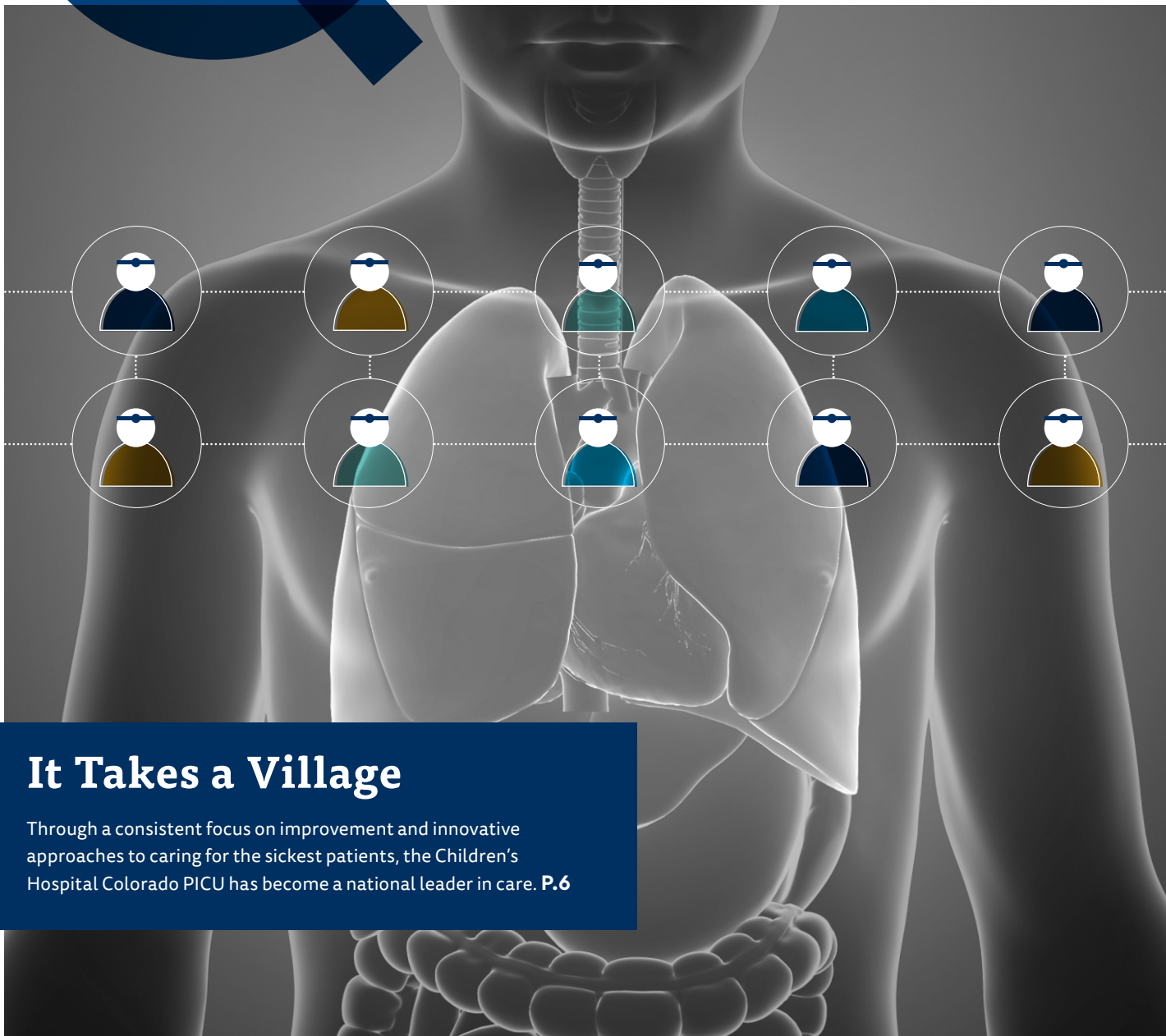




ISSUE 12 • FEBRUARY 2023



Advances and Answers in Pediatric Health



It Takes a Village

Through a consistent focus on improvement and innovative approaches to caring for the sickest patients, the Children's Hospital Colorado PICU has become a national leader in care. **P.6**

10 | THE BIONIC PANCREAS

Children's Colorado researchers participated in a 13-week trial of an artificial pancreas used for managing Type 1 diabetes. The results could have a major impact on care.

12 | A CLEARER PICTURE

Researchers at Children's Colorado are exploring the benefits of using MRI scans and a quantitative risk scale to diagnose serious placenta issues in pregnant patients.



Children's Hospital Colorado



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Anschutz Medical Campus

It starts with a Q:

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

Dear colleagues,

In Colorado, and nationwide, kids are struggling. Even before the COVID-19 pandemic exacerbated mental health issues among young people, the mental health crisis had already been building. In fact, in 2019, suicide was the leading cause of death among people ages 10 to 24 and rates of depression, anxiety, thoughts of suicide and behavioral health emergency room visits were rising. Since the start of the pandemic, these numbers have continued to grow in scale.

So, we are committed to building a more solid foundation for addressing mental health, and its connection to physical health, in Colorado and beyond. In May 2021, Children's Hospital Colorado declared a state of emergency for pediatric mental health — a first for Colorado. Although I started as the inaugural Mental Health In-Chief in 2021, Children's Colorado has long been working to address this emergency, and I look forward to the opportunity to implement some of our most transformative interventions in 2023.

As part of our strategic vision and plan, we will focus on advancing a coordinated child- and family-centered system of care alongside a collaboration of local, state and national partners. Together, we will help ensure equitable access to high-quality, evidence-based care and prevention. This means expanding access to outpatient specialty mental health care and redesigning crisis services to focus on early identification and connecting kids and families to care close to home. It also means partnering with school districts, primary care providers and other healthcare professionals, and embedding mental health expertise where kids and families live, learn and connect.

As we build a better mental health future for our kids, we are focused on four key areas:

1. Build, strengthen and diversify our mental health workforce.
2. Increase access to purpose-built care environments and technology.
3. Integrate best-in-class research and innovation into clinical practice.
4. Invest in family support, engagement and advocacy programs.

Looking ahead in 2023, we will be focused on lending our expertise across Colorado and the country as a leader in pediatric mental health. Now is the time to build a better system of mental health care and future for our children.

Best regards,



K. RON-LI LIAW, MD

Cannon Y. and Lyndia Harvey Chair in Child and Adolescent Psychiatry Chair, Pediatric Mental Health Institute
Mental Health In-Chief, Children's Hospital Colorado
Visiting professor, vice chair Diversity Equity and Inclusion
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Explaining the Unexplained

PULMONOLOGY

Sudden unexplained infant death (SUID) has perplexed both parents and physicians for decades. While rates have dropped since the early 1990s, thanks in part to greater public education, the U.S. still records 3,400 SUID deaths annually, according to the Centers for Disease Control and Prevention.

The persistence of SUID as a public health issue is of great interest to Children's Hospital Colorado's physician scientist Csaba Galambos, MD, PhD. Dr. Galambos is currently working on his study on SUID, which builds upon his past findings of improper lung vascular development that leads to SUID. He's undertaking this work with support from a team of researchers, including Steve Abman, MD, Director of the Children's Colorado Pediatric Heart Lung Center.

Dr. Galambos and his team already understood that hypoxemia, or fatally low blood oxygen levels, could cause SUID, but the lung-related microanatomical mechanisms contributing to that hypoxemia remained unclear.

His findings bring those mechanisms to light. Specifically, Dr. Galambos' research shows how abnormal or underdeveloped lung growth can lead to the recruitment of bronchopulmonary anastomotic vessels, which cause blood to bypass the lungs' gas exchange units and return, deoxygenated, to the heart. This results in hypoxemia and sudden death. In fact, tissue examination revealed evidence of underdeveloped pulmonary vasculature in 80% of SUID cases researched.

Overall, the study proposes that impaired distal lung growth and prominent intrapulmonary shunt vessels are two contributing factors to SUID, and that these factors may be identifiable in some infants before they become catastrophic. This could significantly advance what we understand about SUID, considering that the devastating phenomenon remains difficult to recognize or explain.

These findings require confirmation by larger studies, but it's an important step in paving the way for interventional strategies that could prevent impaired lung development and reduce sudden infant death worldwide. ●



Bouncing Back

ORTHOPEDICS

In the past, posterior spine fusion, a surgery for scoliosis patients that entails fusing vertebrae to straighten the spine, required patients to wait six to 12 months before returning to sports. Researchers have raised concern about the impact of such a long recovery period on adolescents' quality of life.

So when Children's Hospital Colorado's Sumeet Garg, MD, noticed adolescents healing much faster with modern techniques, he wondered if they could be cleared for sports sooner. "We saw how good they looked, and said, 'There's no reason to restrict them,'" Dr. Garg explains.

He led a study on student athletes to determine whether kids could indeed get back to sports sooner than previously believed. Researchers prospectively enrolled 26 patients between the ages of 10 and 18 who had idiopathic scoliosis — scoliosis without an identified cause — with an angle between 40 and 75 degrees. The study showed that after surgery, patients returned to sports at a median rate of 2.7 months, and all but two returned within one year following surgery.

"I don't think patients are surprised, because they're feeling good a month or so after surgery. They feel like they are strong enough to start again," Dr. Garg says.

This is the first study on pediatric scoliosis recovery using PROMIS scores, a patient-reported health assessment that considers physical, mental and social well-being. His pioneering research study evaluated factors such as change in physical activity scores after surgery, the extent that pain interfered with playing sports and change in depressive symptoms.

In addition to helping scoliosis patients return to sports sooner, which improves their quality of life in numerous ways, this research provided a basis for Dr. Garg to use patient-reported assessments across his work in pediatric orthopedics. "Now every patient that walks into my office gets those same scales done, just as part of their care," he says. ●

Rare Disease, Rare Expertise

Q: How do Children's Hospital Colorado cardiac anesthesiologists make administering anesthesia safer for kids with a rare genetic disorder?

Only about 50 people in the world have been diagnosed with multisystem smooth muscle dysfunction syndrome, or MSMDs. Providers at Children's Hospital Colorado have cared for four of them through 25 to 35 procedures. MSMDs is an incredibly rare genetic mutation that impacts actin, one of the key proteins that makes up smooth muscle throughout the body. As a result, patients experience complications anywhere smooth muscle is found, from their vasculature and intestines to their bladder and eyes. The condition is particularly tricky when it comes to anesthesia, something patients often need due to the complicated and widespread effects of MSMDs.

The primary concern when it comes to administering anesthesia to kids with MSMDs is that anesthesia can cause changes in blood pressure. When a healthy child undergoes anesthesia, their body compensates for drops in blood pressure by signaling smooth muscle to squeeze. But because MSMDs weakens the smooth muscle in blood vessels, these patients are prone to dangerous

blood pressure drops that reduce blood flow to their organs. What's more, MSMDs often causes abnormalities of the blood vessels around the heart and to the brain, increasing patients' risk of stroke or aneurysm while under anesthesia.

"These kids have extremely complex anatomy and physiology. So, we've got a child that's going to need multiple anesthetics in their life and is at risk of complications during anesthesia," says cardiac anesthesiologist Nicholas Houska, DO. "It's really a perfect storm."

That's why their multidisciplinary care team always includes a pediatric anesthesiologist like Dr. Houska or Richard Ing, MD. Their role is to not only create and implement tailored anesthesia plans for kids with MSMDs, but also to maintain communication with the various other specialists caring for each patient to make sure all concerns are addressed.

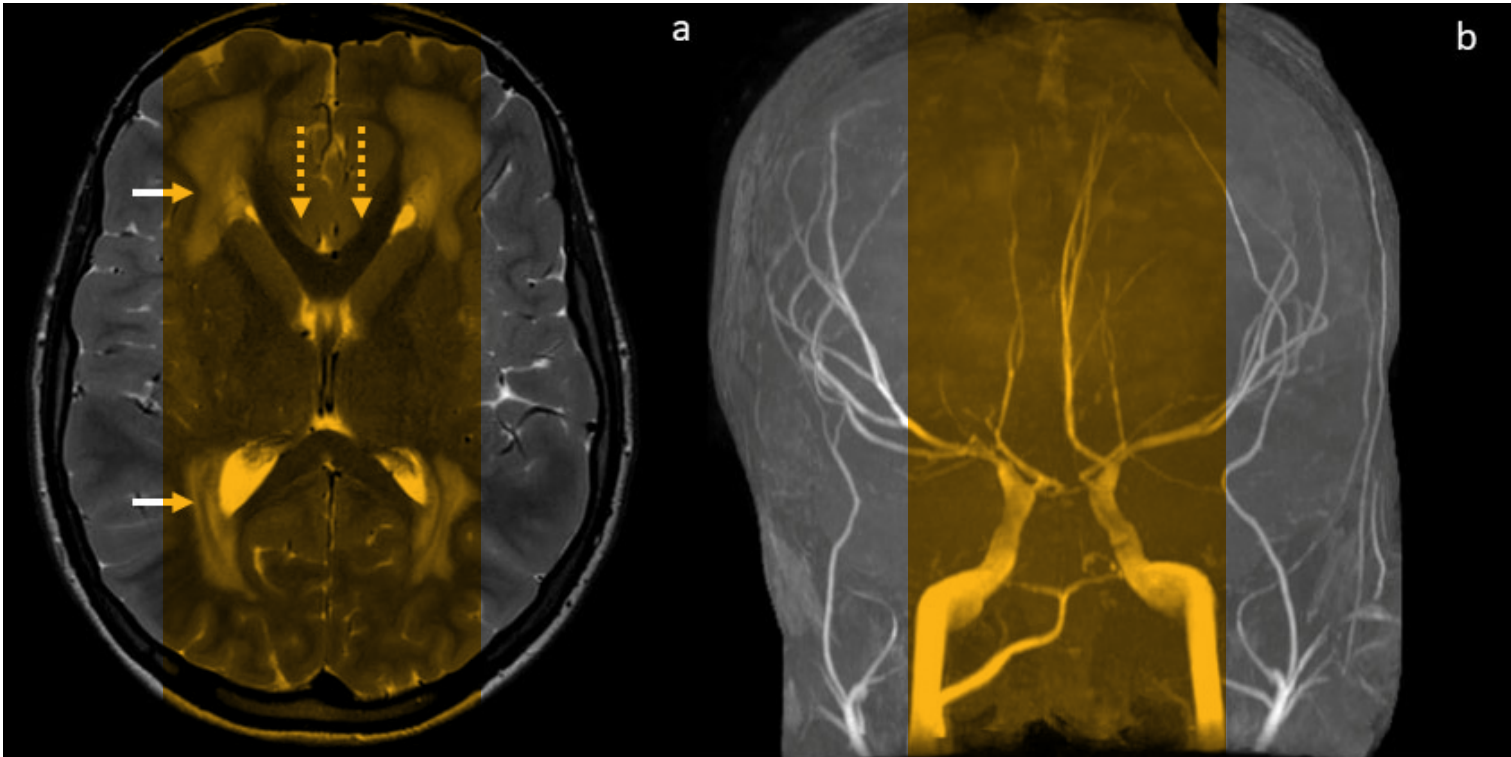
The work starts before surgery begins. The team consolidates as many procedures as possible into one single anesthesia experience and considers complications that could arise based on the patient's current medical concerns and therapies. Additionally, the team works with caretakers to ensure patients get plenty of clear fluids before procedures, as dehydration can further lower blood pressure.

Drs. Houska and Ing also work with Children's Colorado's child life specialists to get an accurate blood pressure reading before administering anesthesia. The specialists help coach the patient to a calm state, which can be challenging given the stressful nature of procedures. This is critical, as knowing each child's "normal" blood pressure allows the team to monitor changes once the patient is under anesthesia.

During the procedure itself, the anesthesiologist watches for changes in blood pressure, or signs of poor blood flow to organs such as the brain, lungs or kidneys. The work is complex, and with so few cases to study, it is particularly difficult to know what to expect. So far, the team has learned a significant amount through the various procedures they've assisted with on kids with MSMDs, and according to Dr. Ing, this experience combined with the team's ability to seamlessly collaborate across disciplines has made a noticeable difference in care.

"What we do know is that when children with cardiac disease are cared for by a team that is trained in the multidisciplinary approach to congenital heart disease, the outcomes are usually a little better," he says.

For these kids in particular, that experience has allowed cardiac anesthesiologists to better devise care plans that reflect each child's individual needs, says Mark Twite, MD, Director of Pediatric Cardiac Anesthesia at the Children's Colorado Heart Institute.



The first image shows abnormalities in the white matter, or deep tissues, of the brain in children with MSMDs. The second image shows abnormal distension of the carotid arteries entering the brain and straightening of the major arteries in the brain in kids with MSMDs.

"It's like tailoring a suit," says Dr. Twite, who also serves as president of the Congenital Cardiac Anesthesia Society. "You have the same pattern for the suit, but a good tailor will trim it to fit you exactly."

And because the team at Children's Colorado has some of the most robust experience in the country treating kids with MSMDs, they are dedicated to sharing their knowledge with the larger community. Drs. Houska and Ing have published all their data, care recommendations and experiences working with these patients in a case review series that was shared in the *Journal of Cardiothoracic and Vascular Anesthesia* (1).

Ultimately, this highly specialized work, requiring quick thinking and a deep, involved understanding of each patient's care across the spectrum of disciplines, is the work that Children's Colorado's pediatric cardiac anesthesiologists do best. The team of eight are committed to caring for the most complex cases, including kids with MSMDs.

"I think what distinguishes the pediatric cardiac anesthesia team is the acuity and the complexity of our patients," Dr. Twite says. "Working together in a multidisciplinary team within the Heart Institute enables us to provide excellent perioperative care." ●

1. Houska, Nicholas et al. "Anesthetic Considerations for Children with Multisystem Smooth Muscle Dysfunction Syndrome and Review of the Literature." *Journal of cardiothoracic and vascular anesthesia* vol. 36,8 Pt B (2022): 3205-3211. doi:10.1053/j.jvca.2022.04.019.



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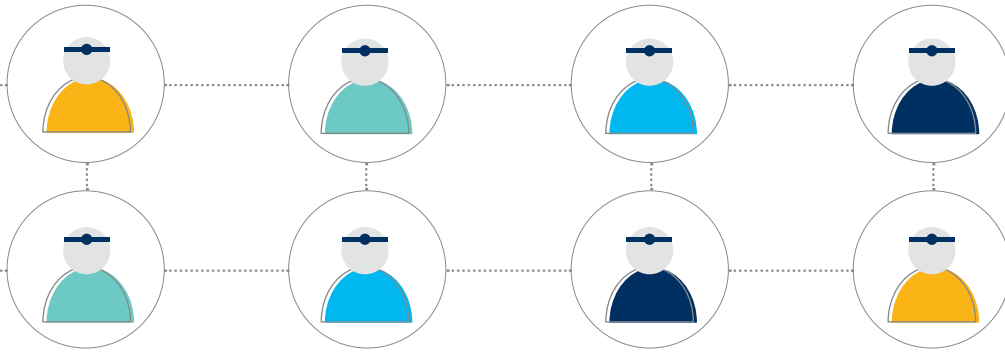
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It Takes a Village

Q: What makes the Children's Hospital Colorado PICU so successful when it comes to saving even the most critical patients?

In late 2021, the Children's Hospital Colorado pediatric intensive care unit (PICU) took on a case that wasn't rare, but was remarkable. The patient was a 15-year-old girl who sought care at Children's Colorado for COVID-19. When she arrived, she had an oxygen saturation in the 70s, pneumonia, a pulmonary embolism and needed to be intubated. Her case was so severe, the team wasn't sure she'd survive.

At the beginning of the patient's stay she was incredibly weak and could barely lift her pinky, says Aline Maddux, MD. Dr. Maddux was the primary PICU provider assigned to the patient, and it was her job to coordinate a multidisciplinary care team in seeking solutions to the complex case. To give the patient her best shot at

survival, the team employed a support machine called veno-venous extracorporeal membrane oxygenation, or VV-ECMO, which takes blood from the body, oxygenates it, removes carbon dioxide and feeds the blood back into the venous system. Where most pediatric hospitals would require that the patient remain sedated with a breathing

tube while on ECMO, the Children's Colorado ECMO and PICU teams took a different approach. Fearing that a tracheostomy and a respirator would cause more damage to the patient's sick lungs and prolong rehabilitation, the team made the bold decision to allow her to remain awake and active while on ECMO.

"She could eat, she could talk and she could participate more with rehab," says Michele Loi, MD, who serves as the PICU's Director of Quality Improvement. "Our PICU attendings spoke to several centers to gather information from adult colleagues on what they were doing and then ended up with this care plan that we carried out for several patients. This is very, very novel, especially on the pediatric side."

According to Drs. Loi and Maddux, this approach was valuable not only in aiding physical recovery, but also in preserving the patient's mental health. While her lungs were healing, the patient was able to see friends and family, visit other units to partake in therapy sessions (like baking

STANDARDIZED MORTALITY RATIO (PRISM III)

Our patients are sicker, but they survive at a higher rate than expected.

STANDARDIZED LENGTH OF STAY (LOS) RATIO (PRISM III)

Our patients are sicker, but they leave the PICU sooner than expected.



CAMERON GUNVILLE, DO, MED

Medical Director of PICU, Co-Medical Director of Children's Hospital Colorado Advanced Practice Fellowship, pediatric intensivist, Children's Hospital Colorado

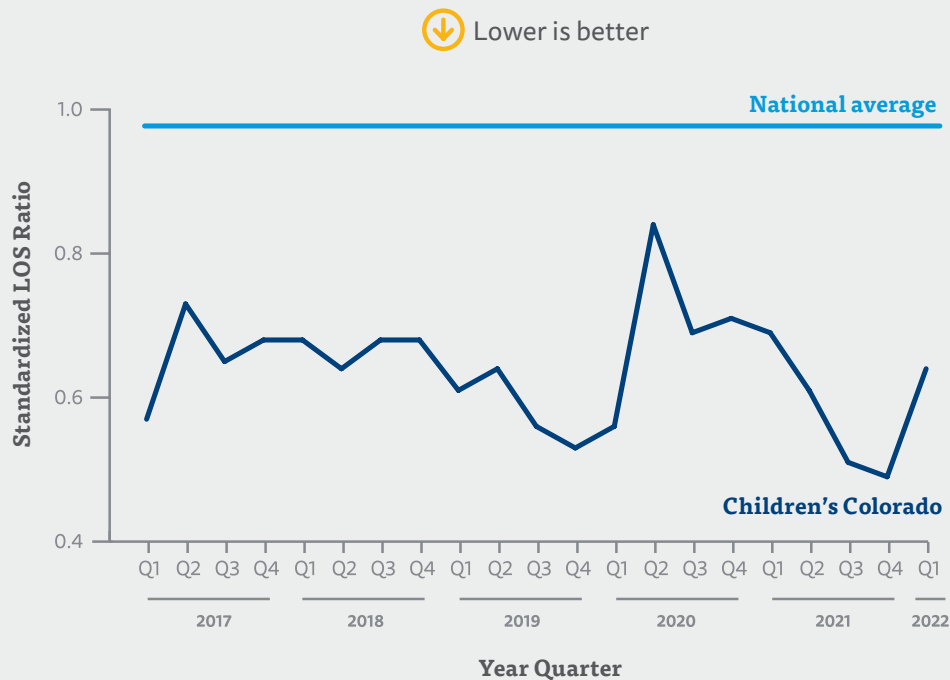
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MICHELE LOI, MD

Quality Director of the PICU, Co-Chair of PICU Morbidity and Mortality Committee, pediatric intensivist, hematologist/oncologist, Children's Hospital Colorado

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ALINE MADDUX, MD, MSCS

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Associate professor, Pediatrics-Critical Care Medicine, University of Colorado School of Medicine

Continued on the following page

It Takes a Village continued

The axis of excellence

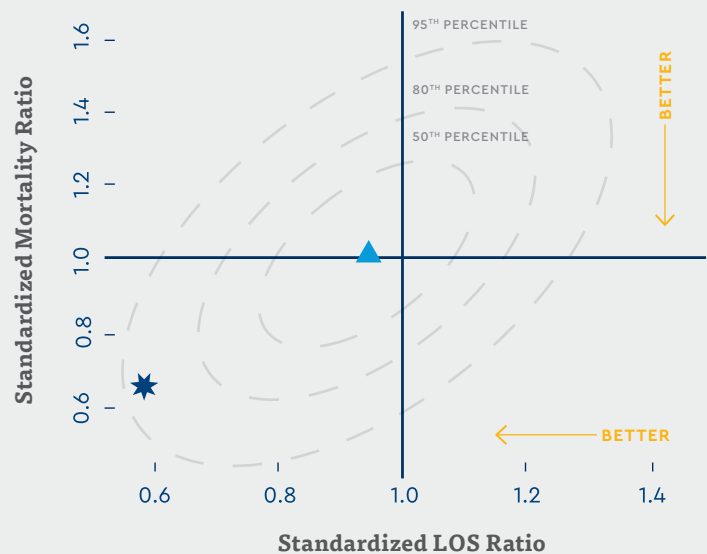
Plotted out with standardized mortality ratio on the y-axis and standardized length of stay ratio on the x-axis, our PICU plots in the lower-left quadrant as measured against national averages. We're in the 95th percentile for both.

★ Children's Colorado

▲ National average

4/1/2019-3/31/2022

STANDARDIZED MORTALITY RATIO (PRISM III) VERSUS STANDARDIZED LENGTH OF STAY (LOS) RATIO (PRISM III) PLOT ACROSS ICUS



brownies in the rehabilitation baking area), and share her ups and downs with providers. This focus on mental well-being isn't always a standard of care in PICUs, often because patients are there for short stays or are unconscious for long periods of time. But Dr. Maddux says it made an incredible difference — enough to change her approach to future patients.

"When our patients are on such significant support as she was on, they're usually not able to interact with us. And so, the only interaction we have is with their family and not directly with the individual because they can't talk to us.

But she could," Dr. Maddux explains. "We understood what she was thinking, what she was feeling, what she was struggling with, and the obstacles and challenges that she was overcoming."

To address these complex needs, Dr. Maddux held weekly meetings with over a dozen specialists from teams across the hospital, including occupational therapy, physical therapy, speech-language therapy, rehabilitation, pulmonology, child life, social work and the ECMO team. The meeting allowed each member of the patient's care team to not only update others on their specific area of treatment, but

also collaborate to address both physical and mental health needs and obstacles.

From utilizing an entire ECMO team (including cardiologists, cardiothoracic surgeons, interventionalists and ECMO specialists) who strategized constantly about her care and working with the early mobilization team to help keep her strong, to addressing the psychosocial well-being of both the patient and her family, the job of saving this patient truly took a village. And after several months in the PICU, she was well enough to return home just in time to attend her school's prom.

AN EYE TOWARD IMPROVEMENT

While this case is, in some ways, an outlier, it's also a testament to the work the PICU has undertaken in recent years to focus on quality and process improvement. According to Dr. Loi and Cameron Gunville, DO, Medical Director of the PICU, these efforts contributed significantly to this patient's positive outcome and have helped the Children's Colorado PICU establish itself as a national leader in pediatric critical care. The team has found such success in focusing on constant improvement that it leads its peers in both

standardized mortality ratio, which measures mortality against illness severity, and standardized length of stay ratio, which measures the length of stay against illness severity.

For this particular patient, numerous innovative approaches to care came together to build a successful outcome, starting with collaboration. According to Dr. Maddux, the sheer amount of time, energy and thought invested by so many different team members made all the difference in the 15-year-old's recovery.

Dr. Gunville agrees: "It took huge coordination between the medical providers, nursing staff, the respiratory therapists, social workers, pharmacists, child life specialists and more. It takes so many people to collaborate and put all their effort into one person," he says. "I think that's why we're as successful as we are. We have multiple teams that we work with and collaborate with in a multidisciplinary way. I think that's hugely important."

Beyond that indefatigable team effort, the patient also benefited from several nurse-led projects aimed at harm reduction and quality improvement. Led by Dr. Loi and nurses Sara Galt, RN, and Liz Diaz, RN, team members meet regularly to discuss potential concerns

and strategize ways to address them. Recent projects have focused on reducing pressure injuries, bloodstream infections and UTIs caused by Foley catheters. Though avoidance is hard to measure, Dr. Maddux is confident that each moment of extra care resulting from such projects contributed to getting her patient home as quickly and safely as possible.

Additionally, the team made successful use of a new approach to care known as early mobilization. Early in her stay, when the patient was intubated and unconscious, providers used the PICU's new set of guidelines to determine whether she would be a good candidate for early mobilization, which aims to manually keep a patient's muscles moving, even while they are sedated or unconscious. Even that passive form of movement can lead to less muscle-tone loss and may ultimately facilitate a quicker recovery.

This case also inspired new areas for improvement, such as high-risk rounding. As part of this, the PICU built a team of providers and nurses committed to visiting patients with complicated cases to check in with bedside nurses, provide help where necessary and teach new skills on the fly.

"Hopefully because of this, we will prevent future hospital-acquired conditions," Dr. Loi

says. "We have data that shows that our rates of central line-associated bloodstream infections and pressure injuries [have decreased], specifically because of high-risk rounding."

LEVERAGING RESEARCH IN THE PICU

High-risk rounding is not the only change driven by this patient's four-month stay in the PICU, according to Dr. Maddux, who also serves as the director of the PICU's clinical and translational research program. The team participated in the national "Overcoming COVID-19" study, which tracks and characterizes complications resulting from COVID-19 in children.

And because of the difficulty the team members experienced measuring the recovery of this patient and others, they are seeking new solutions, including a device that evaluates recovery by measuring activity in kids as they get back to their everyday lives. The hope is to optimize the recovery period so patients can return to their previous activity level quickly, while also moving social and emotional recovery forward.

Cases like these, that involve intense collaboration among dozens of team members across a variety of disciplines, not only strengthen the case for teamwork, but also actively improve it. Dr. Maddux says

that as a result of this patient's stay, the PICU built strong bonds with the rehabilitation and pulmonology teams that have spawned new studies aimed at helping future kids.

"We're launching a study that is going to look at pulmonary function recovery as well as physical recovery in children with bad lung disease who are in our PICU," Dr. Maddux says. "This patient wasn't a part of those studies, but as we were working with her, it brought up some of those questions and facilitated some of those collaborations."

That constant drive to not only improve, but to back those improvements in process and treatments with data is something that sets the Children's Colorado PICU apart, says Dr. Gunville.

"We have grant-funded basic and clinical science researchers, we have experts in quality improvement, experts in education. That's a unique skill set to have at an academic center, and I think we all complement each other," he says. "When you're sending a kid to us, you're sending a kid to a center of experts." ●

Breathing Breakthroughs

PULMONOLOGY

Pediatric fibrosing interstitial lung disease (ILD) is a group of rare, chronic disorders that can cause pulmonary scarring and diminished lung function. ILD can be associated with decreased quality of life, and there are currently no effective treatments for these serious conditions in children. While the structural changes caused by fibrosing ILD are permanent, the drug nintedanib is an evidence-based treatment that has been used to slow the progression of ILD in adults since its approval by the FDA in 2014.

Robin Deterding, MD, Director of the Children's Hospital Colorado Breathing Institute, found the outcomes for nintedanib in adults encouraging. Dr. Deterding, along with the Children's Diffuse and Interstitial Lung Disease Research Network and other leaders in the field, noted an acceptable safety profile in the adult studies on nintedanib and hypothesized that the fibrotic process in adults and children would be similar. Amidst an urgent need for new pediatric treatments, the team sought to discover if nintedanib might also help children and adolescents with ILD.

This led to the launch of the InPedILD trial with Dr. Deterding as the international principal investigator. This is the first ever placebo-controlled clinical trial evaluating the dose exposure and safety of nintedanib for pediatric patients. Spanning 21 countries, the InPedILD trial randomized 39 participants aged 6-17 with clinically significant or progressive disease. Twenty-six patients received nintedanib and 13 received a placebo for the first 24 weeks, after which all received nintedanib. Dosage was individualized based on weight to recreate effective adult exposure levels.

Like the adult studies, nintedanib demonstrated effective blood levels with weight-based dosing and an acceptable safety profile. While the study was not designed to determine impact on lung function, results trended positive for those receiving nintedanib on two core indicators of lung function: forced vital capacity and blood oxygen saturation. The results supported a positive benefit-risk assessment for the use of nintedanib in children and adolescents with fibrosing ILD.

This was a landmark study because it demonstrated that clinical trials of rare disease in children could be pursued globally, and that the findings could lead to new and needed FDA-approved medication for children with ILD. "The nintedanib InPedILD trial was the first for children with ILD, but won't be the last," says Dr. Deterding. "More new drugs are being developed for this condition, and we have provided a blueprint for how to study it in children." ●

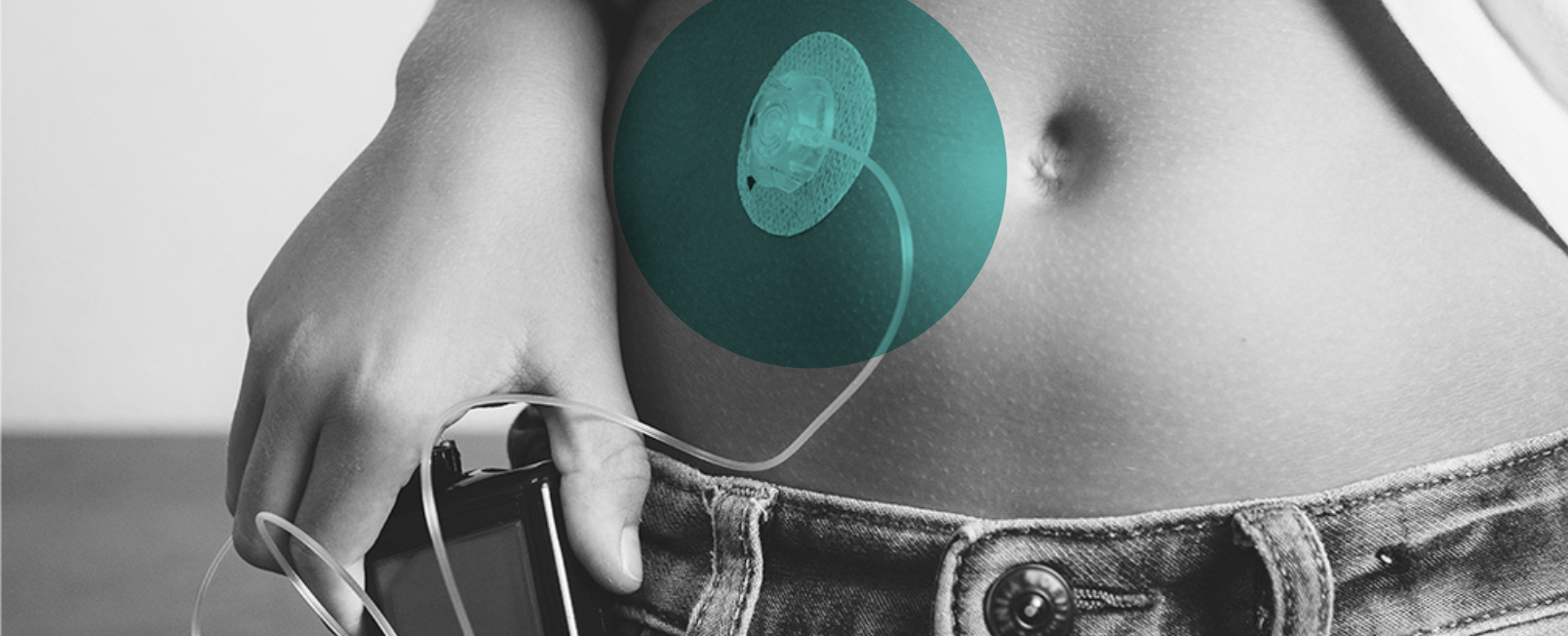
Closing The Loop on Type 1 Diabetes

Q: How close are we to bridging the gap from standard glucose monitoring to a true artificial pancreas?

The Barbara Davis Center for Diabetes at the University of Colorado School of Medicine, led by site principal investigator Paul Wadwa, MD, of Children's Hospital Colorado, was one of 16 sites that recently participated in a 13-week trial of an artificial pancreas used for managing Type 1 diabetes. The resulting study (1), published in the New England Journal of Medicine, was funded by the National Institute of Diabetes and Digestive Kidney Diseases, part of the National Institutes of Health. The study used levels of hemoglobin A1C (HbA1C) as the primary outcome measure and included a large group of participants — children and adults between the ages of 6 and 79. Participants were randomized in a 2-to-1 ratio to the Beta Bionics iLet® Bionic Pancreas or standard of care insulin delivery with a pump or insulin pen.

INTRODUCING THE CLOSED-LOOP SYSTEM

For the last few decades, the medical field has seen technological advancements that make the administration of insulin safer, more reliable and easier. Blood glucose level control is vital for people to live healthy lives but can be complex and burdensome — especially for children who are much more unpredictable in their activities and may not know how to communicate their needs well.



“While we haven’t found a cure,” Dr. Wadwa says, “this is a big step for treatment with a fully closed-loop system — basically, an artificial pancreas that continuously monitors glucose and pumps insulin when needed.”

Complete with a glucose monitor, insulin pump and monitoring app, the bionic pancreas does the work of a real pancreas, automating insulin delivery. Except for occasionally refilling the wearable insulin reservoir, the device requires minimal effort from the patients. Unlike existing hybrid closed-loop systems, which require a combination of insulin delivery inputs (e.g., carbohydrate to insulin ratio, total daily dose or basal rates), the closed-loop system uses an advanced algorithm that continuously monitors glucose and automatically administers the correct dose of insulin to meet patients’ needs. Simply enter the weight of the patient to get a baseline for the dose scaling and the algorithm continuously adapts. Instead of counting carbohydrates, users are only required to indicate when they’re eating breakfast, lunch or dinner and if their portions are smaller or larger than usual. That’s it. Simple.

“Closed-loop systems mean fewer painful finger pricks, fewer manual insulin injections and less room for error,” Dr. Wadwa says. “Every single dose is determined by the artificial pancreas.”

ENCOURAGING RESULTS

Overall, the study showed that the closed-loop system improved participants’ blood glucose control throughout the day and even while sleeping when the risk for dangerously low glucose levels is the highest. The incidence of severe hypoglycemia (although a little higher) did not significantly differ between the two study groups.

“The difference observed for incidence of severe hypoglycemia was not statistically significant and overall low for both the intervention and standard care group,” Dr. Wadwa says.

The most impressive finding was that HbA1C levels decreased from 7.9% to 7.3% in the bionic pancreas group while they remained

unchanged at 7.7% in the standard care group — indicating that glucose control was indeed better in the bionic pancreas group.

What’s more, the bionic pancreas group spent just as much time as the standard care group under glucose levels of 54 mg per deciliter — a key secondary outcome of the study indicative of good glucose control.

REDUCING THE BURDEN

The fully closed-loop bionic pancreas offers a glimpse into the not-so-distant future of diabetes technology, where medical advancements have decreased the burden of diabetes management and improved quality of life through less poking and prodding — where patients’ minds are at ease while an automatic system makes decisions about how to best manage blood sugar.

“As groundbreaking as this technology is,” Dr. Wadwa says, “the impact to public health and quality of life is just as monumental. With more closed-loop systems being approved by the FDA and more clinically available options, we believe people on insulin for their diabetes will see overall improved diabetes control which could mean fewer long-term effects of hyperglycemia, such as eye disease, kidney disease and nerve damage.” ●

1. Bionic Pancreas Research Group, Russell SJ, Beck RW, et al. Multicenter, Randomized Trial of a Bionic Pancreas in Type 1 Diabetes. *N Engl J Med*. 2022;387(13):1161-1172. doi:10.1056/NEJMoa2205225



PAUL WADWA, MD

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Director of Telemedicine, Director, Pediatric Clinic,
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Professor of pediatrics, University of Colorado
School of Medicine

Providing a Clearer Picture

Q: Can doctors use MRI scans and a quantitative risk assessment to alert for serious placenta conditions in pregnant patients?

Currently, doctors rely on ultrasounds to identify potential problems with the placenta in pregnant patients. New studies from Mariana Meyers, MD, Director of Fetal Imaging at the Colorado Fetal Care Center, Children's Hospital Colorado, and her colleague at the University of Colorado, Erin Englund, PhD, are exploring the benefits of MRI scans and developing a quantitative risk scale to confirm these serious conditions. Their work will not only help expectant patients make more informed decisions about their pregnancy and birth, but it will also better equip care teams when creating treatment plans for those with high-risk placenta complications. This new approach could open doors for more radiologists to feel confident reading these types of images, too, creating better access to this information.

For pregnant patients with placenta accreta, where the placenta grows too deep into the uterine wall, a pre-labor diagnosis is essential. This condition inhibits the patient's ability to have a vaginal delivery and can increase the risk of hemorrhaging. Typically, this condition is caught during a routine pregnancy ultrasound, which triggers the placenta team, a multidisciplinary group of

experts across the Anschutz Medical Campus, to come together and formulate the best care plan. Usually, this means scheduling a cesarean section followed by a hysterectomy.

Rather than just relying on ultrasounds to identify conditions like placenta accreta, Drs. Meyers and Englund are advocating for MRIs, so care teams can access more details to implement the best approach to care for the patient.

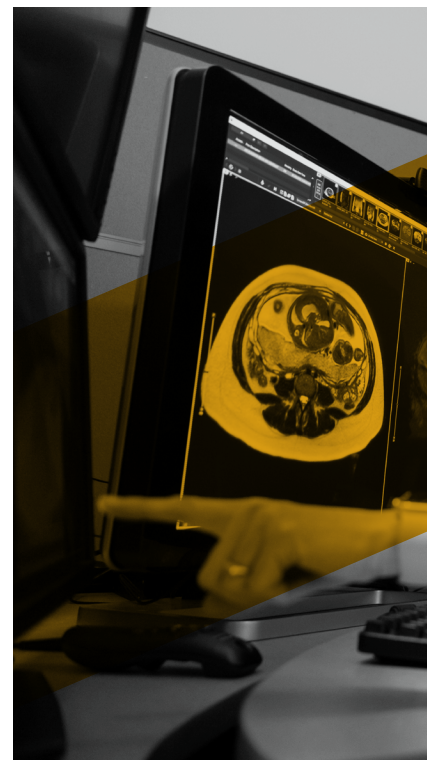
"Locally, it's a lot more common to do MRIs, and that is, in large part, because of Dr. Meyers' expertise," Dr. Englund says. "She's advocated for more of these moms to be getting MRIs, so that she can help to define whether they need to have a C-section for their delivery or hysterectomy and go through some of those delivery planning processes."

A NEW APPROACH

In their current study, Drs. Meyers and Englund are combining their expertise in hopes of finding a new approach to provide the multidisciplinary placenta team with more information when these conditions are identified and to provide other radiologists the tools to confidently use MRIs in the diagnosis process.

Dr. Meyers' expertise is extremely specialized — she is one of only two doctors on the Anschutz Medical Campus who reads fetal MRI studies along with David Mirsky, MD, and nearly 300 fetal MRIs were performed at the Colorado Fetal Care Center last year alone. Her expertise is complemented by Dr. Englund, an assistant professor in the University of Colorado's department of radiology, who uses her expertise in bioengineering to focus on the technical aspects.

"A lot of times, my work is theoretical application," Dr. Englund explains. "Being able to work with Dr. Meyers on



this project helps me see the clinical impact, and seeing how it could impact an individual patient is a really motivating aspect of the research for me."

And for Dr. Meyers, the feeling is mutual: "Vice versa for me. If I know something is needed clinically, but I don't know how to achieve it from a technical standpoint, that's where Dr. Englund chimes in."

Together, they developed a quantitative risk scale to analyze MRI scans and confidently determine whether a patient meets the threshold for placenta accreta. They then confirm the severity of it to help dictate what should go in their care plan. The team does this by taking MRI scans from pregnant patients and circling the areas on the placenta that



appear unusual. Then, Dr. Englund runs her analysis on the identified spots to evaluate the differences of the placental appearance in normal regions and abnormal regions. The pair presented their process and initial pilot study findings to the Radiological Society of North America last November.

Now in the image analysis phase of the study, they are currently having other doctors identify spots to circle on the MRI scans to see if confidence in reading these images and identifying the spots can accurately extend beyond Dr. Meyers' expertise.

"These studies are very hard to read," Dr. Meyers says. "Sometimes, when the findings are very subtle, even for people who see these types of studies

often, it is still hard. If there is a way we can provide more assurance in those moments, I think that would help because then the radiologist would be clearer in how the report is written."

NEXT UP: TWIN-TWIN TRANSFUSION SYNDROME

The pair is taking the lessons they've learned from the placenta accreta study to launch a new study exploring the placenta and risk assessment in twin-twin transfusion syndrome, or TTTS. TTTS is a rare pregnancy disorder where identical twins share the same placenta, which can cause one of the twins to receive more amniotic fluid than the other. If the balance between the

twins becomes too uneven, intervention is needed to increase chances of survival.

The Colorado Fetal Care Center, which offers state-of-the-art testing and innovative care for this rare condition, granted seed funding to Drs. Meyers and Englund to apply the same quantitative risk scale concept to provide more detailed information in TTTS cases.

The team is analyzing MRI scans to evaluate not just the placenta structure, but also various functions like blood flow to each twin, oxygen levels and how readings differ between the maternal and fetal aspects. They are scanning the twins' brains and placentas before and after selective fetoscopic laser photocoagulation (SFLP), the procedure designed to bring balance to both fetuses. This is a procedure the Colorado Fetal Care Center has performed more than 300 times in the past

decade with a survival rate for both twins that surpasses the national average. With images before and after this procedure, not only can Drs. Meyers and Englund compare the twins to each other, but they can compare images before and after SFLP to see what they can learn about fetal neurodevelopment. They are developing a score sheet to determine how the brain structure might change.

"I think this really does have the potential to help us understand the pathophysiology and the things that are changing in twin-twin transfusion syndrome, and then to potentially help dictate clinical care in the future," Dr. Englund says. "As we get the twin-twin transfusion project up and going, I think that's going to be a really exciting area of research and a productive place for us to contribute — not only to advancing the knowledge, but also being able to potentially help individual patients." ●



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Neighborhood of Care

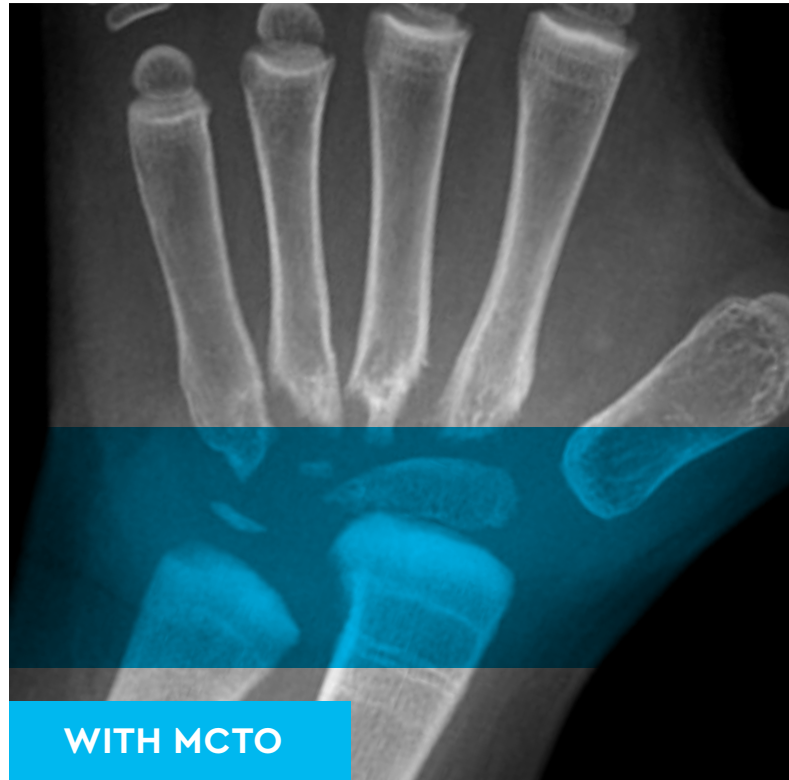
Q: How can a team of experts collaborate to slow the progression of a rare genetic disorder known as multicentric carpotarsal osteolysis?

When Children's Hospital Colorado's whole-exome sequencing uncovered 2-year-old Sophie Rosenberg's very rare disease, there were fewer than 60 patients with multicentric carpotarsal osteolysis, or MCTO, described in the literature (1). MCTO is a genetic disease that can lead to the progressive loss of some of the bones in the hands and feet, as well as kidney failure. When Sophie's mom, Lauren Rosenberg, learned just how rare this condition is, she enlisted a team of experts from around the world to create a better understanding of MCTO. Her hope was they could learn enough to slow the disease's progression. That's how the nonprofit Sophie's Neighborhood was born.

In March 2020, just days before COVID-19 shut down the United States, Rosenberg and her family learned the news of Sophie's MCTO diagnosis, marking the start of a worldwide search for answers.

When Sophie was just 15 months old, she started experiencing pain while trying to stand up. Initial tests revealed inflammation in her ankles and an underdeveloped talus bone in her right foot. Once doctors confirmed she had MCTO, both her family and her care team at Children's Colorado were learning about this condition for the first time and realizing very little medical information exists on MCTO.

"There was a huge learning curve happening all at once in that period of time," Rosenberg says. "When we heard the words that no one knew how to treat this effectively or really understood what



it was at all, I said, 'Well then, we are going to be the ones to figure this out.'"

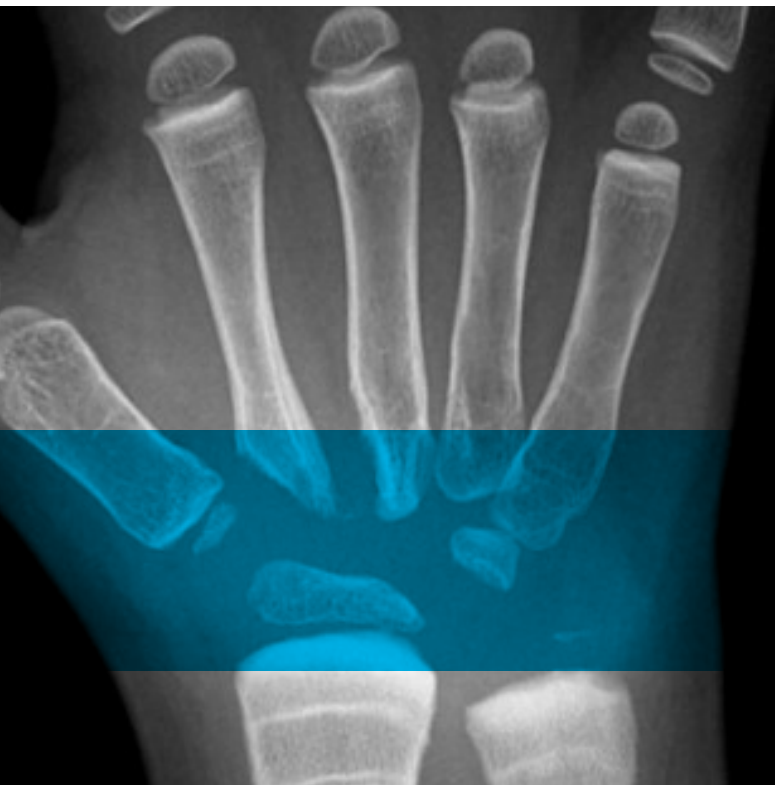
ASSEMBLING THE TEAM

Pediatric endocrinologist Nina Ma, MD, spearheads Sophie's clinical care at Children's Colorado. In a serendipitous alignment of events, at the time of Sophie's diagnosis, Dr. Ma was in the process of establishing Children's Colorado's Pediatric Bone and Mineral Metabolism (BAMM) Program that includes a clinic with a multidisciplinary, comprehensive care approach for children with various bone and mineral conditions.

"Sophie's story motivated and inspired me to expedite the launch of the BAMM clinic. It's a multidisciplinary clinic tailored to benefit someone like Sophie," says Dr. Ma, who is the founder and director of the BAMM clinic and program at Children's Colorado.

The BAMM multidisciplinary clinic team huddles once a month and brings together Dr. Ma; Nancy Hadley-Miller, MD, from orthopedics; Bradley Dixon, MD, section head of nephrology; a nutritionist and nurse coordinator.

"MCTO requires care coordination across various subspecialties, and we were able to extract that expertise from within Children's



Colorado," Dr. Ma says. "We very quickly went from having no structured approach to the care of MCTO to being a team of care providers determined to help develop evidence-based care for patients with MCTO."

The care team collaboration at Children's Colorado does not end there. The team extends to rheumatologist Jennifer Soep, MD, child life specialists, occupational therapists and others.

"None of Sophie's doctors had any experience with the condition before, but I have been blown away by their care, concern and interest in learning more and trying to help Sophie," Rosenberg says. "None of her doctors have shied away from not knowing. They just wanted to learn and help us."

ADVANCING THE RESEARCH WITH SOPHIE'S NEIGHBORHOOD

While the Children's Colorado care team continues to collaborate and learn more about this rare condition through Sophie's unique case, the nonprofit Sophie's Neighborhood is all about bringing together a global team of experts to advance the research related to MCTO. The group is exploring several concurrent research projects to investigate not only the specifics of the disease, but also the history.

The team needed a bone marrow specialist and someone who understood the intricacies of supporting research for rare diseases — and that's when Children's Colorado's hematologist-oncologist Craig Forester, MD, joined Sophie's Neighborhood to help drive new research projects.

"This is part of our obligation as pediatricians," Dr. Forester says. "We have parents who have children with conditions the world may have never seen before. They are confused, they have a lot of questions and they are scared. It's part of our obligation to learn more and to help families understand more about their children."

Dr. Forester is no stranger to rare diseases. His work revolves around gene expression and how it impacts rare conditions like pediatric bone marrow failure. "I'm interested in understanding what we don't know anything about," Dr. Forester says. "Initially, I made myself a hub to collect and store valuable samples to answer questions about Sophie and other kids with MCTO."

With his research experience of rare conditions, Dr. Forester built the protocols and designed experiments to store blood samples from

Continued on following page

Neighborhood of Care continued

patients with MCTO, isolate different parts of the samples and then analyze them further by dispersing those samples out to various partners for testing to learn more. As visibility for this rare disorder grows, more institutions are sending in samples to Dr. Forester's team and other University of Colorado biorepositories to build up this database and contribute to the process.

"Dr. Forester has been amazing," Rosenberg says. "He's able to try to think about this from the perspective of hematology and of the role that the bone marrow may be playing in this."

In addition to Dr. Forester's work and collaboration with institutions like Stanford University, Sophie's Neighborhood has tapped into biosciences and biotech companies in Boulder, Colorado to learn more about MCTO specifics like proteins that could be targeted for treatment, looking into Sophie's exact mutation and doing transcription analysis on MCTO. The group is collaborating with Satoru Takahashi, MD, PhD, in Japan on additional research models to identify possible FDA-approved medications that might be able to work for MCTO treatment, and the next step is narrowing down that list.

Dr. Ma is leading the natural history study for MCTO, as they are interested in learning more about the natural history of rare bone diseases by collecting and storing medical and radiographic information for pediatric and adult patients with MCTO.

"Sophie's Neighborhood helped facilitate the alliances created between various scientific and research teams and the clinical team," Dr. Ma says. "We are hopeful that these early collaborations will help yield meaningful results soon."

LOOKING AHEAD

With research and clinical care happening side-by-side, Sophie's Neighborhood has made real progress in the search for more information about MCTO and determining options for the best care possible.

"Having all of those important doctors in Sophie's care communicating with each other and understanding each other's roles has made the experience so much more comfortable for our family," Rosenberg says, "and we feel that they all really understand and know Sophie."

Children's Colorado's doctors have been alongside Sophie and her family on this MCTO journey for nearly three years now. They

continue to work hard to try and slow down the rate of progression of Sophie's disease.

"She's comfortable, she's not in pain and she's mobile. Whereas a lot of children with this disease are wheelchair bound and can't really have function of their hands very well, she still does," Rosenberg says.

Sophie, now 5, enjoys art, singing, dancing and swimming, which is a part of her warm water occupational therapy that helps strengthen her muscles while remaining gentle on her joints. She has inspired her care team at Children's Colorado to continue learning about this rare condition and step up as leaders on MCTO.

"Lauren has a natural ability to inspire people to want to help, research and devote professional time to studying MCTO," Dr. Ma says. "She's really done a tremendous job of bringing together global thought leaders in the health sciences."

Dr. Ma has now dedicated a significant part of her time to understanding MCTO and sharing knowledge on the international stage. She and colleagues also recently published a paper describing a contemporary perspective on the skeletal phenotype of MCTO (1).

"If we keep our eye on the prize, which is to improve the care and outcomes of patients with MCTO, collaboration is crucial," she says. ●

1. Ma, Nina S et al. "Multicentric Carpotarsal Osteolysis: a Contemporary Perspective on the Unique Skeletal Phenotype." *Current osteoporosis reports*, 10.1007/s11914-022-00762-7. 7 Dec. 2022, doi:10.1007/s11914-022-00762-7



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The Toll on Health Disparities

Healthcare experts have long acknowledged the existing health disparities by racial, ethnic and socioeconomic status, but new research shows that the COVID-19 pandemic has disproportionately affected historically marginalized groups, shining a bright spotlight on health inequalities.

In a recent retrospective cohort analysis, yet to be published from the Children with COVID-19 in Colorado study, senior authors Jill Kaar, PhD, and Kelly Graff, MD, studied records of 1,572 Children's Hospital Colorado patients ages 2 to 20 with COVID-19 from March 2020 through October 2020.

"The environment in which we are born, learn, work and play has a major impact on our health and well-being. It is these social determinants of health that play a central role in the disparities that we see and help explain the disproportionate impact that COVID-19 has had among minority communities," Dr. Graff says.

The research team had previously demonstrated that Hispanic and Latino children were disproportionately affected with severe COVID-19 early in the pandemic in a study published by Dr. Graff and her colleagues in *The Pediatric Infectious Diseases Journal* in 2021 (1). "In examining the ways COVID-19 disproportionately impacted certain communities, we found that severe COVID-19 disease in Hispanic and Latino children is associated with underlying comorbid conditions (e.g., obesity) and socioeconomic disadvantages (e.g., language barriers and insurance status) that may have influenced access to care," Dr. Graff says.

Dr. Kaar adds, "The data confirmed our suspicions that although Hispanic ethnicity is associated with severe COVID-19 illness, it is confounded by various social determinants of health."

While being an ethnic minority shouldn't be a risk factor for severe disease, Dr. Kaar suggests a more granular and targeted approach to messaging and mitigation efforts with a firm grasp of those deep-rooted social determinants of health.

"I want public health officials and pediatric providers to use this knowledge to go further with outreach efforts to better target patients with comorbidities, as well as those in low-income or non-English speaking households," Dr. Kaar says. ●

1. Graff K, Smith C, Silveira L, et al. Risk Factors for Severe COVID-19 in Children. *Pediatr Infect Dis J*. 2021;40(4):e137-e145. doi:10.1097/INF.0000000000003043



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Journey to Better

UROLOGY

Opioids can treat pain after major surgery, but they also put children and adolescents at risk of misuse, dependency and overdose. Additionally, opioid use can slow both breathing and GI tract function, which can impact recovery. Alternative postoperative pain management could minimize the impact of opioids, but finding effective strategies is challenging in patients with spina bifida, who aren't always good candidates for traditional pain relief techniques.

Children's Hospital Colorado's Kyle Rove, MD, and colleagues, conducted research to help overcome this very challenge. Dr. Rove co-authored a multicenter, retrospective observational study to understand if regional, catheter-based analgesia — a tube inserted under the skin to numb the surgery site — could reduce opioid needs in spina bifida patients after surgery.

The team based its data on patient-reported pain scores during the preoperative periods, beginning on the day of surgery.

The study divided 158 patients with spina bifida into two groups: those who received regional analgesia via catheters, and those who didn't. Patients in the catheter group didn't require additional pain management through opioids, while those without catheters saw a significant increase in postoperative opioid use. This reinforced the researchers' hypothesis that regional analgesic catheters could reduce opioid needs after surgery without increasing pain scores.

Additional outcomes demonstrated the benefits of a multimodal approach to pain reduction. For example, opioid use decreased when used in combination with analgesic catheters, scheduled acetaminophen or intravenous morphine equivalents. Overall, these findings could reduce postoperative opioid use among children and adolescents with spina bifida, thereby lowering the risk of prolonged use and dependency while increasing patients' quality of life. ●

Advancements in Surgical Care

SURGERY

In May 2022, Children's Hospital Colorado achieved Level 1 Children's Surgery Verification (CSV) from the American College of Surgeons (ACS) for its Surgical Quality and Safety Program. The effort was led by the perioperative quality and safety committee which began seeking this designation in 2020.

The American College of Surgeons first implemented its verification program in 2017 to ensure that pediatric surgery patients would have access to high-quality care. To measure this care, the organization created a set of standards, which evaluates quality improvement, research, education, data surveillance, resources and more.

"This was a significant undertaking during the pandemic, but our team came together to ensure this milestone," says Surgeon-in-Chief Duncan Wilcox, MD. "The ACS verification reinforces Children's Colorado's commitment to delivering high-quality services and upholding a commitment to transparency with referring providers, patients and families, and the broader community."

More recently, Children's Colorado expanded its work toward those commitments with the appointment of Ankush Gosain, MD, PhD, who joined the team as the new Chief of Pediatric Surgery. Dr. Gosain completed postgraduate training at the University of Tennessee Le Bonheur Children's Hospital and St. Jude Children's Research Hospital. His lectures on pediatric surgery and Hirschsprung's disease have reached international audiences, and he has published more than 100 articles.

In this new role, Dr. Gosain will further the reputation of the Center for Children's Surgery in a variety of ways. This includes developing regional and international magnetic programs, fostering faculty research and increasing regional and international recognition of the department's surgeons and clinical programs. Additionally, he will work to recruit more patients for his research on Hirschsprung's disease, liver tumors and trauma.

These two advancements not only demonstrate Children's Colorado's quality and safety in surgery, but also its relentless dedication to advancing national standards for surgical care. ●

A(:) List **Recent awards and accolades**



Pediatric Pancreas Center

GASTROENTEROLOGY

*National Pancreas Foundation
Center of Excellence*

Children's Hospital Colorado's Pediatric Pancreas Center is now recognized as a National Pancreas Foundation (NPF) Center of Excellence. The NPF is the leading foundation dedicated to patients suffering from all forms of pancreas disease, and this designation is given only to institutions that pass a rigorous application process.

To become a Center of Excellence in pediatric pancreatitis, institutions must meet certain criteria. For example, centers must have specific, expert pediatric physician specialties working together to provide comprehensive state-of-the-art care. Overall,

the NPF looks for institutions that prioritize multidisciplinary treatment of pancreatitis and treating the whole patient.

The Center meets NPF standards with a team of gastroenterologists, endocrinologists, anesthesiologists, radiologists, pulmonologists, surgeons, nurses, nutritionists and psychologists. These experts use the most advanced technology and collaborative approaches to diagnose and treat all pancreatic disorders in kids. From ongoing research studies to family-based care, the Center focuses on improving quality of life for every patient.

"We are honored that Children's Hospital Colorado has been recognized by the National Pancreas Foundation," says Jacob Mark, MD, Pediatric Pancreas Center Medical Director. "Having the NPF Center of Excellence designation will help families know that the Pediatric Pancreas Center is dedicated to providing the best and most innovative care possible."



David Howell, PhD, ATC

PEDIATRIC SPORTS MEDICINE

PRiSM President 2023-24

The Pediatric Research in Sports Medicine Society (PRiSM) recently appointed Children's Hospital Colorado's David Howell, PhD, ATC, as its 2023-24 president. PRiSM is an organization comprised of multidisciplinary pediatric sports medicine professionals who seek to advance the field through collaborative research and education efforts.

As PRiSM's president, Dr. Howell looks forward to furthering the organization's mission of promoting overall athlete wellness. "By creating space to advance the understanding of injuries and pathologies specific to pediatric athletes — among clinicians and researchers from many different backgrounds — the society is truly special," Dr. Howell says.

His 2023 goals include continuing to unite diverse perspectives to foster greater knowledge-sharing and discovery. "Specifically, we will focus on including younger trainee members, populations typically underrepresented in STEM and our international sports medicine colleagues within PRiSM," he adds.



Jill Chang, MD

Robert Dietz, MD, PhD

NEONATOLOGY

Children's Hospital Colorado welcomes Jill Chang, MD, who will work alongside Robert Dietz, MD, PhD, in neonatal brain injury research. Both are neonatologists providing care at Children's Colorado.

Dr. Chang's work focuses on two different prenatal conditions — intrauterine growth restriction and bronchopulmonary dysplasia, the most common chronic lung disease affecting preterm newborns. Specifically, Dr. Chang will explore how these conditions may increase the risk for cerebral palsy — and how they can be identified earlier to improve diagnoses and therapies for recovery.

Meanwhile, Dr. Dietz studies brain ischemia, a disruption in the brain's oxygen supply that occurs in newborns after lifesaving CPR. Dr. Dietz's past research identified a protein essential for boosting resiliency and restoring cognitive function, and new research will explore ways to increase that protein and minimize brain injury.

While Drs. Chang and Dietz study different disease processes, they both belong to the Newborn Brain Society, which started in 2020. The organization actively provides weekly educational seminars on Zoom, as well as publishing guidelines, to improve care for babies with brain injuries. Their collaboration will pave the way for greater understanding in the burgeoning field of neonatal brain injury research.



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

Follow us on Twitter

A Twitter account for pediatric healthcare professionals where we share our latest research, clinical innovation and news

 Follow us **@ChildrensCO_Pro**



Ranked among the best of the best

Kids are incredibly different, and they need incredibly different care. Here, that's what we do — every second of every day. We do it through a focus on quality and safety. We seek out advanced treatments and transformative research. Every moment of every day, we do it for the kids. That's not only helped us build the kind of deep expertise that we are known for — it's also earned us a #7 ranking, once again placing us among the Top 10 pediatric hospitals in the nation, with five specialties in the Top 10. That consistency sets us apart, but it's our unwavering commitment to kids that makes the difference. Always.

Here, it's different.

We rank among the best in all 10 recognized specialties:

Cancer: #8
Cardiology and Heart Surgery: #14
Diabetes and Endocrinology: #4

Gastroenterology and GI Surgery: #4
Neonatology: #19
Nephrology: #22

Neurology and Neurosurgery: #12
Orthopedics: #12
Pulmonology: #6
Urology: #7