providing a translationally relevant benchmark. Importantly, the experiments rely on primary cells from patients with CF, rather than immortalized cell lines, ensuring that results reflect real-world genetic and biological variability.

Correcting the cells from the airway in the lab, however, is only the first step. Those cells must then be delivered back into the airway.

"The airway is not a passive surface. It's a living, dynamic tissue that responds to mechanical forces. To successfully introduce new cells, we have to understand how to prepare the airway so those cells can survive and integrate."

– *Tendy Chiang, MD, otolaryngologist and principal investigator in the Center for Regenerative Medicine at Nationwide Children's*

Conditioning the Airway to Make Room for Repair

To deliver corrected cells back into the airway, Drs. Vaidyanathan and Ranzau are collaborating with pediatric otolaryngologist Tendy Chiang, MD, otolaryngologist and principal investigator in the Center for Regenerative Medicine at Nationwide Children's.

"The airway is not a passive surface," Dr. Chiang explains. "It's a living, dynamic tissue that responds to mechanical forces. To successfully introduce new cells, we have to understand how to prepare the airway so those cells can survive and integrate."

Years of chronic inflammation, infection, and mucus obstruction can fundamentally alter the airway environment in cystic fibrosis, creating barriers to cell attachment and survival. Dr. Chiang's work focuses on how mechanical forces, epithelial injury and local signaling cues influence whether transplanted basal stem cells can successfully engraft and begin rebuilding the airway lining.

"A lot of early work in cell therapy assumed that if you put the right cells in the right place, everything else would take care of itself," Dr. Chiang says. "But the airway has been injured for a long time. It's not a blank slate."

Drawing on surgical and regenerative medicine principles, his team is exploring ways to transiently condition the airway, creating a window in which corrected cells are more likely to integrate and expand. They believe timing is also critical. Because airway structure and repair capacity change with age, Dr. Chiang evaluates when cell-based therapies might be most effective, particularly before irreversible airway remodeling occurs.

By addressing the physical and biological context in which gene-edited cells are delivered, Dr. Chiang's work helps bridge the gap between laboratory success and real-world clinical application.

Guiding Stem Cells to Rebuild the Airway

After corrected cells are reintroduced, they must differentiate into the specialized cell types that maintain airway health. That challenge is being addressed by Susan Reynolds, PhD, principal investigator in the Center for Perinatal Research at Nationwide Children's.

"We're trying to understand what drives airway stem cells to become the two major cell types that keep the airways clean, goblet cells and ciliated cells," Dr. Reynolds says. "If we want a cell therapy to truly restore a functional epithelium, the replacement cells can't just sit there as stem cells. They have to differentiate appropriately."

Dr. Reynolds' team has identified Notch signaling as a central regulator of this process. While earlier work emphasized transcriptional control, her group has shown that post-translational processing of key ligands plays a decisive role.

"What really matters is how these ligands — Jagged1 and Jagged2 — are processed," she explains. "It's those post-translational events that determine whether signaling promotes goblet cell differentiation, ciliated cell differentiation, or something else."

Her findings challenge the idea that progenitor cells simply toggle between two fates. Instead, these differentiation pathways appear to be independent programs that require precise signaling thresholds and timing. In mouse transplantation models, Dr. Reynolds' team has observed that corrected stem cells often remain undifferentiated.

"If the cells don't receive the right Notch cues or if the ligands aren't processed properly, they can't move forward into the specialized cell types needed for airway clearance," she says.

Her group is continuing to investigate how to reproduce or influence the microenvironment required for successful integration and differentiation of corrected basal cells.

Delivering Gene Therapy and Precision Gene-Repair Machinery

While cellular transplantation offers one route, Mark Peeples, PhD, principal investigator in the Center for Microbe and Immunity Research at Nationwide Children's, is focused on the development of gene delivery systems that would provide a functional CFTR gene or gene-repair machinery directly to the airway cells that need it.

"All respiratory viruses know how to get through mucus and into specific types of cells," he says. "The challenge is harnessing those properties without the destructive aspects of viral infection."

Dr. Peeples's lab primarily studies respiratory viruses and the cell types they target. They focus on cell entry and how the airway environment influences the ability of the virus to infect.

"You can't develop a successful airway therapy unless you understand the barrier you're trying to cross," he says. His

"We can't have a future where 90% of patients do well and 10% are left behind. Our goal is to build solutions that work regardless of the mutation a child is born with."

– *Sriram Vaidyanathan, PhD, principal investigator in the Jerry R. Mendell Center for Gene Therapy at Nationwide Children's*

lab uses cultures of human airway cells derived from lungs not useful for transplantation to study how viruses penetrate the mucus coating of the airways. Working with Dr. Reynolds and Estelle Cormet-Boyaka, PhD, director of the Cell Physiology and Biochemistry Core for Cure CF Columbus, and professor at The Ohio State University, they are also using "precision-cut lung slices" and similar advanced airway culture systems that provide access to the airways in the context of the lung.

The idea of using a respiratory virus as a vector to deliver the CFTR gene to CF airway cells builds on work from the Peeples' lab 15 years ago. His team engineered the CFTR gene into respiratory syncytial virus (RSV). When applied to well-differentiated airway cells from a patient with CF, the virus delivered the CFTR gene to ciliated cells, where it produced the CFTR protein.

"We were actually able to 'cure' CF in a dish," Dr. Peeples says, "at least for a week. RSV infects ciliated cells, and delivering CFTR that way corrected the defect. That told us we may not need to target every cell type to see a meaningful effect."

With new funding from the Cystic Fibrosis Foundation, Dr. Peeples' group is now expanding that concept by evaluating viral platforms for their ability to deliver therapeutic cargo, such as healthy CFTR genes or CRISPR-based repair tools to the airway epithelial cells. The ultimate goal would be delivery of the CFTR gene to the basal cells that regenerate throughout a person's lifetime and differentiate into all of the cell types.

Pursuing Therapies That Work for All Patients

Across these laboratories, a unifying theme is the commitment to ensure no patient is excluded from the next era of CF therapy.

"We can't have a future where 90% of patients do well and 10% are left behind," says Dr. Vaidyanathan. "Our goal is to build solutions that work regardless of the mutation a child is born with." ■

New Health Challenges in the Post-CFTR Modulator Era

The remarkable progress in CF care has also revealed new challenges. As individuals with CF live longer, clinicians are seeing higher frequencies of complications and other downstream health concerns that rarely emerged in the past and are now focused on aging-related diseases and maintaining their overall health.

Karen McCoy, MD, pediatric pulmonologist and renowned expert in cystic fibrosis, describes the shift in clinical concerns "For many years, everything we did was aimed at keeping children with CF from losing weight. Now, for some patients, we're counseling about obesity. That is a sea change."

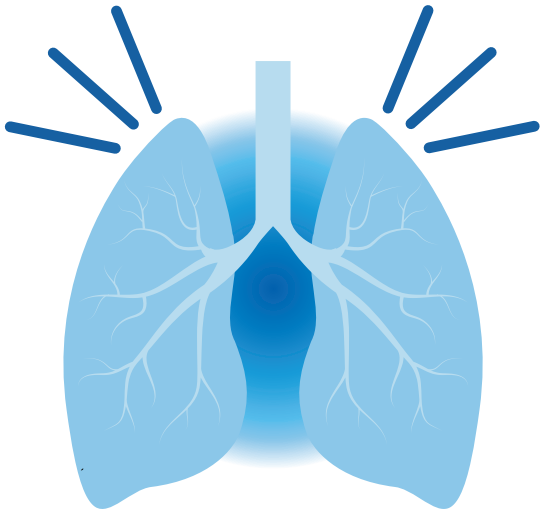
Improved nutritional status and decreased energy expenditure appear to be driving weight gain in some patients. Pregnancy is also becoming increasingly common, having risen from 200 to 300 per year between 2010 and 2019 to over 600 per year since 2020, explains Dr. McCoy.

"We're seeing more young women with CF planning pregnancies or becoming pregnant because they finally feel well enough to do so," Dr. McCoy says.

She notes that with longer life expectancy also comes conditions that historically emerged later, such as diabetes and cardiovascular disease. But the complication with the most import is colon cancer.

"Colon cancer is significantly more common in people with CF than in the general population," emphasizes Dr. McCoy. "As a result, we begin screening decades earlier than we would in individuals without CF. For patients who have undergone a lung or other solid-organ transplant and require immunosuppression, we start even earlier, often in their 20s, because the immune system plays a critical role in protecting against cancer."

Clinicians are now updating care models to meet the needs of a generation experiencing both unprecedented health and newly emerging risks, as scientists continue to develop new insights and potential new treatments.



Decoding Pediatric Asthma: From Cells to Care

How clinician-scientist teams are mapping the molecular drivers of wheezing and asthma to guide smarter, faster and more personalized treatment

written by Madison Storm

Asthma is one of the most common reasons children visit the Emergency Department (ED) at Nationwide Children's Hospital. While frontline clinicians work quickly to stabilize breathing, researchers across the hospital are probing deeper: What's happening inside the airway at the cellular level? Why do some children respond to standard treatments while others don't? How can this knowledge lead to better care?

From point-of-care sample collection during ED visits to advanced cellular modeling and novel preclinical testing, teams at Nationwide Children's are collaborating to uncover the mechanisms behind asthma severity and treatment resistance.

From Emergency Care to Discovery

For Adjoa Andoh, MD, emergency medicine physician at Nationwide Children's, the questions begin the moment a child arrives with respiratory distress.

"When a child comes in with severe asthma, it's all hands on deck," says Dr. Andoh. "The first thing we do is assess the severity of their asthma and start standard treatments, such as bronchodilators and steroids, but families often ask, 'Why isn't my child responding [to treatment]?' and right now, we don't have a clear answer. We just know some kids respond and some don't. That's where the research comes in."

Practitioners rely on physical exam findings and real-time responses to medications, but this model has limits.

"We have no way to clinically predict who will improve and who won't. That's frustrating for families and for us," says Dr. Andoh.

These gaps sparked a collaboration with two research teams: Katherine Bline, MD, critical care physician and principal investigator in the Center for Microbe and Immunity Research, and Rodney Britt, PhD, ATSF, principal investigator in the Center for Perinatal Research.

Together, they launched Pathophysiology of Asthma-Induced Critical Illness (PACI), which is an innovative project collecting and analyzing blood samples from children across the spectrum of asthma severity. These samples may reveal biomarkers that predict treatment response, paving the way for personalized care.

"We want to collect samples early, before treatments alter their immune profile," explains Dr. Andoh. "There have been very few studies that look at what's happening immunologically during an acute asthma exacerbation; it's almost exploratory in nature."

Inside the ICU: When Asthma Turns Critical

While many patients improve with standard ED care, others require intensive support. In the Pediatric Intensive Care Unit (ICU), Dr. Bline sees the most severe end of the asthma spectrum.

"For kids with asthma, being hospitalized is a big deal. Some improve with additional treatment, but others persist or become more severe," says Dr. Bline. "There's an enormous spectrum of illness severity."

Dr. Bline's research focuses on myeloid-derived suppressor cells (MDSCs) — immune regulators that may play a dual role depending on context.

"In infection, MDSCs can be harmful because they suppress T cells," she explains. "But in asthma, where there's a lot of inflammation, MDSCs might help bring the lungs back toward immune homeostasis. Some patients may have MDSCs that simply aren't doing what they need to do, especially in the context of steroids."

Dr. Bline's team investigates how these immune cells behave across asthma severities and whether their properties might predict steroid resistance.

"The ultimate goal is precision medicine," says Dr. Bline. "If we can define distinct immunologic phenotypes, we can tailor therapies instead of relying on a one-size-fits-all approach."

Why Some Don't Respond to Steroids

From a mechanistic standpoint, one of the common questions in asthma care is why corticosteroids, the foundation of acute treatment, work for some but not for others.

For Dr. Britt, this question is central. His lab studies inflammatory regulators in airway smooth muscle, the tissue that controls airway tone (how well the airways open and close) and contributes to obstruction when it contracts and thickens.

Using human primary airway smooth muscle cells, immune cells and allergen mouse models, his team examines how different inflammatory pathways (Type 1, Type 2 and Type 17) change airway smooth muscle behavior and shape asthma severity.

"We've treated airway smooth muscle cells with cytokines from each pathway alone and in combination, and then in the presence of steroids," explains Dr. Britt. "In complex inflammatory environments, airway smooth muscle hyperresponsiveness and thickening persist despite steroid treatment. Meanwhile, the eosinophil is highly sensitive to steroids, but the T cell populations driving more severe disease behave differently. Steroids don't impact neutrophils the way they do eosinophils. That's a key part of why steroid-resistant asthma exists."

Dr. Britt's team is also exploring combination therapies.

"We've found that steroids and vitamin D receptor agonists synergize in our models. We don't fully understand how yet, but it's a promising direction for reducing steroid burden," says Dr. Britt. "Understanding that complexity is essential if we want the right treatment for the right child."

His long-term vision includes defining the molecular intersections among pathways to uncover targeted treatments.

That complexity becomes even more pronounced during virus-triggered attacks, one of the most common

"We've found that steroids and vitamin D receptor agonists synergize in our models. We don't fully understand how yet, but it's a promising direction for reducing steroid burden. Understanding that complexity is essential if we want the right treatment for the right child."

– *Rodney Britt, PhD, ATSF, principal investigator in the Center for Perinatal Research at Nationwide Children's*

"Goblet cells produce mucus, and in asthma, there are too many of them. We're looking at the Notch signaling pathway that drives basal cells to become goblet cells. If we can prevent that overproduction, we can reduce mucus plugging."

– *Susan Reynolds, PhD, principal investigator in the Center for Perinatal Research at Nationwide Children's*

drivers seen in the ED and ICU. Viral infections can tilt immune pathways toward mixed, steroid-insensitive patterns and may even program long-term risk in early life.

Viruses and the Asthma Connection

Respiratory viruses are a major trigger for asthma attacks and may even shape long-term risk. Mitchell Grayson, MD, chief of the Division of Allergy and Immunology and principal investigator in the Center for Clinical and Translational Research, is studying how early life respiratory viral infections influence wheezing and can drive the development of asthma.

"Infants hospitalized with severe RSV have an increased risk of recurrent wheeze and possibly even developing asthma," says Dr. Grayson. "The question is: why would a viral infection drive allergic disease?"

Dr. Grayson's lab has shown that mice with viral infections produce IgE antibodies — the same antibodies involved in allergic responses — against respiratory viruses.

"In our models, we've found that mice make IgE (the allergic antibody) against the virus, and that's required for them to develop asthma-like symptoms."

His team uses Sendai virus (murine parainfluenza type 1), respiratory syncytial virus (RSV) and human bronchial epithelial cell cultures to model human disease mechanisms.

"Almost all asthma attacks are virally induced," emphasizes Dr. Grayson. "Understanding virus-specific immune responses could help us interrupt the path from infection to chronic asthma, as well as preventing subsequent exacerbations in those with asthma."

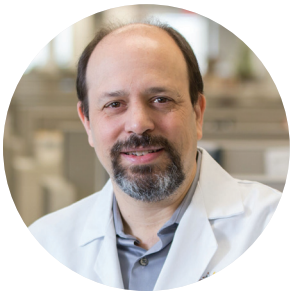
Too Much Mucus: Untangling Airway Epithelium Biology

Another critical player in asthma is mucus, specifically, too much of it. Excess mucus can block small airways, making breathing difficult. In the Center for Perinatal Research, Susan Reynolds, PhD, principal investigator, studies the airway epithelium — the cells lining the respiratory tract — to understand why this happens.

"Asthma is one of several diseases that are characterized as muco-secretory lung disease," says Dr. Reynolds. "The airway epithelium produces too much mucus, and in the small airways, that mucus can plug the tube completely. That prevents air from getting in and carbon dioxide from getting out. Physiologically, the lung changes its function in response [to the carbon dioxide]."

Her lab focuses on basal cells, the originator of goblet cells that produce mucus.

"Goblet cells produce mucus, and in asthma, there are too many of them," says Dr. Reynolds. "We're looking at the Notch signaling pathway that drives basal cells to become goblet cells. If we can prevent that overproduction, we can reduce mucus plugging."



"Infants hospitalized with severe RSV have an increased risk of recurrent wheeze and possibly even developing asthma. The question is: why would a viral infection drive allergic disease?"

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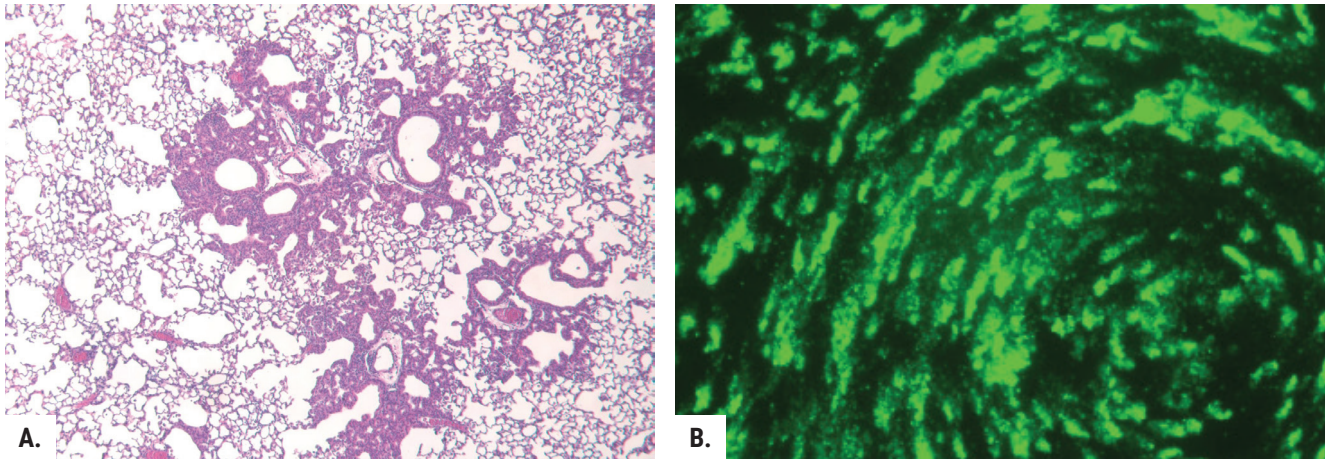

A. Microscopy image of lung immunohistochemistry of mouse lung infected with Sendai virus. B. Microscopy image of human bronchial epithelial cells in culture 48 hours after inoculation with RSV that expresses green fluorescent protein. The image shows the distribution of virus through the cell culture.

Recent work has revealed a surprising twist in the Notch signaling pathway.

"We've discovered that Notch ligands are not just activating the receptor — they're undergoing processing within the ligand-expressing cell," says Dr. Reynolds. "Our data suggests that ligand processing regulates whether that cell will change its fate. It's a novel sub-mechanism, and we're excited about it."

Dr. Reynolds' work could inform therapies not only for asthma, but also for conditions such as cystic fibrosis and chronic obstructive pulmonary disease.

Modeling Human Airways More Accurately

Most preclinical models lack the mucus producing glands needed to effectively study how they influence the development of asthma — and how they respond to potential treatments. In response to this challenge, Thomas Lynch, PhD, principal investigator in the Center for Perinatal Research, has developed an allergic airway inflammation model in ferrets that is now available to colleagues across the research institute.

"Ferrets have airway glands similar to humans and our initial experiments have been really promising," says Dr. Lynch. "Structural changes like goblet cell hyperplasia and gland hypertrophy appear quickly. This model helps us test therapies that target mucus production in a system that mirrors human anatomy."

Beyond mirroring human airway structure, the ferret model gives teams a shared platform to probe questions raised elsewhere. For example, how early-life respiratory viruses might 'set the stage' for later wheeze and asthma, a central focus of Dr. Grayson's group. By layering controlled viral exposures onto allergic inflammation, investigators can test whether virus-driven immune responses shift mucus-gland growth, airway smooth-muscle behavior and steroid responsiveness — before moving to human studies.

The model also complements Dr. Reynolds' epithelial work by allowing researchers to examine how Notch-guided basal-to-goblet-cell decisions play out in an intact, gland-rich airway and whether candidate therapies that modulate those pathways reduce mucus plugging *in vivo*.

"This model gives us a platform to study those pathways and test therapies before moving into human trials," says Dr. Lynch.

Just as importantly, the readouts from this model (structural changes, immune signatures and treatment responses) feed back to the bedside. As biomarkers and candidate steroid-sparing combinations emerge, Drs. Andoh and Bline can integrate them into ED and ICU studies such as PACI to stratify children earlier, avoid unnecessary side effects and escalate the right care faster. ■

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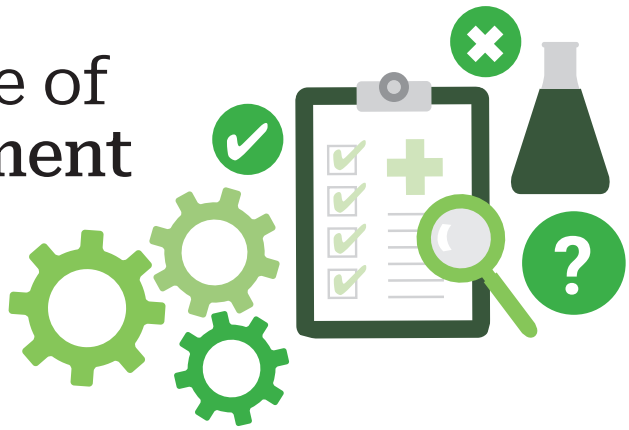
Meeting the Challenge of Clinical Trial Recruitment and Retention



written by Lynn Dosky

Participant recruitment and retention strategies are crucial features of any successful clinical study design.

In fact, an article published in the *Journal of Clinical and Translational Science* noted, "up to 85% of clinical trials fail to recruit or retain a sufficient sample size, leading to failures to meet accrual targets in four out of every five trials, even though nearly $1.9 billion is spent on recruitment annually." In other words, insufficient recruitment or retention planning can be a costly error.

Digital media, shifting patient communication preferences and the lingering effects of the COVID pandemic are just some of the factors contributing to the need for creative new recruitment and retention strategies.

For Nationwide Children's Hospital, integrating research and clinical care remains at the heart of its strategic plan. This integration and successful planning helps to get cutting-edge treatments to families. More than 3,100 clinical studies are currently open, and a second institutional review board (IRB) was recently established to accommodate the increased trial activity.

These experts share what has worked to keep their research program growing, evolving and achieving recruitment and retention goals. With a solid understanding of target populations and making participants and their families the priority, recruitment and retention can be less burdensome and more successful.

Where to Get Started: Feasibility, Accessibility and Communication Tactics

When planning a protocol, it is essential to think about what is feasible and how to achieve recruitment and retention goals.

"Think of feasibility first and build it into the protocol, including realistic volumes, conversion rates and staffing. Don't overestimate eligibility numbers before you start," says Smitha Sasindran, MS, MBA, senior research program manager for the Center for Biobehavioral Health at Nationwide Children's and pediatric administrative director of the Clinical and Translational Science Institute at Nationwide Children's and The Ohio State University.

"We review data early to make sure a study can realistically meet its recruitment and retention goals. Launching a clinical trial takes significant planning, and success depends on enrolling and keeping participants," says Myeshia Harmon, MHA, CCRP, PRAM, senior administrative director of clinical research operations for Clinical Research Services at Nationwide Children's. "If enrollment falls short, sponsors may not invite our site to participate in future studies. If families do not feel supported or informed, they may choose to leave the study. We are responsible for guiding families through the informed consent process, making sure they understand the study and feel comfortable."

Once the research team understands what is realistic, they can think about how to make it easier for people to participate.

Convenience and accessibility, both to reach a target audience and schedule study visits, are crucial to reduce visit burden, make it workable for participants with flexible scheduling, and align visits with routine care when possible.

Then, think about which tactics will help best reach the target audience. Will printed flyers or brochures handed out in clinic be enough, or will the team need to consider a multi-channel approach that combines digital media, adding the study to online registries such as ResearchMatch or clinicaltrials.gov, coordinating with patient and family advocacy groups, and community outreach?

These types of questions can help determine how to best reach the target population.

Community-Engaged Research Approaches

According to Cynthia A. Gerhardt, PhD, chief clinical research officer at the Abigail Wexner Research Institute at Nationwide Children's, study recruitment often focused on reaching patients and parents directly at the hospital bedside, in clinic or other in-person methods, but COVID vastly changed access and required investigators to pivot strategy.

Families now might be less likely to answer direct calls or email recruitment but may respond to a text or social media contact, such as Facebook ads or closed Facebook groups, she says. Others are more responsive to community-based engagement through trusted leaders or advisers in their local area.

The Yale School of Medicine defines community-engaged research as "a process that incorporates input from people who the research outcomes will impact and involves such people or groups as equal partners throughout the research process. This involvement may include co-designing research questions to solve problems, make decisions, influence policies and create programs and interventions that affect their own lives."

"We often work with community leaders to gain access to specific populations to design research that accommodates the population's language, culture and needs," says Dr. Gerhardt. "When you have a community member who is vouching for the work you are doing, it builds trust, encourages others to participate and lowers barriers for better representation. Working with community stakeholders and community advisory boards helps to guide researchers toward what families would be willing to do and gain access to closed groups."

"Funding agencies such as PCORI (Patient-Centered Outcomes Research Institute) have really focused on community advisory boards to engage the community in designing studies that are important to the population and making sure they are a part of interpreting results. This helps make the study easier to implement," she adds.

Take Advantage of Internal Resources

The Clinical and Translational Science Institute (CTSI) is a partnership between Ohio State and Nationwide Children's to speed the translation of scientific discoveries into clinical therapies to improve human health for all. Under the National Institutes of Health (NIH), the National Center for Advancing Translational Sciences (NCATS) supports the Clinical and Translational Science Awards (CTSA) Program. The CTSI is part of a national network of more than 60 leading medical institutions that receive CTSA funding. The CTSI offers researchers support with grant writing, funding, community engagement, recruitment, retention and more.

With CTSA Program funding, these institutions provide expertise, resources and collaborative partnerships at both the national and local levels to strengthen the health of individuals and communities. In addition, the CTSA Program advances the field of clinical translational science by offering education, training and career development opportunities across all stages of professional growth.

Many institutions also have internal resources to assist investigators and study teams. Megan Robb, BA, ACRP-CP, is a senior training and compliance coordinator with Clinical Research Services at Nationwide Children's. One of her many tasks is working with research teams to promote investigator-initiated trials and industry-sponsored clinical trials.

> "Think of feasibility first and build it into the protocol, including realistic volumes, conversion rates and staffing. Don't overestimate eligibility numbers before you start."
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> *– Smitha Sasindran, MS, MBA, senior research program manager for the Center for Biobehavioral Health at Nationwide Children's and pediatric administrative director of the Clinical and Translational Science Institute at Nationwide Children's and The Ohio State University*

> When we take the time to connect with families during the recruitment process, it not only increases the likelihood of participation in the current study but also helps make research more understandable and less intimidating. I believe this approach reduces anxiety and builds trust, so that when families are approached for future studies, the experience feels less overwhelming and they may be more inclined to take part."
>
> *– Megan Robb, BA, ACRP-CP, senior training and compliance coordinator with Clinical Research Services at Nationwide Children's*

While she starts with the same checklist to make sure investigators understand all the steps involved, when it comes to recruitment and retention, her team advises having a plan A, B and C in place before taking anything to the IRB to prevent any delays in study approval. Any piece of information used for recruitment must be approved by the IRB before it is presented to a potential participant.

Evolve Tactics to Meet Participant and Family Needs

To reach a wide audience, past recruitment tactics could have included flyers posted in public areas, phone calls or direct mail to certain zip codes. Digital marketing, social media advertising and electronic health record messaging have allowed more direct targeting for specific patient populations.

"Now it's much more patient-centered and operationalized: designing trials around what people can realistically do; using multiple channels; and being intentional about trust, representation and accessibility," says Sasindran. "There's also a bigger emphasis on inclusive enrollment — not just hitting sample size but making sure participants are demographically representative. And in general, recruitment today is less about posting a study and more about building a study people can join and stay in."

This includes designing the study with the family in mind. Experts suggest keeping scheduling flexible. Add QR codes for access to videos, online surveys or websites. Write information in plain language so it's easy for the family to understand and remember. Make sure potential participants (including all family members you approach) fully understand the study, what will happen and how it will benefit them. This direct interaction is important and helps with retention. When a member of the study team meets with the family, it can mean more than a message through an online patient portal or email. Finding the right level of interpersonal connection is important.

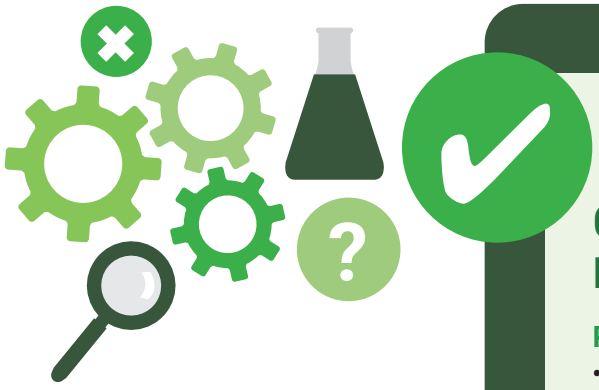
"It is a partnership and families are part of that process. If there is part of that study that is cumbersome and a family wants to withdraw because the study isn't conducive to their lifestyle, we want to know about it. Providing that feedback to the study team is important. Patients and families come first," says Harmon.

"When we take the time to connect with families during the recruitment process, it not only increases the likelihood of participation in the current study but also helps make research more understandable and less intimidating. I believe this approach reduces anxiety and builds trust, so that when families are approached for future studies, the experience feels less overwhelming and they may be more inclined to take part," says Robb.

Moving from a Physician Approach to a Team Approach

Harmon adds that recruitment strategy has pivoted from physician driven to a collaborative team approach.

"We have a comprehensive team that meets and discusses what studies are open and available. Research staff and nurses are integrated with the medical team as part of clinical care when rounding to see inpatients on the floor. This has always been part of operations in hematology-oncology but is now more common in many other medical specialties. Research coordinators and research nurses are part of the integrated medical care team. Where appropriate, coordinators and



nurses are trained to consent as part of medical care and can provide support if a patient has questions about a particular study," says Harmon.

Evolving from a physician-driven recruitment model to a collaborative team approach marks a shift to integrating clinical care with clinical research. By embedding research coordinators, nurses and support staff directly into clinical care workflows, institutions can create a more seamless, responsive and patient-centered experience.

Effective clinical trial recruitment and retention ultimately depend on thoughtful planning, genuine community partnership and a commitment to meeting families where they are. By prioritizing feasibility, accessibility and clear communication, research teams can design studies that are not only scientifically rigorous but also realistic and respectful of participants' lives. As digital outreach evolves and community-engaged approaches become increasingly essential, institutions that embrace flexibility, trust building and team-based collaboration will be best positioned to sustain strong enrollment and long term engagement. ■

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CLINICAL TRIAL RECRUITMENT CHECKLIST

PRE-PLANNING

- Begin recruitment strategy before funding approval
- Define target population:
  - Demographics (age, gender, location)
  - Behaviors and lifestyle
- Identify barriers (transportation, cultural, literacy)
- Align visits with routine care when possible

RECRUITMENT STRATEGY

- Use multichannel approach:
  - Community events and professional networks
  - Social media (paid ads, closed groups)
  - Flyers and QR codes
  - Video content for engagement
- Prepare HIPAA-compliant screening tool (e.g., RedCAP)
  - Keep questions concise
  - Plan follow-up method (phone, email, text)

COMMUNITY ENGAGEMENT

- Involve community leaders and advisory boards
- Ensure cultural responsiveness:
  - Materials in multiple languages
  - Diverse research team representation
- Build trust through transparency and education

PARTICIPANT ENGAGEMENT

- Family-centered approach:
  - Engage parents/caregivers and children
  - Explain study in plain language
- Provide incentives where appropriate
- Ensure empathy and rapport building
- Offer digital tools for convenience (QR codes, videos, websites)

RETENTION STRATEGY

- Create video resources for ongoing engagement
- Reduce visit burden (remote options, flexible scheduling)
- Maintain open communication and answer all questions
- Treat participants as partners and collaborators

MONITORING AND EVALUATION

- Track recruitment progress regularly
- Adjust strategy based on response rates
- Document barriers and feedback for future studies

Professionalism in Pediatric Medicine: *Why We Must Get It Right*

Ashley Fernandes, MD, PhD, primary care pediatrician and director of Faculty Professionalism and Resident Ethics Education at Nationwide Children's and professor of Pediatrics, director of Professionalism Competency and associate director of the Center for Bioethics at The Ohio State University College of Medicine

A talented junior attending physician on a high acuity service is impatient on rounds and visibly irritated by nursing concerns, making trainees and team members uncomfortable and anxious about speaking up.

A senior medical researcher pushes the limits on deadlines for important grants and requests for proposals with his team, overcommitting to mentor gifted research fellows, lacking prompt communication, and causing team dysfunction in a critical and normally very productive lab.

A family that is very late to a primary care appointment is asked to reschedule. They become irate with the front registration staff, having missed work, and then a bus, to try to make the appointment. A primary care physician agrees to see the patient and family, though it may keep him over his normal clinic time.

The three cases above are disparate in their content but contain a common thread — in the intellectually challenging and demanding work of modern pediatric medicine, a mastery of science alone will not suffice to provide high-quality, safe and ethical care. Re-reading those cases we may ask ourselves, "What are the downstream effects of physician behavior on clinical care beyond the incident described? What impact might such behavior have on the public trust?"

Professionalism's Latin root suggests that medical professionals "declare openly" our commitment to certain internalized values, what both "the public and individual patients can expect regarding shared competency standards and ethical values," says Wynia *et al.* The American Board of Internal Medicine identifies these values in the primacy of patient welfare, patient/family autonomy and social justice.

The moral commitments of professionalism are deeply integrated into both the history of medicine and bioethics. And they are rooted in the practitioner-patient relationship. The family and patient are sick and need the doctor's humane and competent skill; the practitioner agrees to hold that trust, deepen it and make visible the dignity of every child and family. This is heavy: professionalism is not "fluff" or an addendum to good medicine. It is central to the act of healing.

IMPACT ON QUALITY AND SAFETY

Beyond professionalism's serious moral obligations, data shows that unprofessional behavior (even mundane infractions) can have a deleterious effect on quality and safety of patients. The Joint Commission summarized: "Intimidating and disruptive behaviors can foster medical errors, contribute to poor patient satisfaction and to preventable adverse outcomes, increase the cost of care, and cause qualified clinicians, administrators and managers to seek new positions in more professional environments."

Unprofessional behavior has even been shown to have a negative effect on clinician's diagnostic and procedural performance. When physicians are unprofessional toward nursing staff, as shown in studies from Riskin *et al.* and Saxton *et al.*, it can lead to increased nursing medical errors and decreased staff retention.

Bhardwaj's persuasive data analysis from 2022 shows that drivers of unprofessional behavior can be broadly divided

into two categories: 1. (lack of) self-care (e.g., burnout, life stressors, substance abuse) and 2. institutional culture (e.g., inadequate supervision, unsupportive work environment/leadership, resource constriction).

This is why our team is continuously making professionalism part of the institutional culture. As a world leader in the care of children, known for our *Zero Hero* culture of safety, we can, together, make excellent even better, and set the gold standard for medical professionalism as we have for so many other things.

PROMOTING PROFESSIONALISM

First, we must intentionally practice virtue. At the heart of professionalism is a commitment to habitual moral practice and improvement. We must actively seek feedback, recognize our shortcomings, build on our strengths and remember that what we do is for the vulnerable children and families in our community. This is an internal process that results in tangible actions raising the dignity of every child.

Second, we must take wellness and self-care seriously. These are not mere buzz words. Physician burnout causes unprofessional care, and unprofessional care causes patient safety incidents, as shown by Hodgkinson *et al*. We should have a plan of how to recoup what our strong commitment to ameliorate the suffering of our patients and families will take from us, whether utilizing institutional resources or our own.

Third, we should make use of opportunities to bolster our understanding of professionalism, and then, to practice it. While Nationwide Children's has an array of resources for faculty and staff, here I will highlight two that I believe are revolutionary and rare in pediatric care.

Nationwide Children's recently trained 14 faculty members in its inaugural Faculty Coaching Program, under the Center for Faculty Development. In this non-punitive, longitudinal, relationship-building and reflective process, a faculty member can be referred or self-refer for help in enhancing or correcting professional behaviors over 6 months. By holding faculty accountable to excellence in professional behavior while still affirming the gifts that make them essential to our institution, the Faculty Coaching Program uses self-directed insights to build skills with a trusted coach on an executive coaching model.

In my role as director of Faculty Professionalism, faculty

with more serious professionalism issues are referred to me, and we develop a working relationship centered around accountability, transparency and remediation. I work closely with Chief Wellness Officer Brandon Kozar PsyD, MBA, because many professionalism issues are also wellness issues.

Finally, we must recognize those very rare occurrences when unprofessional behavior moves beyond coaching or remediation and crosses the line into the illegal, the unethical or the demeaning. We must then have insight to recognize threats to the patient, the institution, the profession or even society. This involves courage — the courage to speak up (even anonymously), utilizing available resources to quickly and ultimately stop such behaviors. ■

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Shorter Antibiotic Courses for Uncomplicated Gram-Negative Bloodstream Infections in the NICU

For years, Pablo J. Sánchez, MD, principal investigator in the Center for Perinatal Research at Nationwide Children's, observed that approximately 7 days of antibiotic therapy appeared sufficient for selected neonates with uncomplicated gram-negative bloodstream infections that do not involve the central nervous system. This practice contrasts with traditional recommendations favoring longer treatment durations. This clinical observation, combined with ongoing neonatal antimicrobial stewardship discussions and a collaborative effort with pharmacy, led to a multicenter retrospective study published in *The Journal of Pediatrics.*

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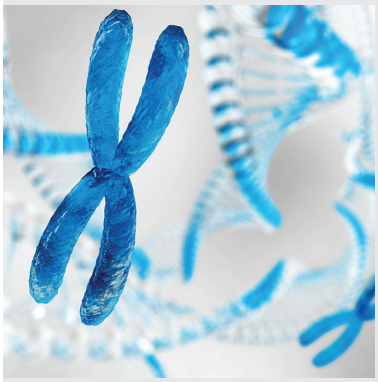

Analysis Suggests Cystic Fibrosis Is More Globally Distributed Than Previously Believed

Cystic fibrosis (CF) has long been viewed as a disease that primarily affects people of European descent. Even as genetic research expanded and highly effective modulator therapies (HEMT) became available, registry data continued to suggest that CF was exceedingly rare in much of Asia, Africa and South America. Now, a study published in *eBioMedicine* analyzing more than 800,000 genomes and exomes challenges that assumption, indicating that these regions may produce as many or more CF affected infants each year as North America and Europe.

PediatricsNationwide.org/CF-Genome

From Biology to Bedside: The Center for Childhood Cancer Research Is Shaping What Comes Next

Now under the leadership of Alexander Bishop, DPhil, director of the Center for Childhood Cancer Research, principal investigator and Richard J. Solove Endowed Chair in Cancer Clinical Developmental Therapeutics at Nationwide Children's, the center is entering a new chapter shaped by his commitment to uncovering the mechanisms behind rare pediatric cancers and translating discoveries into clinical progress. Learn how his experience in sarcoma research is shaping his vision for the future.

PediatricsNationwide.org/Alexander-Bishop

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