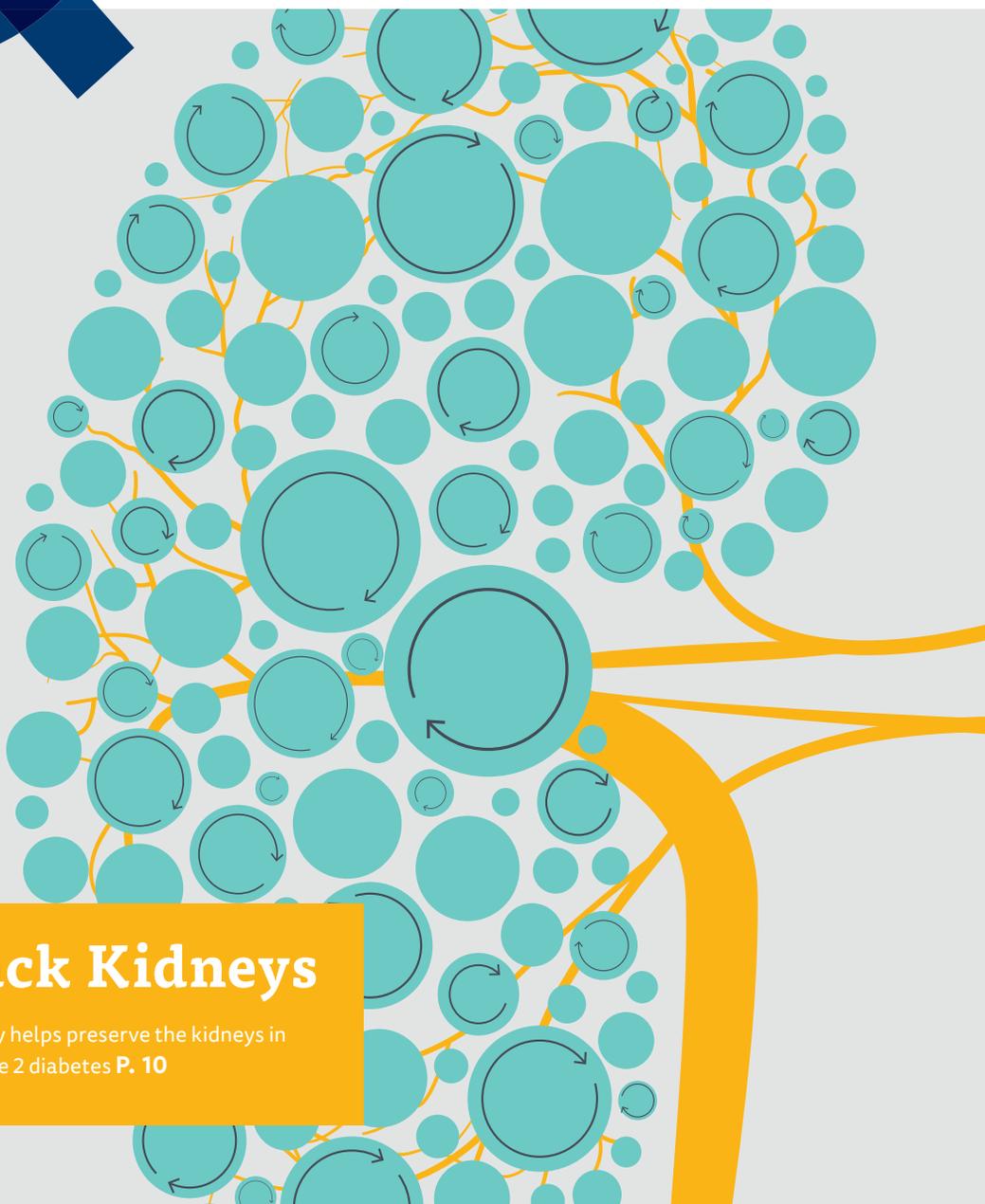




# Advances and Answers in Pediatric Health



## The Comeback Kidneys

Understanding how bariatric surgery helps preserve the kidneys in severely obese adolescents with type 2 diabetes **P. 10**

### 4 | DILATION COMPLICATION

How intra-abdominal dilation can predict complex gastroschisis

### 14 | CHARTING A NEW COURSE

Changing the paradigm of clinical research



# It starts with a Q:

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

For me, one of the really fascinating aspects of a career in child health is the inquisitive nature of our young patients. Their gears always churning, yearning to understand how things work and why, and wondering how we, as doctors, can help them experience change they can feel — change that will offer them a healthier childhood.

Like the children we treat, we're creating a campus culture that continuously inspires curiosity. In doing so, we're unlocking a new realm of pediatrics — one that is swapping insular science and medicine for collaborative, progressive approaches to advancing and accelerating discovery. Questions once asked within the silos of specific specialties are more and more commonly being addressed across multidisciplinary planes. These approaches are producing the remarkable advances that we feature in the following pages.

By prioritizing and advancing research, education, clinical work and process improvement, we're speeding the integration of our discoveries into the clinical engine, treating our patients and patients around the world in new and innovative ways. A unique and strong partnership with University of Colorado Anschutz Medical Campus provides fresh perspectives and invaluable expertise, as do our relationships with national and international research consortiums, industry partners and children's hospitals.

We're incredibly grateful for a university dean and chancellor, a chair of pediatrics, and a hospital executive team who have not only encouraged this collaborative approach to child health research, but have actively paved the way for it, because they understand it's a distinguishing factor.

Here, we imagine the future and simultaneously create it.



**THOMAS H. INGE, MD, PhD**  
Associate Surgeon-in-Chief

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#### We rank among the best in all 10 recognized specialties:

Cancer: #14	Gastroenterology and GI Surgery: #6	Neurology and Neurosurgery: #13
Cardiology and Heart Surgery: #12	Neonatology: #18	Orthopedics: #20
Diabetes and Endocrinology: #7	Nephrology: #20	Pulmonology: #7
		Urology: #14



## A Bright Idea

### GASTROENTEROLOGY

Pediatric gastrointestinal doctor Joel Friedlander, DO, sits in an operating room with three of his coworkers, Emily DeBoer, MD; Jeremy Prager, MD;

and Robin Deterding, MD, each of whom is about to perform an anesthesia-based procedure with a respective scope. Dr. Friedlander, who traditionally uses an endoscope, fiddles with the bronchoscope and wonders aloud, "If we could get a kid to swallow this, could we use it to perform an unsedated endoscopy?"

That idea sparks what ultimately becomes a fruitful study. As it turns out, unsedated endoscopy is a quicker procedure at a fraction of the cost of sedated endoscopy, and both parents and kids prefer it. But because bronchoscopes aren't technically made for

the esophagus, Dr. Friedlander finds he needs to build something more specific.

With additional support from Dr. Deterding, Medical Director for the Children's Hospital Colorado Center for Innovation, Dr. Friedlander and his partners form a company, Triple Endoscopy Inc., and begin to develop what they call a turnkey kit for hospitals: a scope, virtual reality goggles to entertain the patient during the procedure, and the software system that ties both of those pieces together. That kit is on track to hit the market later this year. ●

### A TURNKEY KIT



## Improving Survival in Childhood Cancer

### CANCER



Pediatric oncologist and hematologist Kelly Maloney, MD, program leader for leukemia and lymphoma at Children's Colorado.

Researchers know intensified postinduction therapy improves survival in children with high-risk B-cell acute lymphoblastic leukemia, or ALL. But does it also improve outcomes for those with standard-risk ALL? The answer is yes for some patients. That's according to recently published data from a high-profile study by Children's Oncology Group, which included more than 5,300 patients, that show a 6-year overall survival rate exceeding 95%.

Led by Kelly Maloney, MD, program leader for leukemia and lymphoma at Children's Hospital Colorado, this is the largest clinical trial conducted to date of children with standard risk ALL — the most common form of childhood cancer. All patients received a 3-drug induction with dexamethasone, vincristine and pegaspargase and were then classified as standard-risk low, standard-risk average or standard-risk high, with researchers administering different treatments for each group in this randomized study.

Of note are the 635 patients classified as standard-risk high who experienced particularly good outcomes with an overall survival rate of 93% despite their poorer risk factors when they received fully augmented therapy. ●

Check out the next edition of Q: for a more in-depth look at Dr. Maloney's work.

# Dilation Complication

**Q: Can abdominal dilation predict complex gastroschisis?**

Timing the delivery of a high-risk baby can be a delicate balance. That's particularly true for gastroschisis, a congenital disorder in which some organs, most commonly the intestines, develop outside the abdominal wall.

In close to 90% of cases, patients are born without complications and cured with a relatively low-risk surgery. The other 10% of cases, however, can become life-threatening in the second trimester.

Fetal surgeon Kenneth Liechty, MD, and his team at the Colorado Fetal Care Center at Children's Hospital Colorado, recently shed light on a predictive factor.

Dr. Liechty had speculated for some time that bowel dilation might correlate with complexity. If the opening in the abdominal wall constricted the intestines, he reasoned, the resulting blockage and buildup of fluid might lead to bowel dilation, either externally or internally. Previous studies, however, had not revealed such a correlation.

"I think the difference between previous studies and this one is really the rigor involved," says Dr. Liechty. "This wasn't just one sampling. We followed 55 patients over time, looking at about a dozen different variables."

One of those variables was distinguishing between extra-abdominal and intra-abdominal intestinal diameter. That turned out to be key. An intra-abdominal diameter of more than 17 mm correctly identified 75% of complex cases. The negative correlation was even stronger, with an intra-abdominal diameter of less than 17 mm identifying 92% of "simple" cases.

"There may be other factors involved," says Dr. Liechty. "There may be inflammatory processes; the bowel being exposed to amniotic fluid may lead to progressive bowel damage. So if these predictive factors are pointing to a poor outcome, it may be better to deliver earlier and decrease the duration of those insults." ●

## Identifying prenatal ultrasound findings associated with the risk of poor gastroschisis outcomes



Gastroschisis is diagnosed as "complex" if the development of the intestines appears to be compromised.

Complex gastroschisis can result in increased infant morbidity and mortality and is often not diagnosed until after birth. Prenatal diagnosis could allow for perinatal management of these patients.

Occurs in

**4.9 of every 10,000 births**

Complex gastroschisis costs

**\$250,000 per patient per hospital stay**

**Q: Can ultrasounds diagnose the risks of complex gastroschisis and poor outcomes?**

### A retrospective review



Dr. Liechty and colleagues had three study objectives:

- 1 Describe differences in ultrasonographic measures between complex and simple gastroschisis
- 2 Determine relationships between ultrasonography measures and patient outcomes
- 3 Identify a potential measure useful in predicting patient outcomes

#### Study criteria

- **ICD diagnosis** code of "gastroschisis"
- **Admitted to a free-standing** children's hospital with a Level 3 NICU between 2007 and 2017
- **No missing** ultrasound report or images

### Variables reviewed



Prenatal ultrasound reports and images from the 55 participants were reviewed for several variables:

#### Ultrasound characteristics

- Intra-abdominal intestinal diameter (IAID)
- Extra-abdominal intestinal diameter (EAID)
- Echogenicity
- Amniotic fluid index
- Abdominal circumference (AC)
- Thickness of bowel wall
- Visceral content in herniation
- Defect size

#### Patient outcomes

- Complex vs. simple gastroschisis
- Enteral feeding
- Length of NICU stay
- 30-day readmission
- Infection complications

### Cohort characteristics



**21 years old**  
Mothers' median age

**2.3 kg**  
Neonate median weight

**36 weeks**  
Median gestational age at delivery

**43 days**  
Median length of stay

**31 days**  
Median time to enteral feeding

**29%**  
Complex gastroschisis (N=16)

### Key findings

- 1 Compared to simple gastroschisis, complex gastroschisis had higher:
  - IAID
  - Fetal AC
  - Amniotic fluid index
  - Bowel wall thickening
 No other differences were significant between the two groups.
- 2 IAID was the only ultrasound finding with a strong enough relationship with patient outcomes to be determined predictive.
- 3 Larger IAIDs were associated with:
  - **20% increased chance of complex diagnosis**
  - **Longer time to full enteral feeding (intake and processing of nutrients through the gastrointestinal tract)**

#### And most importantly:

- 4 **A 17 mm IAID at 32 weeks gestational age reliably distinguishes between complex and simple cases**

Complex cases	Simple cases
<b>IAID of &gt;= 17 mm</b> correctly identified 75% (sensitivity)	<b>IAID of &lt;17 mm</b> correctly identified 92% (sensitivity)
<b>75% chance</b> with an IAID >17 mm (PPV)	<b>-92% chance</b> when an IAID <17 mm (NPV)

### Conclusions

**A: Based on the study's findings, IAID is associated with a longer time to full enteral feeding and the diagnosis of complex gastroschisis.**

The study titled "Examination of Prenatal Sonographic Findings: Intra-Abdominal Bowel Dilation Predicts Poor Gastroschisis Outcomes" was published in the August 2019 issue of *Fetal Diagnosis and Therapy*.

## AAP Recognizes Bariatric Surgery for Adolescents

### BARIATRIC SURGERY

Recent data report the prevalence of severe obesity in youth has nearly doubled since 1999 and affects about 4.5 million children in the United States. In an effort to combat this rising public health concern, the American Academy of Pediatrics now recognizes bariatric surgery as a viable treatment option for severely obese adolescents.

The AAP's release of its stance and best practice guidelines is

due, in part, to findings from the multicenter clinical study Teen Longitudinal Assessment of Bariatric Surgery, or Teen-LABS, led by Thomas H. Inge, MD, PhD, associate surgeon-in-chief at Children's Hospital Colorado. When compared to older adults, the study found adolescents who undergo bariatric surgery have higher rates of remission of hypertension and type 2 diabetes. ●



## A Passion That's Bone-Deep

### ENDOCRINOLOGY

Pediatric endocrinologist Nina S. Ma, MD, CCD, will lead a new Bone and Mineral Metabolism Program at Children's Hospital Colorado as the Ed and Jeannette Kerr Family Endowed Chair in Endocrinology. Dr. Ma, whose clinical expertise is in pediatric osteoporosis and nutritional and genetic forms of rickets, came to Children's Colorado from Boston Children's Hospital, where she directed the Bone Health

Program and DXA Center from 2012 to 2019.

Dr. Ma is shaping the new program to be comprehensive and multidisciplinary, focusing not only on the evaluation and treatment of pediatric bone conditions, but also on research and education. "These aspects are crucial," she says. "We need to be amassing our scientific knowledge, while also educating the next generation of doctors and researchers, so that we are perpetually helping these children."

To that end, Dr. Ma has approval to begin two research studies in children with achondroplasia: one on the natural history of the condition and the other an interventional drug trial to help improve bone growth. Both are part of larger, multicenter studies with participating sites around the world. ●

## Joint Venture

**Q: What is postoperative life like for a kid who undergoes a total joint replacement?**

*Outside of solid tumors, a total joint replacement is a rare surgery for adolescents. There isn't a lot of information on surgical outcomes for this age group, so researchers at Children's Hospital Colorado are starting to collect it.*

As a pain control surgery, a total joint replacement is ideal for a person who is later in life — someone who likely won't have to worry about replacing the replacement. That's not the case for a kid, says orthopedic surgeon Nathan Donaldson, DO, because it won't last their whole life. And each time the device is replaced, there's a catch.

"The patient loses function," Dr. Donaldson says. "Less bone and muscle, more scar tissue. It makes it harder on the surgeon and the patient."

Other methods to control the pain are preferable, but when those methods fail, a total joint replacement can offer relief.

But because it isn't a common surgery for kids, there isn't much data to show what postoperative life is like after one, let alone several over a lifetime. What is their pain level? Are they physically doing well? What about mentally?

Dr. Donaldson and affiliate researcher Nathan Rogers, MPH, are surveying a cohort of about 140 kids who've already undergone a total joint replacement at Children's Colorado in the last 16 years to start collecting those answers.

**"The novelty of our study is that we're asking, 'Are you, as a person, happy with what we've done to your joints?' and that's really the most important thing we want to know."**

NATHAN DONALDSON, DO

### ARE YOU HAPPY?

Most studies on total joint replacements look at physician-reported scores, which include assessment of pain, but they overlook other important markers like mental health.

"The novelty of our study is that we're asking, 'Are you, as a person, happy with what we've done to your joints?'," says Dr. Donaldson, "and that's really the most important thing we want to know."

They receive answers from patients through a survey given over the phone or privately in clinic.

This method of patient-recorded outcomes is increasing in practice, Rogers says, because in addition to what a physician is assessing, it's important to understand what a patient thinks. Feedback differs depending on group, but overall, Rogers is seeing that both physical and mental scores for Children's Colorado patients fall within the national average.

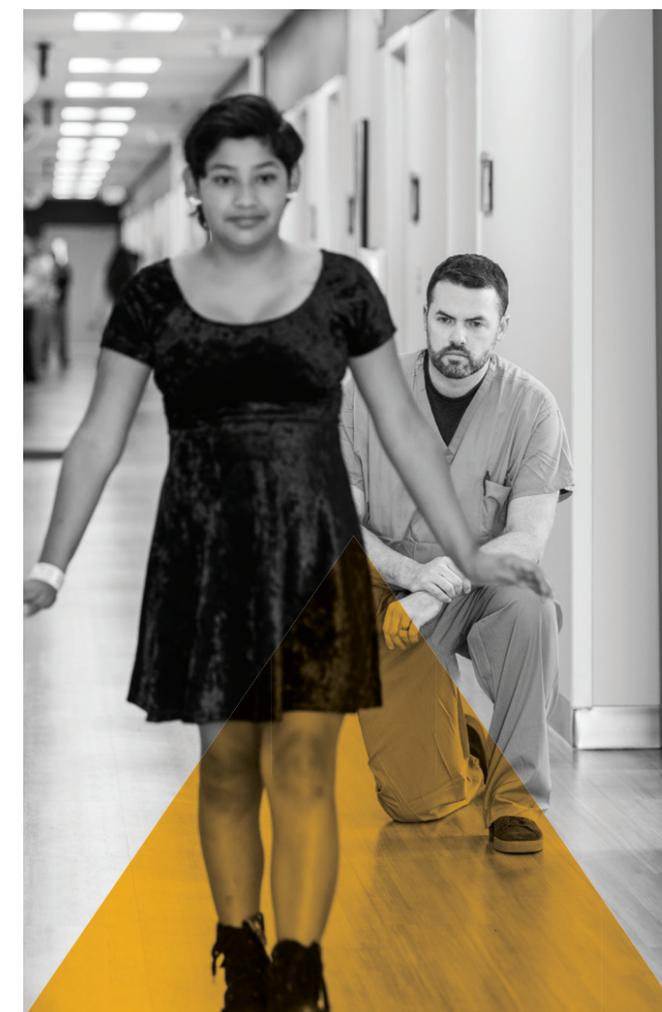
### WHAT'S NEXT?

Rogers and Dr. Donaldson hope to continue enrolling patients as long as they're practicing.

"The biggest thing for us is continuing to get a comparison of quality of life and functional ability before and after their surgery," says Rogers. "It's the idea of saying, 'You start here and then you go up.' That's the goal of the research."

Postoperatively, they plan to follow up with a patient at two weeks, six weeks, three months, six months, one year and two years. They'll have the patient complete the outcomes survey each time, and they'll compare that with the physician assessment.

What's harder to gather is information on how often kids need replacements. That takes years to build. Ideally, they'd like to follow patients for at least 25 years. Over a lifetime is even better.



*Pediatric orthopedic surgeon Nathan Donaldson, DO, thoroughly evaluates and documents a patient's functional ability and quality of life post-surgery.*

This type of long-term assessment could also help them track health-related quality of life. For example, there isn't yet a definitive link between joint replacement and heart health, but Dr. Donaldson says one could assume that kids are more active after a total joint replacement — meaning they might maintain a healthier heart.

Kids go off to college, move away or transition to adult medical care. Historically, that's why this information has been so hard to record. But what Rogers and Dr. Donaldson see so far is, at least for a kid hitting 5 or 10 years out, that survival of the joint is good, and function is good. "The kids — some who are now adults — are all pretty happy with it," says Rogers. ●

# A: Collaboration Is Key

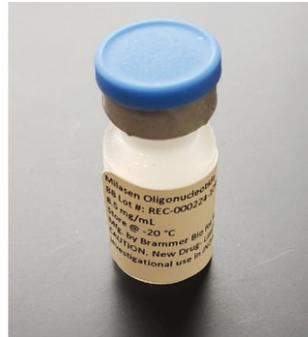
## The Cords That Bind

### CARDIOLOGY

As one of just eight centers in the country participating in Mayo Clinic's Hypoplastic Left Heart Consortium, Children's Hospital Colorado allows pregnant women with a prenatal diagnosis to participate in groundbreaking clinical trials studying stem cell therapy via the collection of umbilical cord blood at birth. With 18 patients enrolled, 5 babies had stem cells

injected during their second HLHS surgery.

The consortium's multifaceted research approach includes imaging and outcomes, human genetics and regenerative medicine, plus a collaboration that facilitates ideation and cross-pollination between researchers from all over the country, decreasing the time from research and discovery to clinical application. Best of all, the multi-site design allows families from all over the country to participate, no matter where they live. ●



Boston Children's Hospital

## FDA Approves First Drug for 1 Person

### NEUROLOGY

9-year-old Mila had perplexing symptoms. Her parents took her to over 100 doctors across the U.S. before they arrived at Children's Hospital Colorado. Genetics specialist Austin Larson, MD, uncovered one of two rare mutations in Mila and diagnosed her with a type of Batten disease only 25 people in the world are known to have.

The location of Mila's second mutation was a mystery until Timothy Yu, MD, PhD, an attending physician and researcher at Boston Children's Hospital, found it hiding in noncoding DNA. With that, he developed a drug solely for Mila to fix her fragmented sequence. It's the first time the FDA has approved a drug for just one person — remarkable progress for precision medicine.

"The drug acts as a molecular patch, allowing the gene to be spliced back together in the proper way," Dr. Yu tells WBUR, Boston's public radio station.

Mila's treatments were initially in Boston, but a growing collaboration between Dr. Yu and Children's Colorado genetic epilepsy specialist Scott Demarest, MD, is now allowing Mila to receive this incredible treatment closer to home. "The fact that Milasen is even possible tells us we have something to aim for and that there's a route we can take to make it accessible to more people," says Dr. Demarest. Using a new machine called Novaseq, Children's Colorado plans to commence its whole-genome sequencing program later this year. ●



## Openhearted

### CARDIOLOGY

Each year, medical professionals diagnose about 42,000 babies in the United States with a congenital heart defect. Yet despite the prevalence of the diagnosis, information on quality of care and surgical outcomes is scarce and confusing to interpret.

Together with Children's Hospital of Wisconsin and Mott Children's Hospital, Children's Hospital Colorado is working with the Pediatric Congenital Heart Association on a website for program-specific pediatric and congenital cardiology data that adhere to uniform tenets like standardized variables and substantiated data.

The goal is not to rank or compare hospitals but to drive conversations between stakeholders. Honest reporting and dialogue are key to improving outcomes, says Jim Jagers, MD, cardiothoracic surgeon and Medical Director of the Heart Institute at Children's Colorado. "When hospitals see other facilities with better outcomes," he says, "it can help them improve their own." ●

## The Mother Whisperer

### Q: Can breathing mitigate the stress of a prenatal diagnosis?

Fetal conditions are stressful. They interrupt families' lives, put new demands on their time and finances, shatter their expectations of what parenthood might be.

That stress has real consequences. In the U.S., about 1 in 7 moms and 1 in 10 dads experiences some kind of perinatal mood or anxiety disorder. In fetal care units, those numbers more than double.

"Most of the mothers in our center are facing very stressful, uncertain situations," says psychologist Allison Dempsey, Director of Behavioral Health Programs at Children's Hospital Colorado's Level IV Neonatal Intensive Care Unit and Colorado Fetal Care Center. "So much feels out of their control."

And what stresses the mother stresses the baby — whose



health, by virtue of their diagnosis, is already fragile. Stress is risk.

Dr. Dempsey is working to counter that risk by teaching mothers how to breathe.

"When you breathe a little slower, a little deeper, your blood vessels dilate, your blood pressure goes down," says Dr. Dempsey. "It calms the autonomic nervous system."

It also increases a phenomenon known as heart rate variability that's been linked to a host of health benefits, most notably stress reduction. Interestingly, heart rate variability decreases naturally during pregnancy. But various studies have shown that biofeedback can help pregnant women increase it, even during the peripartum period.

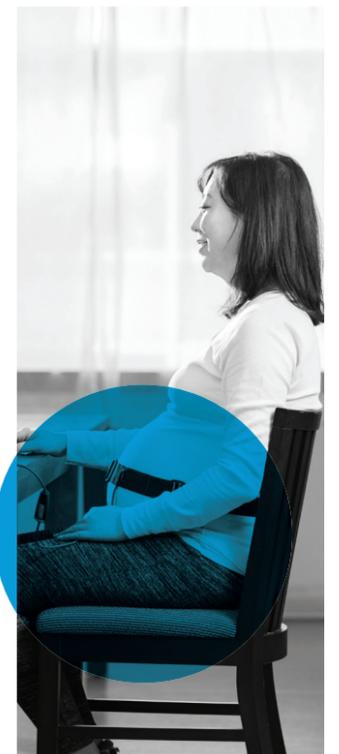
"It's well-established for anxiety," Dr. Dempsey says. "But never in the high-risk population."

For that, Dr. Dempsey is using an established 5-session protocol that focuses initially on helping mothers slow their breathing to about 6 breaths

per minute (the average person breathes at about 12 to 18). In later sessions, patients turn their attention directly to heart rate variability using a variety of programs and games. In one game, for example, patients can clarify a blurry picture by increasing their heart rate variability.

So far, patients have reported lower stress. Dr. Dempsey hopes to quantify her results by recording objective outcomes data — does heart rate variability improve with practice? — as well as more subjective measures of stress, anxiety, depression and post-traumatic stress symptoms. She's also working on a research protocol in which she hopes to follow subjects for at least a year.

"We're giving them something tangible they can use to focus on their physical reactions and change their mental health," says Dr. Dempsey. "It can't just be an afterthought. Mental health affects physical health. We need to address it in real time." ●



One in 7 mothers experiences a perinatal mood or anxiety disorder. In fetal care units, that number doubles.

Above: A prenatal diagnosis is stressful — and stress comes with risks. Dr. Dempsey is working to counter those risks by teaching mothers how to breathe.

# The Comeback Kidneys

**Q: Why does bariatric surgery help protect the kidneys in severely obese youth with type 2 diabetes?**



Treatment methods to impede diabetic kidney disease in obese youth with type 2 diabetes are largely ineffective, save for one: weight loss surgery. Endocrinologist Petter Bjornstad, MD, is working to find out why that is and if there's a way to leverage its effects for patients who can't have surgery.

According to a U.S. renal data system report from 2016, diabetic kidney disease continues to be the leading cause of renal failure in the United States, accounting for approximately 45% of all cases that progress to end-stage and dialysis. At a time when other common causes of end-stage kidney disease are not increasing in prevalence, says Petter Bjornstad, MD, that information is particularly disturbing, because it means more people — more adolescents — are developing type 2 diabetes. And compared to adult-onset type 2, youth-onset type 2 is markedly more difficult to treat.

"We don't know why," Dr. Bjornstad says, "but youth with type 2 have a more aggressive phenotype with greater insulin resistance and more rapid beta cell failure. They also have a higher rate of complications including diabetic kidney disease. And not only higher rates, but also earlier onset. That's scary."

Left: Pediatric endocrinologist Petter Bjornstad, MD, discusses the particulars of his research with bariatric surgeon Thomas H. Inge, MD, PhD.

Two previous, separate studies related to obese youth and type 2 diabetes are the foundation of Dr. Bjornstad's current research to find a better cure for diabetic kidney disease.

One of those studies, led by Children's Colorado pediatric surgeon Thomas H. Inge, MD, PhD, and funded by the National Institutes of Health, is called Teen-Longitudinal Assessment of Bariatric Surgery, or Teen-LABS. It prospectively evaluated outcomes of adolescents who underwent bariatric surgery at one of five U.S. centers.

It was knowledge of this study and its novel findings that led Dr. Bjornstad to hypothesize that youth who undergo bariatric surgery to manage other health impacts might also lower their risk of diabetic kidney disease. A secondary analysis of the data could likely tell him, but he needed a comparison group.

That led him to a study managed by Phil Zeitler, MD, PhD, chief of endocrinology at Children's Colorado, called Treatment for

Type 2 Diabetes in Adolescents and Youth, or TODAY. Funded by the National Institute of Diabetes and Digestive and Kidney Diseases, its purpose was to investigate strategies to achieve durable glycemic control through medical therapy.

After frequency matching the TODAY cohort with Teen-LABS, Dr. Bjornstad had a subset of obese participants from each study to follow for five years.

## THE RESULTS

Focus was on two primary markers: elevated urine albuminuria excretion, or UAE, and hyperfiltration. Both are early signs of diabetic kidney disease.

Elevated UAE means a damaged kidney filtration barrier, and the kidneys release more protein into the urine. Beyond being a marker for kidney disease, it's a strong risk factor for heart disease.

With hyperfiltration, the kidneys filter blood at a supraphysiological rate. That might be due, in part, to the fact that the body is spilling a large amount of sugar, and the kidneys respond by increasing their filtration of the blood — a counterproductive response. It's an energy-expensive process and the kidneys ultimately can't keep up.

**Q: Is surgical therapy a more effective treatment method for diabetic kidney disease than medical therapy in severely obese adolescents with type 2 diabetes?**

### Cohort

**Severely obese adolescents with type 2 diabetes**

BMI > 35

**93 patients** across two cohorts after frequency matching for race, sex, age, ethnicity



### Intervention

#### Teen-LABS

Subset of 30 patients who underwent metabolic bariatric surgery

#### TODAY study

Subset of 63 patients who underwent standard medical therapy with metformin alone or with rosiglitazone or intensive lifestyle intervention with insulin therapy given for glycemic progression

### Results

#### Elevated urine albuminuria excretion (UAE)



#### Hyperfiltration



### Conclusion

Teen-LABS had **27-fold lower odds** of elevated UAE than TODAY and Teen-LABS had **16-fold lower odds** of hyperfiltration than TODAY

**A: Bariatric surgery (Teen-LABS) protects against diabetic kidney disease better than standard medical therapy (TODAY).**

Continued on the following page

The Comeback Kidneys continued

**“It’s incredibly multidisciplinary. Interventional radiology, endocrinology, nephrology, bariatric surgery — all these departments and sections are working together to do innovative research.”**

PETTER BJORNSTAD, MD

After analyzing these markers, the magnitude of his findings was surprising: At five years out, he saw 16-fold lower odds for hyperfiltration and 27-fold lower odds for elevated UAE in those who underwent bariatric surgery compared to the standard medical group.

“We did expect people who underwent bariatric surgery to have better results, because we know it improves blood sugar, we know it promotes weight loss, we know it improves blood pressure, we know it has all these beneficial effects,” says Dr. Bjornstad, “so we obviously expected it to have a more favorable outcome than those who underwent standard medical therapy. But what we didn’t expect was the magnitude of the difference.”

The most obvious next question is, “Why?” And the answer, he says, could propel the industry toward new and better treatments for diabetic kidney disease. Digging deeper offers the opportunity to understand how weight loss surgery helps protect the kidneys.

“Because we don’t know yet. Is it all related to weight loss? No. Is it all related to change in lipids and triglycerides? No. All these things play a role, but they don’t completely account for the difference we saw.”

Not everyone is a candidate for bariatric surgery. If he can figure out what’s causing the difference, maybe there’s a way to mimic the effect that surgery affords.



#### WHERE DO WE GO FROM HERE?

Dr. Bjornstad and his team are forging ahead with the next phase of research, called IMPROVE-T2D, where they’re already enrolling youth who are scheduled for bariatric surgery. Participants will undergo a gold-standard renal physiology assessment both before and after surgery.

From a physiological perspective, researchers will use iohexol clearance to measure glomerular filtration rate — how well the kidneys are filtering blood. And through para-aminohippurate clearance, they’ll measure effective renal plasma flow, or the amount of blood that moves through the kidneys. These methods provide remarkably accurate information about kidney health, but they’re cumbersome and challenging from a technical standpoint.

“Few places currently use these methods in pediatric diabetes, if any,” says Dr. Bjornstad. “I truly don’t know of any other pediatric sites doing this in North America. We’re going one step further and looking at things in a new way. It may be more laborious, but we feel like it’s worth it. And we have the tools to do it right.”

Participants will also undergo a state-of-the-art, functional MRI so researchers can look at how much oxygen is in the kidneys. Then, they’ll look at how much oxygen is being consumed by the kidneys, and they’ll look at the perfusion of the kidneys.

Metabolic factors are also a focus, including measuring beta cell function and insulin resistance. That’s in addition to looking at certain markers of mitochondrial function by metabolomics, looking at the heart, and looking for fatty liver. “So yes,” Dr. Bjornstad says, “it’s an extremely comprehensive assessment.”

But a comprehensive assessment like this will only get them so far.

“We need to know what’s actually going on at the tissue level. We need tissue and we need to leverage the advances that have been made in genetic medicine to really look at the code of the cells to see if we can see the differences or changes that bariatric surgery activates.”

And for that, they’ll work with Children’s Colorado interventional radiologists Patricia Ladd, MD, and Roger Harned, MD, to safely perform ultrasound-guided kidney biopsies. Once they have the tissue, they’ll send it off to measure the single-cell transcriptomics — a process that sequences out individual cells. With each cell, they’ll look at its code to see what genes are turned on and what proteins are translated. “It gives you an amazing chance to really understand what early diabetic kidney disease looks like at a molecular level,” says Dr. Bjornstad.

The biopsies are part of a larger, multicenter project by the NIDDK called the Kidney Precision Medicine Project. Its goal is to build a

kidney tissue atlas to better understand the molecular- and tissue-level differences of different types of kidney disease. Children’s Colorado is the only current participating site that will glean pediatric data.

Overall, it’ll likely be at least another year or maybe even closer to 18 months before they have enough information from IMPROVE-T2D to analyze. Dr. Bjornstad emphasizes that they’ll need to harmonize data collection and analyses with what researchers are doing at other sites so they can compare and contrast. But Children’s Colorado is unique in performing these progressive methods in obese adolescents and young adults with type 2 diabetes.

“And it’s incredibly multidisciplinary,” he says. “Interventional radiology, radiology, endocrinology, nephrology, bariatric surgery — all these departments and sections are working together to do truly innovative research. That’s rare, and it speaks volumes to what our Research Institute is able to do here.”

The research “Effects of Surgical Versus Medical Therapy on Diabetic Kidney Disease Over 5 Years in Severely Obese Adolescents With Type 2 Diabetes” was published in the American Diabetes Association journal *Diabetes Care* in January 2020. ●



## Equal Opportunity Health Record

**Q: Can Epic function as a more efficient research tool?**

*When pediatric urologist Vijaya Vemulakonda, MD, JD, set out to study demographic disparities in hydronephrosis treatment, she had a hard time finding enough data. To get it, she and her team created new capabilities for the electronic health record that could change the paradigm of multi-site clinical research.*

Prenatally diagnosed with hydronephrosis, babies of ethnic minorities get surgery sooner than white ones, often within the first year. That's well documented (1). Vijaya Vemulakonda, MD, JD, wanted to know why.

It's a trickier question than at first it seems.

"We started back in 2016 with a qualitative study, interviewing parents and physicians to understand the decision-making process," Dr. Vemulakonda says. "We realized it's probably the surgeons who are really influencing those decisions. But we also found that there's no clear algorithm that determines the criteria for surgery."

Her early research suggested the role of implicit bias (2), but what wasn't clear was how, or at what point during the process, it came into play. What imaging studies do surgeons order, and how do they

interpret the findings? How do those interpretations influence the decision whether to do surgery, or when?

"Standardizing care may reduce those disparities," says Dr. Vemulakonda. "But you need a robust pool of data to figure that out."

A robust pool of data is difficult to come by when you're dealing with a rare disease like hydronephrosis, which affects between 1 and 5% of pregnancies — just one case in a thousand of which are concerning for uteropelvic junction obstruction.

But the electronic health record is a good place to start.

### "THE NUANCE WE'RE LOOKING FOR"

A massive, near-ubiquitous repository of information on hundreds of aspects of care, the electronic health record has been co-opted for clinical research in hundreds of ways for years. Especially when multiple centers are involved, comprehensive chart review can reveal all sorts of hidden variables and relationships in care.

But that approach has its drawbacks. For one thing, data entry is not consistent across sites or even across providers. Different institutions use different codes. Even the codes themselves can be applied inconsistently.

"Hospital-level coding doesn't have the nuance we're looking for," says Dr. Vemulakonda. "We care about how the surgeon interprets the images and makes decisions. It's difficult to get that kind of insight with chart review."

It's also difficult to do.

"For example, providers in Urology at Children's Colorado write notes in Epic using a feature called Smart Lists," says Josiah Schissel, a clinical informaticist at Rady Children's Hospital in San Diego. "At Rady, our providers use a whole different paradigm."

That variation means researchers like Dr. Vemulakonda need informatics people like Schissel to identify the right information and technical professionals to build programs to extract it — at every site.

That demand on resources can be a major obstacle to mining quality data. It certainly was for Dr. Vemulakonda and her research partners at Rady, Texas Children's Hospital, University of Virginia Hospital and Yale New Haven Hospital. And it would make the study difficult to expand to other sites. But other sites would be essential to gathering the type and amount of data they needed.

Dr. Vemulakonda and Schissel wondered if the process could be simpler. What if you could build a research-specific module right into the electronic health record? Instead of a retrospective

*Continued on the following page*

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VIJAYA VEMULAKONDA, MD, JD

*Equal Opportunity Health Record* continued

chart review, they could gather clinically relevant data prospectively, asking surgeons to plug it in while they were already charting anyway.

As a former chair of the Pediatric Urology Steering Board for the electronic health record company Epic, Dr. Vemulakonda had some experience partnering directly with the software developer on clinical data solutions. But she also knew from experience that it could take years to see an idea like that actually implemented and rolled out.

So she and Schissel built it themselves. They defined their data elements and standardized them into a kind of “data dictionary” that allows easy aggregation from any institution.

“As far as we know,” she says, “we’re the first group to create these kind of customized templates to capture surgical data.”

## INTEGRATING RESEARCH INTO DAILY PRACTICE

The templates they built are allowing them to follow a very small cohort of infants who get pyeloplasty over time. The goal: evaluating variations in practice, how those variations inform surgical decisions, and how variations in decisions and timing affect outcomes over time. The study is up and running at three sites now, with two more coming online soon.

But the beauty of the study design is that it really allows any site to participate, with minimal investment on the front end.

“We took a lot of time working with Epic to build out the data elements necessary for the research, to make it shareable with other organizations,” says Schissel. “It’s a lot of front-end work, but when someone on the other side of the country wants to participate, the ease of integration makes it worthwhile.”

“We can just send them the data capture tool,” says Dr. Vemulakonda. “It’s easier to get up and running than chart review,

and we’ve gotten rid of all these issues with data quality, because we’re not using administrative data to answer clinical questions.”

Indeed, compared to traditional chart review in a random 10% sample, the correlation is strong (3)(4) — at a fraction of the time and expense.

“We’re integrating research into daily practice,” she says. “It’s just checking buttons.”

It’s an approach that could apply to a wide variety of research questions across clinical specialties, pulling together research groups from all over the country.

In the Department of Urology at Children’s Colorado, clinicians and researchers are already starting to apply it: to identifying predictive factors of patient no-shows (5); to better understanding and leveraging practice patterns around pediatric urologic consultation (6); and to studying health equity barriers to accessing patient healthcare portals (7) — just to name a few.

And ultimately, it has implications far beyond urology and even health equity, extending throughout the entire pediatric field. Already, Schissel is adapting the platform to four other research projects between Rady and Children’s Colorado.

“The problem with rare disease — and that’s really what we deal with in so much of pediatrics — is that no single center can generate enough data to know what best practice is,” says Dr. Vemulakonda. “That’s what we’re trying to find out.” ●

## RESEARCH PARTNERS

George Chiang, MD, Rady Children’s Hospital San Diego  
 Josiah Schissel, Rady Children’s Hospital San Diego  
 Nicolette Janzen, MD, Texas Children’s Hospital  
 Sean Corbett, MD, University of Virginia Hospital  
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# A Drop in the Bucket

## Q: Is there a better way to identify measurable residual disease?



Children’s Colorado pediatric oncologist and hematologist Amanda Winters, MD, PhD, is using a special type of polymerase chain reaction called digital droplet PCR, or ddPCR, to more reliably identify MRD in acute myeloid leukemia.

Despite aggressive and highly toxic chemotherapy, measurable (or minimal) residual disease, or MRD, is seen in a variety of cancers and has become a powerful tool to predict relapse and survival in patients with leukemia. These leukemia cells that stick around after treatment are the likely cause of most relapses within five years of diagnosis.

Pathologists in the U.S. currently identify a majority of MRD with flow cytometry — a method that allows for detection of 1 in 10,000 leukemia cells by identifying two or more proteins that are never expressed together on normal cells. Pathologists in Europe use other molecular methods, but the goal of these techniques is the same: to more accurately measure the disease that predicts relapse.

Flow cytometry helps risk stratify patients in a far more accurate way than is possible using a microscope, the historical way to detect disease. In fact, hundreds of papers describe different groups of patients for whom flow cytometry has consistently proven to be a predictor of relapse-free survival. But there’s something it doesn’t take into account.

“Cell surface markers can change over time, particularly after leukemia cells have seen chemotherapy or immunotherapy,” says Children’s Colorado pediatric oncologist and hematologist Amanda Winters, MD, PhD. “This makes it difficult to distinguish a malignant white blood cell population from a variety of normal ones.”

She says a more reliable way to identify MRD is to measure abundance of leukemia-associated mutations, which are not present in normal cells.

To accomplish this, she’s working in collaboration with Dan Pollyea, MD, MS, a leukemia physician at UCHHealth, and in the lab of Craig Jordan, PhD, a leukemia researcher at the University of Colorado, to create a special type of polymerase chain reaction called digital droplet PCR, or ddPCR. It’s highly sensitive and can detect one mutant gene copy in 10,000 to 100,000 copies. That’s at least as sensitive as flow cytometry, says Dr. Winters, and it’s often much easier to interpret.

The effect the ddPCR creates is similar to a typical PCR, except that, as the name implies, it emulsifies into individual

droplets when it combines with an oil, capturing individual copies of DNA in each droplet. Different color fluorescent tags help distinguish the mutant versions of the gene from the normal, or wild type, allowing Dr. Winters to calculate abundance of mutant DNA.

So far, she’s been able to validate more than 60 mutation-specific ddPCR assays to identify MRD in a cohort of adult patients with acute myeloid leukemia. She says these assays can differentiate patients who will ultimately relapse from those who have lower relapse risk based on presence or absence of acute myeloid leukemia mutations. She also sees the same correlation between MRD status and outcomes in these adult patients after a bone marrow transplant.

On the pediatric side, although some patients with acute myeloid leukemia have overlapping mutations with adults, most have chromosomal translocations that adults don’t have. An important next step in the research is for Dr. Winters to design ddPCR assays for these translocations so that she can more reliably monitor MRD in pediatric patients. ●

*A digital droplet polymerase chain reaction, or ddPCR, is similar to a typical PCR, except that it emulsifies into droplets, capturing individual copies of DNA in each droplet.*

# New Paradigm

## 4 Studies in: Cystic Fibrosis



When it comes to Trikafta, pediatric pulmonologists Scott Sagel, MD, and Edith Zemanick, MD, don't mince words.

"It's the best treatment for cystic fibrosis ever," says Dr. Sagel, "no question."

"It's a breakthrough," echoes Dr. Zemanick. "The most effective we've seen."

Approved by the FDA in late 2019, Trikafta combines three rescue therapies for the cystic fibrosis transmembrane conductance regulator, or CFTR, the defective protein that results from the more than 1,900 mutations implicated in CF. By targeting F508del, the most common mutation, Trikafta substantially improves CF markers like sweat chloride, lung function and rates of infection. And once it's approved for patients younger than 12, it's expected to work for 90% of them.

That kind of broad efficacy represents a paradigm shift for specialists at Children's Hospital Colorado, the largest CF referral center in the nation. Which means the work of clinician-researchers like Drs. Sagel and Zemanick is far from done.

*The research: four major Cystic Fibrosis Foundation-sponsored, multicenter studies that aim to better understand Trikafta's biology and long-term effectiveness — and zero in on the next paradigm.*

### 1 PROMISE

CF impacts organ systems throughout the body, from the lungs to the sweat glands to the digestive tract. The clinical trials for Trikafta measured clinical outcomes including lung function, growth, pulmonary exacerbations and patient reporting on quality of life. But they didn't study many comorbidities, including airway infection, mucus biology, liver disease and CF-related diabetes, to name a few.

The PROMISE study, nationally co-led by Dr. Sagel and pediatric hepatologist Michael Narkewicz, MD, digs deeper. By analyzing sweat, blood, sputum, urine and bronchoalveolar lavage fluid samples from more than 400 patients at 50 national sites, investigators are

gathering a detailed picture of Trikafta's effects on organ systems throughout the body. Children's Colorado's two Cystic Fibrosis Foundation-designated National Resource Centers, the Center for Biochemical Markers and the Center for Sweat Analysis, will process and analyze samples focused on systemic inflammation and sweat chloride measurements.

### 2 CHEC-SC

Clinical trials for Trikafta showed the treatment produced a reduction in sweat chloride, the marker by which CF is diagnosed. Nationally co-led by Dr. Zemanick, the CHEC-SC study is enrolling more than 5,000 patients nationwide to understand: 1. The factors that contribute to that reduction,

and 2. How sweat chloride values relate to long-term outcomes.

"If we can understand how well the patient is responding to these modulators," says Dr. Zemanick, "maybe we can reduce the burden of treatment."

### 3 SIMPLIFY

That burden is enormous. Patients spend one or two hours just breaking up airway mucus — every day.

The SIMPLIFY study will examine the possibility of safe withdrawal from standard of care therapies like inhaled mucolytics. Along with studies like PROMISE and CHEC-SC, SIMPLIFY aims to reduce the time patients spend dealing

with CF. "We've never been able to consider taking patients off therapies," says Dr. Sagel. "This is the first time we think the burden of treatment is going to go down."

### 4 RARE

Ninety percent efficacy leaves 10% of patients behind. Dr. Sagel doesn't mince words about that, either: "It's not good enough. We need 100% of patients on highly effective treatment."

As one of six national site leaders for the RARE study, Dr. Zemanick is collecting cells from patients with rare mutations to put toward a national culture bank that will be used to test and ID potential new therapies for future development. ●

## A(:) List Recent awards and accolades



### Vijaya Vemulakonda, MD, JD UROLOGY

*American Urological Association Rising Stars in Urology Research Award*  
When Children's Colorado pediatric urologist Vijaya Vemulakonda, MD, JD, won an Agency for Healthcare Research and Quality career development award two years ago, it made her eligible for the American Urological Association's Rising Stars award: up to five years of supplemental salary support for ongoing research. She was one of two winners in 2019, and the first pediatric urologist to win this award since its inception. *Dr. Vemulakonda's research is featured on p. 15.*



### Amy Brooks-Kayal, MD NEUROLOGY

*American Epilepsy Society Founder's Award*  
The American Epilepsy Society's 2019 Founder's Award went to Amy Brooks-Kayal, MD, Chief of Pediatric Neurology at Children's Hospital Colorado. The society's most prestigious distinction, this \$10,000 award recognizes a lifetime body of work in epilepsy, including the dozens of field-leading research projects Dr. Brooks-Kayal conducts, mentors and oversees.



### Ron Sokol, MD DIGESTIVE HEALTH INSTITUTE

*Peak of Excellence Award presented by The American Liver Foundation*  
The Pediatric Liver Center at Children's Hospital Colorado was one of the first of its kind in the U.S. As one of its key founders, and current Chief of Pediatric Gastroenterology, Hepatology and Nutrition, Ronald Sokol, MD, has been a National Institutes of Health-funded investigator since 1986, and has received more than \$200 million in support in that time. He's helped untold numbers of kids with liver disease. The American Liver Foundation's Peak of Excellence Award recognizes the accomplishments of his long career.



### Center of Excellence: Obstetric Anesthesiology FETOLOGY

*The Society for Obstetric Anesthesia and Perinatology*  
This year, the Society for Obstetric Anesthesia and Perinatology — or SOAP — designated Children's Hospital Colorado a Center of Excellence, one of the most prestigious accreditations in obstetric anesthesiology care. This award recognizes a range of exacting criteria, from the experience of our providers to our use of evidence-based protocol, setting a higher benchmark for care nationwide.

## The Best Is Yet to Come



### Danielle Soranno, MD NEPHROLOGY

Pediatric nephrologist Danielle Soranno, MD, is an innovator and a collaborator. Her involvement in no less than eight ongoing, multidisciplinary research studies — from hydrogels to metabolomics to sex as a biological variable in cardiorenal disorders — is a testament to that. An NIH-funded investigator with an impressive list of accolades, including a career development award, Dr. Soranno is one to watch.



### Anandani Nellan, MD CANCER

The body doesn't like uncontrolled inflammation. That's one of the reasons CAR T-cells haven't worked in brain tumors, suspects pediatric neuro-oncologist Anandani Nellan, MD, MPH: The activity of the CAR T-cells attracts myeloid cells that inhibit them from killing the tumor. Working with two small animal models of ependymoma developed by her mentor, neuro-oncologist Nick Foreman, MD, Dr. Nellan is studying the immune microenvironment of ependymoma-targeting CAR activity with the goal of getting clinical trials online within two years. And with the capability to produce novel CARs in-house, she'll be one to watch.



## 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 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](http://childrenscolorado.org/SpecialtyNews)



## Hear our view

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, iTunes, Google Podcasts and Google Play**



## Ranked among the best of the best

Children's Colorado earned a spot among the best-of-the-best children's hospitals on the Honor Roll, and for the first time ranked in the top 20 in all ten recognized specialty areas.



## 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's Department of Pediatrics is ranked sixth in the nation by *U.S. News & World Report*, and is among the National Institutes of Health's top-funded research institutions.



## Cath Mods

A commercial low-radiation cath lab setup has a lot of capability. Rotational angiography, for example, can allow all the detail of a CT scan at a fraction of the time and radiation. Pediatric interventional cardiologists Jenny Zablah Alabi, MD, and Gareth Morgan, MD, knew they could make the system do even more. So Dr. Zablah manipulated the software to process the images in a novel way that lets her print 3D models right in her office. "The company that created this system," she says, "they don't know half the potential it has for congenital heart disease."

See what they're doing at Children's Hospital Colorado in the next issue of Q: