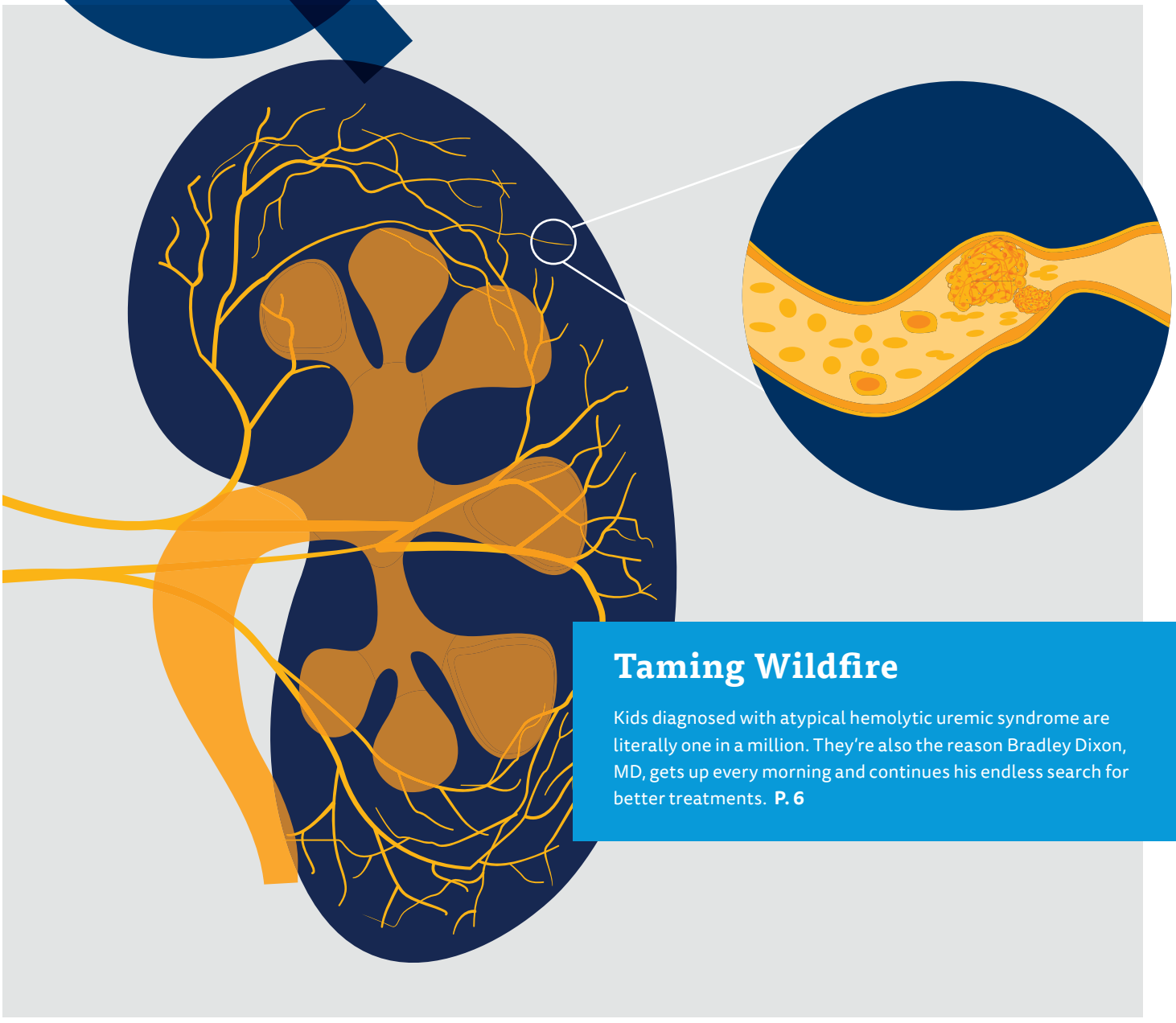
ISSUE 19 • NOVEMBER 2024

Q: *Advances and Answers in Pediatric Health*



Taming Wildfire

Kids diagnosed with atypical hemolytic uremic syndrome are literally one in a million. They're also the reason Bradley Dixon, MD, gets up every morning and continues his endless search for better treatments. **P. 6**

Children's Hospital Colorado

Affiliated with University of Colorado Anschutz Medical Campus

It starts with a Q:

A letter from a fellow questioner at Children's Hospital Colorado

Dear colleagues,

With the formal launch of the Colorado Child Health Research Institute (CCHRI), we are excited to push discovery to new limits and share more about how we are prioritizing child health research. In the last issue of Q: magazine, Chief Scientific Officer Ronald Sokol, MD, announced the official partnership between Children's Hospital Colorado and the University of Colorado Anschutz Medical Campus to advance child health, building on years of existing collaboration.

The robust infrastructure of the CCHRI provides our investigators with centralized resources supporting the execution of high quality, safe and compliant research — allowing them to focus more on the science and less on administrative work. We offer financial services, regulatory services, study coordinators and personalized support through the research process.

This formal partnership gives our leadership team a strategic view of research happening across the hospital and campus, so we can ensure we are aligned in our efforts to improve child health at every stage of life. This also strengthens our campus research collaborations — across disciplines, across stages of research and across the lifespan.

While we remain focused on improving today's operations, we are also looking to the future to ensure we are well positioned to support tomorrow's discoveries. A key part of this vision is fostering the next generation of researchers and embedding diversity, health equity and inclusion initiatives into every aspect of our research efforts. As an investigator myself and the Clinical Research Director of the CCHRI, I feel fortunate for the support and investment of both the university and hospital, who are coming together to advance our shared mission to improve the lives of children.

Sincerely,

DARCY THOMPSON, MD, MPH
Clinical Research Director, Colorado Child Health Research Institute
Pediatrician, Children's Hospital Colorado
Professor, Department of Pediatrics-Nutrition, University of Colorado School of Medicine

Contents

For a digital version of this publication visit:
childrenscolorado.org/Qmagazine

Share articles with colleagues, discover related research and sign up for our specialty-specific email newsletters.

Reader Survey: A Q for You

We want our content to reflect the creativity, curiosity and commitment to improvement that fuel research and innovation across the child health field. To ensure we're meeting our readers where they are and continue offering content that engages and inspires, we're turning to you.

Please consider scanning the QR code to take a short survey. Your responses will help us shape our work to fit your needs as we transition this magazine to a digital-first approach. Thank you for your participation and your readership.

When Medicine is Like Magic

NEONATOLOGY

A neonatal intensive care unit team at Children's Hospital Colorado developed a transformative sedation protocol for high-risk, premature infants with lung disease, resulting in less pain medication, fewer side effects and calmer, happier babies.

Neonatologist Satya Houin, MD, worked alongside Kathleen Hannan, MD, and five other neonatal colleagues to publish this unprecedented study. "You don't have a magic bullet very often in medicine, but it almost felt magical just to see how quickly they improved," Dr. Houin says.

Neonatal patients with severe lung disease typically require long-term use of ventilators, and with that comes high levels of various medications, such as opioids and several sedation drugs, including benzodiazepine and dexmedetomidine (an alpha 2 agonist). Because of this constant sedation, babies build up a tolerance to the medicine. When it comes time for a procedure such as a tracheostomy, they require even higher doses of additional pain and sedation medication due to their tolerance. This results in unwanted side effects, including delirium and agitation, and it can be very difficult to wean patients off such high doses of medicine.

Drs. Hannan and Houin saw these babies struggling and knew they needed a change. That's when they reached out to colleagues in the pediatric intensive care unit (PICU) to learn more about a propofol-washout technique. Propofol is an intravenous anesthetic, so during a washout, the team starts a continuous infusion. They monitor the baby closely, and if the baby remains calm, the team rapidly weans the sedation medications while monitoring for any signs of agitation or withdrawal. This washout desensitizes receptors that opioids and sedation drugs usually attach to and resets them, so the patient's drug tolerance drops. After 24 hours, the propofol is stopped and sedation medications can be added back in as needed at much lower doses.

The PICU had used this approach on some babies and young toddlers, but until now, this technique had not been widely used in the neonatal population. The team documented a case study involving three high-risk infants with a 24-hour propofol infusion following tracheostomy placement (1). Researchers determined that the approach was safe and viable for rapid reduction in pain and sedation drugs. From 24 hours prior compared to seven days following the propofol infusion, the team saw an 83% reduction in opioid administration, a 74% reduction in benzodiazepine administration, and all infants achieved discontinuation of alpha 2 agonist infusion.

"Just being there bedside and watching this every couple of hours — turning down the meds and turning down the meds — it was almost stunning," Dr. Houin says. "It was just very gratifying to see how much calmer and happier these babies were and see their medication needs disappear."

The team hopes these positive results can help other high-risk infants and inspire future collaboration around complicated issues for this population.

"I think that these patients are seen as a very challenging population to take care of," Dr. Hannan says. "They have really unique needs, but we can adapt things from other populations that are kind of innovative and really think differently about how we can treat them to give them the best care possible." ●

1. Hannan, Kathleen E et al. "Successful and Rapid Reduction in Neurosedative and Analgesic Medications in Complex Infants with Severe Bronchopulmonary Dysplasia After Tracheostomy Placement: Experience with 24-hour Propofol Infusions." The Journal of pediatrics vol. 270 (2024): 114040. doi:10.1016/j.jpeds.2024.114040.

SATYA HOUIN, MD

Neonatologist and Perinatologist, Children's Hospital Colorado

Assistant Professor, Department of Pediatrics-Neonatology, University of Colorado School of Medicine

KATHLEEN HANNAN, MD

Neonatologist, Children's Hospital Colorado

Assistant Professor, Department of Pediatrics-Neonatology, University of Colorado School of Medicine

Information, Insight, Impact

Q: How do you bridge the gap between decades of research and clinical practice — and how might that work evolve the collective understanding of a destructive pediatric disease?

People with cystic fibrosis (CF) are born with a genetic mutation that causes the body's fluid secretions — normally slippery and conductive — to become thick and sticky. Since these altered secretions most often cause blockages in the lungs and lead to decreased breathing function, CF is generally considered a lung disease. But these changes can also affect the digestive system, including the pancreas and liver, the latter of which has been historically understudied. At Children's Hospital Colorado, home to the largest pediatric cystic fibrosis research center in the nation, hepatologist Michael Narkewicz, MD, has spent 40 years researching the link between cystic fibrosis and the liver. Now, researchers are closer than ever to understanding not only the risks of this disease, but also how to potentially mitigate its progression.

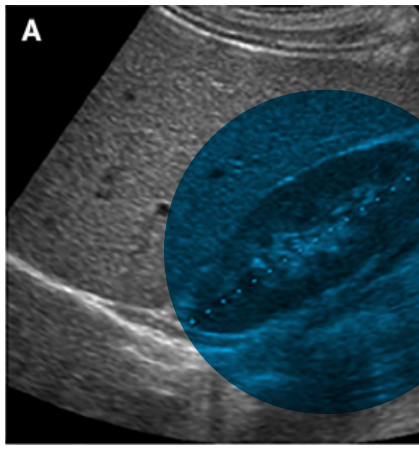
INVESTIGATING INVOLVEMENT

Roughly 30% to 50% of people with CF will see the disease manifest to their liver, but in most of those individuals, it does not influence their overall health outcome. A small percentage of that group, however, will face more significant challenges. "About 7% to 10% of people with CF develop what we now call advanced cystic fibrosis hepatobiliary involvement or what used to be called advanced cystic fibrosis liver disease," Dr. Narkewicz explains. "Our research is focused on trying to identify who's at risk for advanced hepatobiliary involvement and why, in the hopes of developing interventional trials that could prevent CF hepatobiliary disease."

Four decades have passed since Dr. Narkewicz first began studying how cystic fibrosis evolves into a liver disease, and in that time, understanding of the disease has undergone a transformation of its own. "We initially thought it was because the cystic fibrosis protein, which sits on bile ducts in the liver, did not function properly. The job of that protein is to add water to your bile so that it can flow properly," he says.

Biopsies from children with cystic fibrosis liver disease show plugs in their bile ducts, which initially led researchers to believe that the dysfunctional cystic fibrosis protein thickened bile and caused liver inflammation, resulting in fibrosis, or tissue scarring, from which the primary disease derives its name.

"As we've evolved, we've realized that there are abnormalities in the liver's blood vessels that develop in some people with CF that lead to fibrosis, but the end result, no matter what the mechanism is, is that people have really advanced

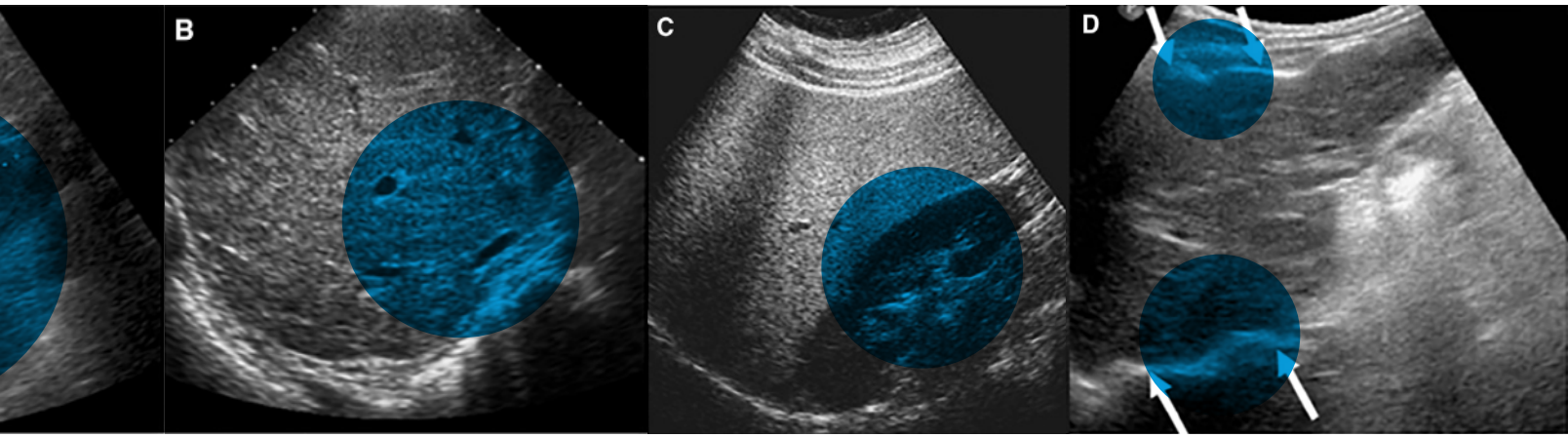


scarring of their liver," Dr. Narkewicz says. "And those with advanced scarring have a shortened lifespan and more complications including nutritional or pulmonary challenges."

A STANDARD FOR INTERVENTIONS

Dr. Narkewicz served as principal investigator on the Cystic Fibrosis Liver Disease Network (CFLD-NET) for nearly two decades. That work, which was supported by the Cystic Fibrosis Foundation and the National Institutes of Health, aimed to identify which patients were at risk of advanced liver disease and how providers could better identify them.

One early breakthrough of the CFLD-NET proved that ultrasound technology provided an affordable, effective way to determine when a CF patient had at least a 50% risk of developing advanced liver disease. Dr. Narkewicz and his team built upon that success by collaborating with radiologists



A. Liver cells are slightly darker than the kidney (blue circle) suggesting early disease.

B. Close up of the liver, where bright patches are apparent indicating scarring.

C. A normal liver, where tissue appearance next to the kidney (blue circle) is uniform.

D. Close up of the liver, where patchy areas inside a nodule signify fibrosis.

to develop standardized order sets for these ultrasounds, which ensure a consistent, comprehensive approach to how the scans are conducted and evaluated.

These standardized ultrasounds are also used in a calculation created by the CFLD-NET, which has been adopted by providers around the world to signal potential liver involvement before a patient's cystic fibrosis progresses. "We developed this prognostic algorithm where you can plug in age, ultrasound finding and a blood test called the GGT-to-platelet ratio that will identify any individual's risk," Dr. Narkewicz says. "Then, we collaborate closely to review all patients who are identified as at risk of having liver disease in that space."

These findings demonstrate the power of translational research — the phase of discovery where findings are directly applied to clinical pathways, bridging the gap between information and impact.

RESPONSIBILITIES OF CARE

Scientific advancement in pediatrics — like those Dr. Narkewicz has helped bring to light throughout his career — can have life-changing impacts and must be handled responsibly. This is especially true when sharing new discoveries with families. For instance, when Dr. Narkewicz and his team prepared to implement their ultrasound methods, they knew it would mean delivering the hard news to families that in addition to the lung complications of cystic fibrosis, their child might also develop liver disease. Anticipating these challenges, the team used standardized scripts to share the ultrasound results in a supportive, empathetic way.

"We tested whether those scripts impacted the parents' perceptions of their kids' quality of life and health outcomes," Dr. Narkewicz says. "We proved that you could add tests that have a little bit of uncertainty to them, but if you approach them in a systematic way and you have standardized language, you will not have a negative impact on how parents perceive their child's disease."

Thanks to this evolution in understanding from the lab to the bedside, providers now have the power to help patients with cystic fibrosis liver disease lead longer, less complicated lives. "Even if we may not have a direct therapy for this, we're going to identify these patients much earlier," Dr. Narkewicz says. "We can manage the disease and its consequences effectively without a liver transplant, and that's a good thing." ●

MICHAEL NARKEWICZ, MD

Hepatologist, Gastroenterologist, Digestive Health Institute, Children's Hospital Colorado

Professor of Pediatrics, Section of Pediatric Gastroenterology, Hepatology and Nutrition, Associate Dean, Health Affairs, Children's Hospital Colorado and University of Colorado School of Medicine

Taming Wildfire

Q: Why is it important to keep iterating on existing treatments for a rare disease and exploring new avenues for deeper understanding?

Bradley Dixon, MD, thinks of the body's powerful complement system as a Ferrari. For most people, the Ferrari is a well-oiled, impressive machine. But if you take something that powerful out for a drive with faulty brakes, someone's getting hurt. That's exactly what happens in patients with an ultrarare genetic disease called atypical hemolytic uremic syndrome, or aHUS. Kids diagnosed with this condition are literally one in a million. They're also the reason Dr. Dixon, a nephrologist at Children's Hospital Colorado, gets up every morning and continues his endless search for better and better treatments.

The complement system is made up of a series of proteins that evaluate danger signals on cell surfaces, such as specific patterns of sugar molecules, to identify and target infectious organisms. An essential part of the human immune system, the complement system is something we are born with, and it's always working in the background. But it's not a perfect system, and sometimes it can't easily recognize our own cells from invaders. In a healthy individual, built-in brakes pull the system back before it can run wild. In aHUS, these regulating factors don't function as they should.

When triggered by something as simple as a cold, the unregulated complement system is a wildfire, causing unmitigated damage across the body. Most concerningly, this process damages the endothelial cells lining blood vessels, signaling platelets to create clots, and causes red blood cells to breakdown. Together, these reactions choke critical organs, limiting oxygen supply and ultimately reducing function.

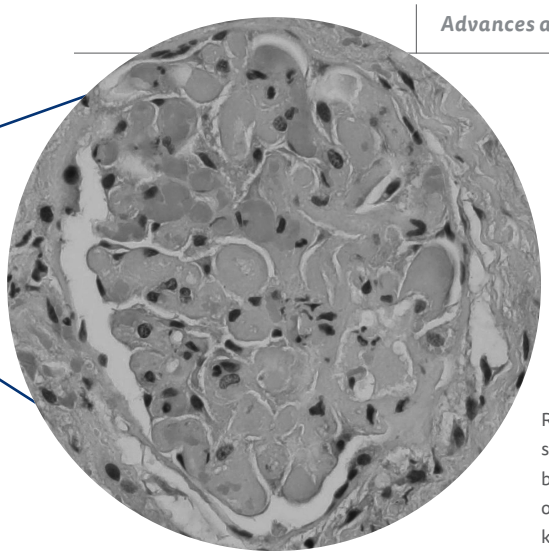
For decades, the condition was a death sentence with unreliable treatment options. Even if patients were able to replace a failing organ with a transplant, aHUS would continue to wreak havoc. But in 2009, the U.S. Food and Drug Administration (FDA) approved a new drug, eculizumab, that completely rewrote the story.

"That was a life changer," Dr. Dixon says. "Patients could come off dialysis. It could suppress the disease from coming back in a transplant. This completely revolutionized the way these patients experience life."

The drug, given by intravenous (IV) infusion every two weeks, was able to stop this runaway train in its tracks. But the inconvenience of lifelong, twice-monthly infusions, plus the challenges of such frequent and painful IVs, necessitated more work and more discovery.

MEET JULIETTE

In 2017, at just 3 years old, Juliette Picard came down with a case of strep. The common childhood illness, routinely treated with antibiotics, kept getting worse. When her pediatricians noticed concerning trends in Picard's bloodwork, they immediately referred the family to Children's Colorado and Dr. Dixon. Within one visit, Picard was diagnosed with aHUS. At the time, Dr. Dixon was beginning a clinical trial for a new drug to treat the condition, and Picard was almost immediately enrolled. Ravulizumab was designed as a variation of eculizumab, but instead of every two weeks, patients could go four to eight weeks between infusions, depending on their weight. Today, that drug is FDA approved. And since beginning treatment, Picard has been symptom-free.



Red blood cells being sheared apart in the tiny blood vessels (capillaries) of the filters of the kidneys (glomeruli).

WORK THAT'S NEVER DONE

With a cure in hand and lives saved, Dr. Dixon could have stopped pursuing new treatments for the pediatric population. But he knew that as patients like Picard continued to age, they'd still be held back by aHUS.

"We've had a great drug for this disorder for many, many years now. But it's all about the patient experience," he says. "It means being able to take vacations, not having school disrupted by having to go to an infusion center, not having to travel great distances if you're in a geographically dispersed region like we are here. Even just the pain and suffering of an infusion itself. I think that's why these continual improvements are needed."

That's what pushed both Dr. Dixon and the Picard family to explore a second clinical trial together. The new drug, crovalimab, can be given via a quick injection under the skin rather than an IV infusion, meaning that instead of spending hours at the hospital, Picard can be in and out in a matter of minutes, and her mother, Erica, recently learned to give the injections at home, eliminating the need for frequent hospital visits almost entirely.

"I'm not really concerned about the disease anymore. I'm more concerned about making sure Juliette can manage this moving forward because at some point, we're not going to be here to take her to the hospital," Erica says. "How do we make sure moving forward, she has the best quality of life and can do all the things?"

Starting in 2025, Dr. Dixon will begin testing yet another improvement to aHUS — this time in adult patients. Instead of injections or IVs, this new option only requires patients to take two pills each day.

"To go from no therapy to one therapy that's good but inconvenient, to lots of options and even something that you can control with oral medication is just, in my mind, a fantastic journey for a rare disease like this," Dr. Dixon says.

THE CRITICAL ROLE OF NAMING

Though treatments for aHUS exist, it's not always easy for the right patients to get the right treatment due to confusing nuances in the disorder's naming conventions. This stems from early understandings of how the disease functioned.

There are two primary ways to categorize hemolytic uremic syndromes: atypical HUS and "typical" HUS (now known as Shiga toxin-associated HUS). The "typical" version is often caused by a bout of food poisoning and usually resolves on its own without long-term medical intervention. Providers have historically distinguished between them based on whether or not the patient has diarrhea, but this symptom can occur in both versions of the condition, creating a significant barrier to accurate diagnosis.

That means that not everyone who needs the drugs Dr. Dixon has carefully worked to test and understand receives them. He's part of a team working to change that.

"About 30% to 40% of patients with atypical HUS have diarrhea. So, 30% to 40% of these patients could be classified incorrectly and may be excluded from receiving these targeted treatments," he explains. "I have had the privilege to be a part of a group of experts to come up with a better name for this so that people aren't inadvertently being denied or being left out of important treatment advances."

Of course, it's not as simple as changing a word, because for decades, those words have held a weighty meaning for patients, families and communities. Chronic conditions like these can become a part of someone's identity and a way to connect with others who share similar experiences. Removing the words that people have organized their lives around can have a powerful impact.

"It can change patients' ability to find each other and be empowered by each other," Dr. Dixon adds. "We have to be very thoughtful about a nomenclature change, not just on the scientific side, but also to make sure patients aren't disadvantaged in any way."

A TEAM EFFORT

Dr. Dixon's work to continuously improve treatments will soon get a boost from colleagues in Children's Colorado's newly minted Precision Medicine Institute. Because aHUS is a genetic condition, understanding the specific mutations at play and how they differ from patient to patient is essential.

For example, researchers and providers already understand that some people require lifelong treatment, while others might have

Continued on the following page

Taming Wildfire continued

"To go from no therapy to one therapy that's good but inconvenient, to lots of options and even something that you can control with oral medication is just, in my mind, a fantastic journey for a rare disease like this."

BRADLEY DIXON, MD

differing genetic factors that allow them to discontinue treatment and remain safe from relapse. By identifying these genetic differences, Dr. Dixon and his colleagues can more precisely target treatments and choose between the growing list of options.

That's where the new institute comes into play.

"There are only a few labs in the U.S. that really have results you can put your money behind," Dr. Dixon says. "Eventually we will have one of those labs because Dr. Alisa Gaskell is just a superb scientist, and she's invested in our program to do this kind of testing."

That genetic testing will live side by side with functional testing, thanks to Dr. Dixon's partnership with other complement scientists on the University of Colorado Anschutz Medical Campus. These partners will be able to run extensive tests related to the complement system itself, so that when genetic testing identifies a mutation, doctors can understand what exactly that mutation alters.

"This is a great campus for studying these disorders because we have lots of people with different experience and different scientific expertise. So, we're poised to be one of the leaders in testing in this field," Dr. Dixon says.

For families like the Picards, whose lives are literally in the hands of providers like Dr. Dixon, this unending commitment to improved treatments, better diagnosis and a more accurate understanding of aHUS is tough to capture in words.

"The team there — I have had the best people," Erica says of the providers who helped her daughter Juliette. "I am always going back to how thankful I am for Dr. Dixon and our research team." ●

BRADLEY DIXON, MD
Nephrologist, Children's Hospital Colorado
Professor, Pediatrics, University of Colorado School of Medicine

From Data to Diagnosis

Q: How is an international effort to redefine sepsis diagnosis criteria bringing better care to more kids and laying the foundation for future improvements?

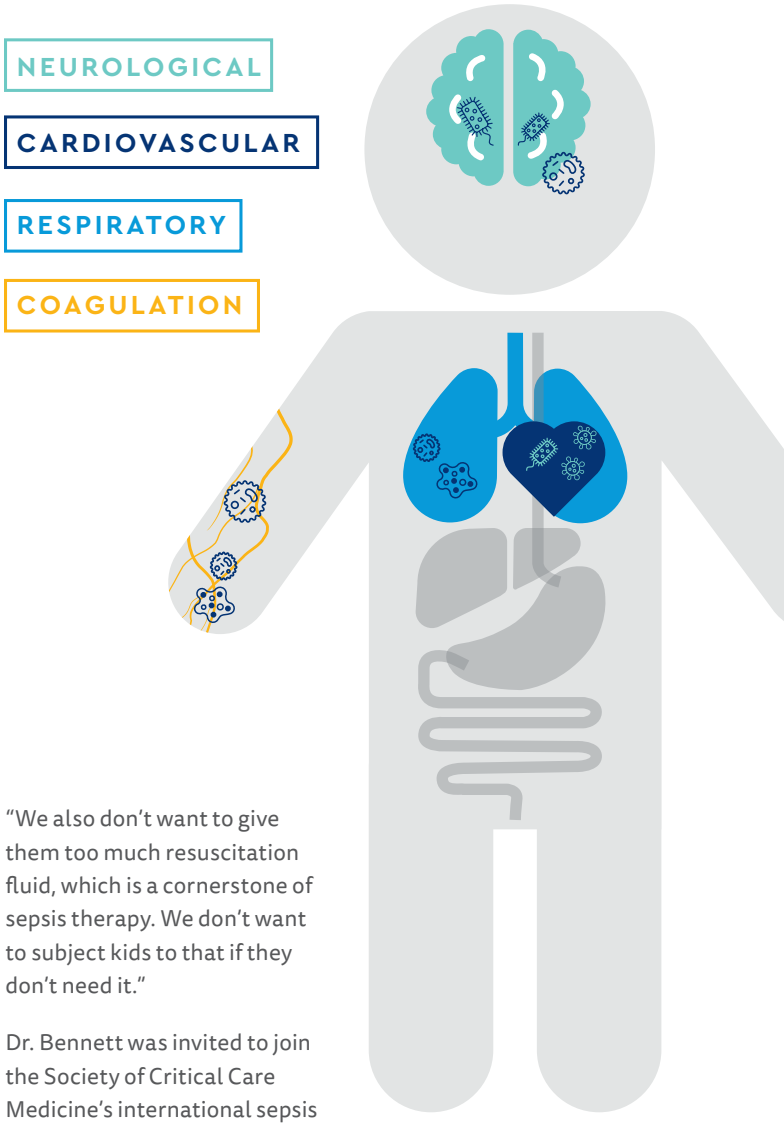
Nearly 20 years ago, a few dozen people sat in a room and made a decision that informed the way doctors diagnose and treat children with sepsis, a host response to an infection that can lead to organ dysfunction. The criteria they developed for a sepsis diagnosis have been used around the world to help providers make decisions about suspected cases of the condition, which affects 25 million children each year. But a lot has changed in 20 years and researchers now have a better understanding of sepsis, data and care across global contexts. For Tell Bennett, MD, an intensivist and informaticist at Children's Hospital Colorado, and his colleagues, the time was right for an update.

There is no single test that can definitively say someone has sepsis. Instead, providers have relied on a set of criteria that add up to a diagnosis. In 2016, a task force updated the adult sepsis diagnosis criteria. In 2019, a similar endeavor geared toward the pediatric population began. Not only were the pediatric criteria inconsistent with the ones used in adults, but they also didn't function well in the clinical space, resulting in diagnostic criteria that were too sensitive to be effective.

"It led to a lot of confusion, and so they were not universally used because of that lack of performance," Dr. Bennett says.

That confusion wasn't just inconvenient for providers. It was dangerous to patients.

"We need criteria that aren't too sensitive so we don't, for example, give kids lots of broad-spectrum antibiotics they don't need, because then they get other infections that can happen when your microbiome is degraded," Dr. Bennett explains.



"We also don't want to give them too much resuscitation fluid, which is a cornerstone of sepsis therapy. We don't want to subject kids to that if they don't need it."

Dr. Bennett was invited to join the Society of Critical Care Medicine's international sepsis task force representing 12 countries and various technical domains, from nursing and emergency department care to intensive care, infectious diseases and informatics. The team, which also included Halden Scott, MD, a pediatric emergency medicine physician at Children's Colorado, was charged with bringing the pediatric sepsis diagnosis criteria into the modern era. To kick off the work, the group held its first meeting in 2019 in Europe before the COVID-19 pandemic forced it to move to a virtual format.

Over the next five years, the participants worked to hash out a new understanding of sepsis and develop easy-to-follow criteria that could serve people in all different contexts, from big cities to rural towns, and from highly resourced countries to those with less

Continued on the following page

From Data to Diagnosis continued

"It's an important step forward, and I hope that it improves the outcomes of kids, but it's also a part of a process. I think we can have even more impact going forward."

TELL BENNETT, MD

developed medical systems. The fruits of their labor, the Phoenix Sepsis Score and the Phoenix Sepsis Criteria, were published in January 2024 (1, 2). Additionally, the team recently published a four-part series of papers designed to add context to some of the task force's key decisions.

THE IMPORTANCE OF INFORMATICS

Because of his experience as a pediatric intensive care unit physician and his focus on informatics, Dr. Bennett was perfectly positioned to make a significant contribution to the task force as it worked to bring the Phoenix Score to life. His clinical work put him close to pediatric cases of sepsis on a regular basis, while his informatics specialty helped the team ensure its final product would be data-driven and evidence-based.

Along with his colleague Nelson Sanchez-Pinto, MD, at Lurie Children's Hospital in Chicago, Dr. Bennett obtained funding from the National Institutes of Health for this work and designed and executed the computing effort for the task force. The team's first role was to determine the best way to measure organ dysfunction, one of the key indicators of a true sepsis case. Using machine learning, Dr. Bennett took all possible measures of organ dysfunction for each organ system (cardiovascular, respiratory, etc.) and identified which were most accurate.

"Then, we took the best ones and put them in a variety of different machine learning models to see how they could best come together to form diagnostic criteria," Dr. Bennett says. "Then we translated those models to an integer score, making sure that we didn't lose accuracy along the way."

His findings were then brought to the larger group, who spent grueling hours weighing different models against each other to determine which would function best in a real-life scenario. Together, they landed on the now-published criteria and decided that if a patient scores a two out of 13 possible points, an official sepsis diagnosis is confirmed.

SEPSIS CARE ACROSS CONTEXTS

With those decisions in place, Dr. Bennett's next step was to ideate ways to put the score into practice. Children's Colorado is serving as one test environment for this endeavor. His team partnered with the Children's Colorado Information Technology Division to code the criteria into the background of the hospital's electronic health record (EHR) and is now testing its ability to accurately diagnosis sepsis. In the next six months, he expects to roll this approach out to other hospital systems, with the understanding that different providers might use the score in different ways.

"Once we've confirmed that it's doing the right thing inside the EHR, we will be able to partner with the clinical and operational teams to figure out how best to change any workflows or surface this information to teams to best impact kids," Dr. Bennett says. "And we anticipate that process being locally calibrated at each institution that uses this."

But not all hospital systems have the same technology or the same access to testing. With that in mind, Dr. Bennett's team also developed

a mobile app for low-resource environments that may not have an electronic health record. Testing for the app is underway, and the hope is to roll it out for free use early in 2025.

"They enter whatever elements of the Phoenix Sepsis Score they have information about, and the application would give them the score and then also whether they meet criteria for sepsis or septic shock," Dr. Bennett says. To ensure accurate diagnosis regardless of environment, the team was careful to build redundancies into its scoring system.

"What we saw is that even in low-resource environments, it was still accurate because they had enough of the elements of the sepsis score that they could get to two points for those kids who actually did have sepsis," he adds.

BEYOND DIAGNOSIS

With the Phoenix Sepsis Score officially out in the world, Dr. Bennett and Dr. Scott are beginning to work toward developing sepsis screening criteria.

The goal is to have a better understanding of the different elements that increase sepsis risk and to develop technology that allows providers to intervene before the condition sets in. So, when kids seek care for something like a simple fever, doctors may get a flag from their electronic health record indicating heightened risk.

Though Dr. Bennett knows there's more work to be done to dramatically decrease the number of children who die of sepsis each year, the Phoenix Sepsis Score will not only improve care, but create a foundation for future improvements.

"I am very happy and proud to have been a part of the work and very proud of the work that our team here and around the world has done," he says. "It's an important step forward, and I hope that it improves the outcomes of kids, but it's also a part of a process. I think we can have even more impact going forward."

1. Schlapbach, Luregn J. et al. "International Consensus Criteria for Pediatric Sepsis and Septic Shock." JAMA vol. 331,8 (2024): 665-674. doi:10.1001/jama.2024.0179.
2. Sanchez-Pinto, L Nelson et al. "Development and Validation of the Phoenix Criteria for Pediatric Sepsis and Septic Shock." JAMA vol. 331,8 (2024): 675-686. doi:10.1001/jama.2024.0196.

TELL BENNETT, MD

Pediatric Critical Care, Children's Hospital Colorado

Professor, Biomedical Informatics, University of Colorado School of Medicine

Preserving Possibility

Children and teens who undergo treatment for cancer can experience lasting effects, including risks to their future fertility and reproductive health. While the primary focus of cancer care is on diagnosis and treatment, Children's Hospital Colorado takes a multidisciplinary approach that also looks toward the future and explores what quality of life could mean for cancer survivors.

One growing area of research for this whole-patient approach to cancer is oncofertility, which helps patients minimize the negative effects of cancer treatment on the reproductive system and fertility, preserving the possibility of having children down the road.

Now, providers have set their sights on standardizing how and when patients receive fertility counseling prior to cancer treatment, both within Children's Hospital Colorado and across North America.

Understanding the Range of Care

SURGICAL ONCOLOGY

The Surgical Oncology Program team at Children's Hospital Colorado is working to flesh out the current climate of pediatric oncofertility care in North America — something that hasn't been documented on this level before. Pediatric surgeon Kristine Corkum, MD, is leading this effort alongside Jonathan Roach, MD.

The multicenter, retrospective study proposed by the Children's Colorado team was selected to be one of the main research focus areas for 2025 by the Pediatric Surgical Oncology Research Collaborative (PSORC), a group of more than 50 institutions across North America that provides oncology care for pediatric patients. Every year the collaborative picks novel research studies to commit to as a group and gathers data from across the continent.

"We are very excited to work with PSORC because this data, in terms of how we practice pediatric oncofertility care here in North America, does not exist," says Dr. Corkum.

"It's one of those areas in comprehensive oncology care that's still up and coming. There are many nuances to oncofertility care that we don't have standard practices for currently," Dr. Corkum says. "We're hoping that this study will give us some insight into what's happening so then we can help improve the delivery of care across the country."

The study will explore the granular details of oncofertility care in North America — what hospitals are doing now, how they approach stratifying patients, how they counsel families, and when they perform fertility preservation procedures. The team is hoping to discover best practices and create a standard of care moving forward, since this area of care differs greatly from hospital to hospital. ●

KRISTINE CORKUM, MD
Pediatric Surgeon, Children's Hospital Colorado
Assistant Professor, Pediatric Surgery, University of Colorado School of Medicine

Encouraging the Conversation

HEMATOLOGY/ONCOLOGY

Pediatric patients who receive a stem cell transplant aren't always aware that the therapies included in their treatment could affect their future ability to conceive.

To help patients and families better understand their risks and options before undergoing treatment, Rohini Chakravarthy, MD, MPH, used her time as a stem cell transplant and cellular therapy fellow at the University of Colorado School of Medicine to increase the number of patients being referred to the Fertility Preservation and Reproductive Late Effects (FPRLE) Program. Dr. Chakravarthy developed and implemented this project under the guidance of Children's Hospital Colorado gynecologist, Leslie Appiah, MD, and pediatric stem cell transplanter Vanessa Fabrizio, MD, MS.

"I really wanted to start with making sure that we are standardizing conversations and making sure that all patients are receiving the appropriate counseling, so they can make the decision that is right for them," Dr. Chakravarthy explains. Creating more consistent patient-family conversations involved implementing changes to the Epic system, such as embedding a referral to the FPRLE team for every patient that has a bone marrow transplant consultation and creating a fertility-preservation checklist for coordinators assisting patients before a transplant.

Ten months after these changes went live in Epic, the number of patient referrals to the FPRLE team increased from 34% to 81%. However, the number of patients pursuing fertility preservation stayed the same. This opens more doors for exploration: What are the barriers and concerns preventing patients from opting into fertility preservation? How might providers anticipate and mitigate challenges to ensure all patients have more options for starting a family if they choose?

"When talking to a family about a new diagnosis and all of the therapies they're going to go through, it's very difficult for them to think past a short-term cure," Dr. Chakravarthy says. "It's up to us as providers to give patients and families all the information not only regarding the immediate effects of their therapy, but the long-term effects, too." ●

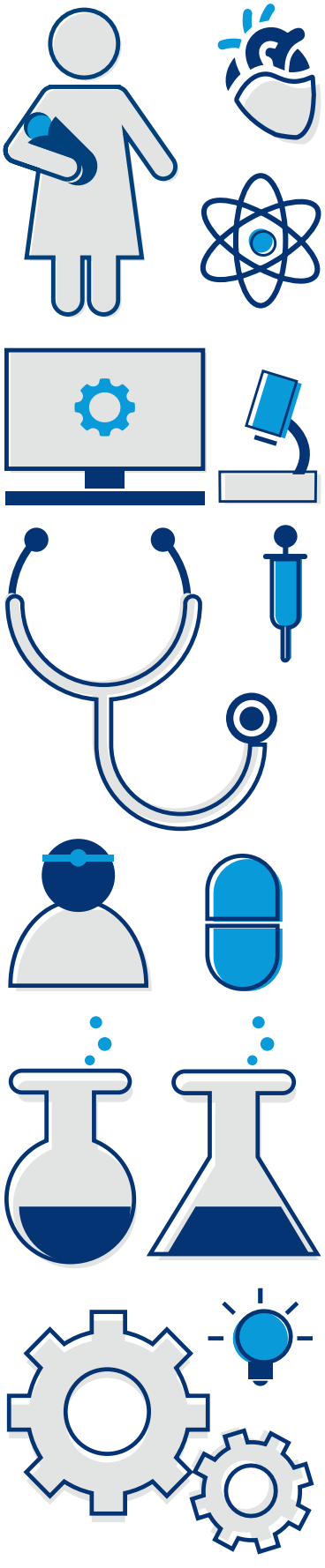
ROHINI CHAKRAVARTHY, MD, MPH

Former Fellow, Pediatric Stem Cell Transplant and Cellular Therapy, University of Colorado School of Medicine

VANESSA FABRIZIO, MD, MS

Hematologist/Oncologist, Center for Cancer and Blood Disorders, Children's Hospital Colorado

Assistant Professor, Pediatrics-Hematology/Oncology and Bone Marrow Transplantation, University of Colorado School of Medicine



PRECISION MEDICINE

Clues to Causation

Q: How can an in-house biobank unlock clues to the genetic variants underlying craniofacial conditions?

The Craniofacial Program at Children's Hospital Colorado sees 400 patients annually, boasting some of the highest volumes nationwide. Although these conditions, such as cleft palate and craniosynostosis, are not rare, they are notorious for their variation in physical presentation. This makes it difficult for providers and researchers to draw conclusions about the genetic variations driving these diseases. University of Colorado senior researcher Cristan Carter is teaming up with Antonio Porras, PhD, Director of Research in the Department of Pediatric Plastic and Reconstructive Surgery, and Brooke French, MD, Co-Director of the Craniofacial Program, to create a repository that will not only uncover these missing links of causation — but also key routes to treating them.

In the past two decades alone, myriad areas of pediatric care have become more targeted thanks to advancements in genetic testing and precision medicine. But for craniofacial researchers, genetics knowledge specific to their field has remained elusive. "We don't know the causes for the pathology in 80% to 90% of these children," Dr. Porras says. "That's a very big deal because you cannot really move toward personalized medicine if you don't fully understand what is causing the disease in the first place."

The barriers preventing more precise treatment of pediatric craniofacial conditions range far and wide. From a research perspective, investigations on craniofacial conditions have been meager, as there aren't many clinics with high enough volumes to conduct significant patient cohort studies. Funding has also been scarce, making it hard to get research projects off the ground.

With few children to study and even fewer financial opportunities to go around, the landscape for genetic research on pediatric craniofacial conditions has been difficult, but it's also been even further impeded by human nature itself. "These children grow very fast and look very different at different ages, so it's very hard to identify common abnormal patterns between children that are at different stages of development," Dr. Porras says.

BUILDING A BIOBANK

More than 30 years ago, the Craniofacial Program at Children's Colorado became one of the first centers focused on multidisciplinary care and long-term treatment. The program grew in scale and scope over time, attracting more patients and specialty providers while expanding its data science research capabilities.

This created the perfect environment for conducting the kind of genetic research that had rarely been performed on craniofacial conditions. In 2020, Carter and Drs. Porras and French stepped in to realize this vision. "We saw a unique opportunity because we had high enough volumes to consider creating a biobank and putting data together that will start giving answers to these questions," Dr. Porras says. "We have become one of the national leaders in data

science research for craniofacial conditions. The only thing missing was the link with genetics."

Under the leadership of Dr. French, who served as principal investigator, Carter executed all the steps needed to create an in-house biobank, which included everything from institutional review board approval paperwork to the logistics of how to store and process tissue samples. The team began collecting blood and affected bone and cartilage in March of 2023, and now gives each patient and family the option to join the research project. After tissue has been collected, Carter extracts cells containing genetic material and takes the sample to the lab — a space lent to the team by University of Colorado School of Medicine medical genetics researcher Tamim Shaikh, PhD. There, research teams can perform a combination of different analyses, from genomic sequencing to changes in RNA and protein expression levels.

"The idea is that once we can process all this information, we can actually have a database of not only tissue samples, but also genetic information, which can be used infinitely," Carter says.

A STRONG FOUNDATION

Unlike traditional science research projects in pediatrics, which receive funding from the National Institutes of Health, the biobank is fully supported by the Center for Children's Surgery at the University of Colorado Anschutz Medical Campus. The center's Director of Operations, Sandra Talley, played an important role in ideating the project and bringing the biobank to life. Plus, this is a strategic partnership because patients visiting the Craniofacial Program benefit from a multidisciplinary care approach that often includes surgery.

"Our surgical interventions are already more personalized than anywhere else in the country right now, but with treatments more targeted to the specific causes of diseases, we can take a multiperspective, personalized approach that addresses or treats every patient differently depending on what exactly their condition is," Dr. Porras says.

With this support, the researchers hope the biobank can serve as a hub for other craniofacial researchers, as it is not just limited to studies on craniosynostosis — its initial pilot research project. In turn, the biobank's creators hope that these collaborations and the findings that result will bring notoriety and resources back to their project. "Because the Center for Children's Surgery has been kind enough to fund this data collection program, we're hoping that basic scientists now are able to leverage the biobank by doing their investigations in partnership with us," Dr. Porras explains.

French points out that the team encourages other investigators to submit their ideas for new areas of research in craniofacial conditions, and hope this will expand the capacity, and benefits of the biobank they worked so hard to create.

"We are excited to explore opportunities with colleagues to diversify and broaden applications through the craniofacial biobank," French says. "This is an incredible time to deepen our understanding and improve the care of children with craniofacial differences."

CRISTAN CARTER

Senior Researcher, Plastic and Reconstructive Surgery, University of Colorado School of Medicine

ANTONIO PORRAS, PHD

Research Director, Department of Pediatric Plastic and Reconstructive Surgery, Children's Hospital Colorado

Assistant Professor, Department of Biostatics and Informatics, Colorado School of Public Health, Departments of Surgery, Pediatrics and Biomedical Informatics, Colorado School of Medicine

BROOKE FRENCH, MD

Co-Director, Craniofacial Program, Department of Pediatric Plastic and Reconstructive Surgery, Children's Hospital Colorado

Associate Professor, Plastic and Reconstructive Surgery, University of Colorado School of Medicine

Mapping Diabetes: Pregnancy to Puberty

Q: What can life course research uncover about diabetes, and how can this approach enhance our understanding of prevention strategies for chronic diseases?

The U.S. government reports that more than 5,000 people are diagnosed with diabetes every day. An additional 1 out of every 3 people have prediabetes, and about 90% of those people don't even know it. This chronic disease, in which the body can't regulate blood sugar, can also cause blindness, kidney failure, heart attack, stroke and lower limb amputation — and disease prevalence is rapidly on the rise. Dana Dabelea, MD, PhD, has committed her career to studying diabetes from every angle. She knows it's not enough to just study the disease in isolation — it's about going deeper to understand why diabetes happens in the first place and what factors and exposures play a role. With that understanding, her goal is to work toward prevention.

Nearly a decade ago, Dr. Dabelea noticed a gap in diabetes research across the University of Colorado Anschutz Medical Campus, with different pockets of work happening side-by-side but not under one unified umbrella. That's when she founded the Lifecourse Epidemiology of Adiposity & Diabetes (LEAD) Center to bridge that gap and focus on research across the lifespan — a novel approach at the time. This holistic, multifaceted approach enables the team at the LEAD Center to set their sights on not just understanding this chronic illness but pursuing a path to prevention. She decided to not just study one aspect of diabetes across age groups, but to expand her work to all the different exposures that can impact disease onset.

"It's not only our molecular structure, our epigenetics, our genetic background, but it's also the above-the-skin environment — the familial environments, the community environments, the structural factors, including social determinants of health and structural racism," Dr. Dabelea says. "Unless you look at the totality of this environment, we will not understand pathogenesis of disease; we will not understand how to promote health by preventing disease."

BEGINNING BEFORE BIRTH

To fully understand all the elements of disease prevention for diabetes, Dr. Dabelea knew she needed to go back to the start of life and zoom out to analyze risk factors through a prebirth cohort. In 2009, the LEAD Center launched a longitudinal research study — the Healthy Start study — to look at the metabolic and behavioral factors during pregnancy and early life that contribute to the development of obesity and related health problems, such as insulin resistance and inflammatory markers.

Funded by the National Institutes of Health, the study enrolled more than 1,400 pregnant women to start collecting data, and the team has continued to follow the children for nearly 15 years.

The researchers started by exploring how women's experiences during pregnancy, such as diet and physical activity, along with environment, could affect their child's growth throughout infancy and childhood. Now, the team is following that same cohort of children through a critical phase of development — puberty — where exposure to risk factors can be more impactful.

"It's not only our molecular structure, our epigenetics, our genetic background, but it's also the above-the-skin environment — the familial environments, the community environments, the structural factors, including social determinants of health and structural racism. Unless you look at the totality of this environment, we will not understand pathogenesis of disease; we will not understand how to promote health by preventing disease."

DANA DABELEA, MD, PHD

"We've never studied such a large cohort as they transition through puberty in terms of metabolic health and obesity development, especially in a group of healthy kids who we have so much information on before they transition to that phase," Dr. Dabelea says. "Puberty is a sensitive period when a lot of chronic childhood diseases develop, such as Type 2 diabetes, insulin resistance and obesity."

Countless findings have been uncovered through this research already, such as the importance of supplementing vitamin D for pregnant patients to reduce the risk of elevated blood pressure in their children. The data also revealed how exposure to tobacco smoke during pregnancy can lead to impaired neurocognitive development in early childhood that impacts academic achievement later in life. And the team published research about how pregnant patients can lower their risk of abnormal blood glucose levels, a key risk factor for developing gestational diabetes, through physical activity, diet quality and mental health care.

Dr. Dabelea hopes the Healthy Start study can continue through the next phases of life for this cohort — transitioning to becoming independent adults and even continuing into the future when they might decide to have kids of their own.

The Healthy Start study also contributes to a larger NIH consortium called ECHO, Enviornmental Influences and Child Health Outcomes, with dozens of other prebirth cohorts looking to analyze all aspects of child health through longer studies.

CONTRIBUTIONS FROM THE COMMUNITY

Another priority area for the LEAD Center is community-based participatory research for populations that are typically not represented in studies.

"If all our knowledge comes from white kids, I think we're increasing disparities, not contributing to decreases," Dr. Dabelea says. "Our campus is great for recruiting, because it has hospitals, but people who touch the hospitals have health insurance. So, while I tap into this population for some of our studies, a lot of our studies are outside campus and the traditional medical campus setting."

Dr. Dabelea has worked closely for many years with the Navajo Nation, a community that has one of the highest rates of Type 2 diabetes in the country. These collaborations have been ongoing for 20 years, with community members actively involved in developing protocols and implementing studies.

Right now, the team is wrapping up a diabetes intervention program that focuses on lifestyle interventions with American Indian children ages 7 to 10. They used a formal group curriculum with 12 different lessons about meal planning, physical activity and stress, along with motivational interviewing sessions with families to identify roadblocks and equip them with a toolbox of local resources. Dr. Dabelea and the team are analyzing the data to see if these interventions played a role in reducing obesity and preventing dysglycemia,or abnormality in blood sugar levels.

"As the risk factors to chronic diseases develop over the life course, disparities develop over the life course as well," Dr. Dabelea says. "That's why it's important that in these multicenter studies that we all do, we always include populations who are clinically underserved from socioeconomic perspectives and who do not participate typically in observational studies or clinical trials." ●

DANA DABELEA, MD, PHD

Associate Dean of Research, Colorado School of Public Health

Director, LEAD Center

A(:) List

Recent awards and accolades

Allison Kempe, MD, MPH/MSPH

PEDIATRICS

2024 Lifetime Achievement Award in Child Health Services Research

Allison Kempe, MD, MPH, was honored with the AcademyHealth Child Health Services Research Interest Group Advisory Committee's 2024 Lifetime Achievement Award in Child Health Services Research. Dr. Kempe's 40-year career has placed a strong emphasis on childhood translational research, reducing health disparities and training the next generation of child health researchers. She was the founding director of the Adult and Child Center for Outcomes Research and Delivery Sciences, a campus-wide program providing training, mentorship and support to researchers, and she has mentored hundreds of new investigators, training them in her rigorous approach to high-quality research. Dr. Kempe was nominated for the award by her former mentee, Andrea Jimenez-Zambrano, PhD, MPH, who wrote: "The transformative impact of [Dr. Kempe's] mentorship extends far beyond individual achievements, resonating across institutions and communities. Through her guidance, a legacy of excellence in child healthcare research has been cultivated, leaving a lasting impression on the field."

Kelly Wolfe, PhD

NEUROLOGY

COMPASS Ancillary Neurodevelopmental Outcomes (CAN-DO)

Kelly Wolfe, PhD, a neuropsychologist who studies heart disease, received a grant to assess how treatments for ductal-dependent pulmonary blood flow impact children's brain development. She is comparing two interventions: transcatheter ductal arterial stents and a surgical systemic-to-pulmonary artery shunt. This new study, which is co-investigated by Jesse Davidson, MD, will include patients from 20 children's hospitals through the Pediatric Heart Network's COMPASS trial, which compares medical morbidities associated with these treatments.

Researchers will assess various preprocedural risk factors such as medical, sociodemographic and genetic factors. Perioperatively, they will examine biomarkers of neural injury to evaluate differences by intervention approach and analyze their predictive utility for neurodevelopmental outcomes. Investigators will also assess targeted biomarkers of neural development both perioperatively and at 36 months to determine their relationship to long-term neurodevelopment.

Emily Bucholz, MD, PhD, MPH

CARDIOLOGY

Associate Editor, Journal of the American College of Cardiology

Emily Bucholz, MD, PhD, MPH, a pediatric cardiologist at Children's Hospital Colorado, was named associate editor of the pediatric section of the Journal of the American College of Cardiology (JACC). The JACC is one of the world's most reputable and widely read cardiovascular journals with 50 annual issues. Dr. Bucholz has extensive experience working with congenital heart disease registries and serves as a Pediatric Heart Network principal investigator for the University of Colorado.

Her areas of interest include sociodemographic disparities in pediatric heart disease, pediatric quality measurement and the development of risk stratification models in congenital heart disease. Much of her research is funded by foundational grants from the American Heart Association and the Thrasher Research Fund to study maternal-fetal risk factors for congenital heart disease outcomes.

Shrey Purohit, MD

NEPHROLOGY

Nephrology Fellowship Graduate Founds Clinic to Ease Patients Into Adult Care

Navigating young adulthood is especially difficult for kids with chronic medical conditions, but a new clinic at Children's Hospital Colorado is dedicated to easing the journey. Shrey Purohit, MD, is leading this transitions clinic, a safe space to help former pediatric nephrology patients ease into adult care. He's one of the first fellows to graduate from the Meds-Peds Nephrology Fellowship at the University of Colorado Anschutz Medical Campus. With training in both adult and pediatric nephrology, Dr. Purohit will see patients at Children's Colorado as they begin to transition into adult care and at UCHealth, where they'll continue their journey.

"I get to take young people and help them through to the point where they can start to become successful adults," says Dr. Purohit. "To give them tools to take away that sense of helplessness is gratifying."

Stephen Daniels, MD, PhD

PEDIATRICS

Robert Suskind and Leslie Lewinter-Suskind Pediatric Nutrition Lifetime Achievement Award

Children's Hospital Colorado Pediatrician in Chief Stephen Daniels, MD, PhD, has been awarded the Robert Suskind and Leslie Lewinter-Suskind Pediatric Nutrition Lifetime Achievement Award by the American Society for Nutrition. This award recognizes a researcher or clinician for lifelong contributions to the field with a focus on the impact of childhood nutrition on health and disease.

Dr. Daniels is renowned for his research on cardiovascular risk factors in children. His studies have focused on understanding the causes of blood pressure elevation and cholesterol abnormalities in children and adolescents, particularly the role that obesity may play in these health issues.

Children's Hospital Colorado
Anschutz Medical Campus
13123 East 16th Avenue
Aurora, Colorado 80045

Non-Profit Org.
U.S. Postage
PAID
Denver, CO
Permit No. 1050

Watch what's new

Professional development videos from our pediatric specialists on a variety of topics, from new research to innovative practices and advances in clinical care

Visit our YouTube channel **Pediatric Healthcare Professional Resources**

Information for you

Email newsletters on the latest research and clinical updates happening at Children's Hospital Colorado within your specific specialty

Sign up at **childrenscolorado.org/SpecialtyNews**

Hear our view

Charting PEDIATRICS

A podcast from our multidisciplinary specialists that examines the latest treatments for the most common complaints in pediatric medicine

Listen to Charting Pediatrics on **Spotify, Apple Podcasts and Google Play**

School of Medicine
UNIVERSITY OF COLORADO
ANSCHUTZ MEDICAL CAMPUS

Connected through care

We partner with neighboring University of Colorado School of Medicine, where many of our care providers serve as faculty. The school is ranked in the nation's top tier by U.S. News & World Report, and is among the National Institutes of Health's top-funded research institutions.

Follow us on X

An X account for pediatric healthcare professionals where we share our latest research, clinical innovations and news

Follow us **@ChildrensCO_Pro**

BEST CHILDREN'S HOSPITALS
U.S.News & WORLD REPORT
RANKED IN 11 SPECIALTIES
2024-2025

The work that sets us apart

With more than 500 researchers, 1,000+ studies underway and 7,000 kids participating in clinical trials, we're learning and solving problems at an unprecedented rate. This year, those efforts have earned us a U.S. News & World Report ranking as one of the Top 10 best children's hospitals in the nation with six specialties ranked in the Top 10 as well. And we are proud to continue serving as pediatric leaders right here in our own community, with #1 rankings in both the region and the state.

Here, it's different.

Correction: In the last issue we incorrectly identified Alex Barker, PhD, as Alex Baker, PhD.