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Q: *Advances and Answers in Pediatric Health*

Shining a Floodlight on the Human Genome

Through a newly minted whole-genome sequencing lab, researchers are excavating a gold mine of genetic data and understanding how mutations profoundly impact the human health experience. **P. 3**

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It starts with a Q:

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

Dear colleagues,

Basic leadership principles are essential to the success of clinical leaders in healthcare. However, few medical schools or postgraduate training programs place emphasis on this key area of professional growth. At Children's Hospital Colorado, we recognized that many of our physicians and providers acting in leadership roles weren't given the essential training they needed to thrive as leaders.

The Provider Leadership Development Program was born to fulfill this need. Each year since 2019, we've reviewed a large pool of applicants and selected 25 to 30 physicians, advanced practiced providers and psychologists from across disciplines. Over the course of a yearlong program, each cohort learns the skills they need to drive meaningful change and inspire their teams.

Dedicated leadership training days provide participants with time off from clinical responsibilities and daily duties so participants can focus on their goals. These training courses emphasize many areas of leadership, including the importance of connecting work to hospital strategy, understanding how each role supports the organization's financial growth and how to lead a team to a shared, meaningful vision. These trainings also help participants build close relationships with other leaders, which become invaluable for fostering resilience, boosting retention in leadership roles and warding off burnout — even as their responsibilities grow.

Now in its fifth cohort, the competitive program has produced more than 100 graduates across the Children's Colorado system of care. All graduates are invited to participate in a continuing education series that builds on lessons learned and rekindles the networks they've built.

It's important to us that the Provider Leadership Development Program stays dynamic, meaning it's always evolving based on feedback from our participants. This ensures content is relevant to the immediate needs our providers face, and to the greater, ever-changing healthcare challenges of our time. Most importantly, the program grounds all lessons and activities in pediatric care, which in turn roots participants in their shared passion: making the world a healthier place for kids.

Sincerely,

DAVID BRUMBAUGH, MD
Chief Medical Officer, Gastroenterologist, Children's Hospital Colorado
Associate Professor, Pediatrics-Gastroenterology, Hepatology and Nutrition, University of Colorado School of Medicine

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Shining a Floodlight on the Human Genome

Q: How does having an in-house whole-genome sequencing lab allow providers to dial in diagnoses, treatments and medication with incredible accuracy?

In 2009, the first human genome sequencing effort opened researchers' eyes to how understanding genetics could help in identifying, diagnosing and treating countless conditions. This novel approach to medicine allowed doctors to peek inside a person's DNA and explore protein-coding regions for possible disease-causing mutations. But that work only dove into 3% of the more than 3 billion nucleotides that make each of us unique. "For the longest time, we thought that the areas of the DNA and the genome that don't code for proteins were just junk," says Alisa Gaskell, PhD, Scientific Director of Precision Medicine at Children's Hospital Colorado. "Oh, how wrong we were."

The other 97% of the human genome is far from junk, it turns out. Instead, it's a gold mine of data that allows us to excavate genetic mutations we never knew existed that profoundly impact the human health experience.

"It's those regions that will tell you what form of that protein to make or how much of that protein to make, and we now realize how much that impacts disease," Dr. Gaskell explains. "Instead of having a tiny little flashlight, we now have a floodlight."

PRECISION MEDICINE

Bringing Whole-Genome Sequencing In House

Once whole-genome sequencing (WGS) became a frequently used tool in medicine, Children's Colorado providers would send blood samples to external partner laboratories with testing capabilities and get a report of genetic mutations that might be at play in a child's disease presentation.

Working that way, providers identified rare diseases, developed drugs targeted at specific mutations and offered more accurate diagnoses than ever before. Still, the process sometimes took months, and fractured lines of communication between external labs and clinicians didn't always allow for thorough investigation and problem-solving.

That's why, a little over a year ago, the team at Children's Colorado's Precision Medicine Institute began laying the foundations of an in-house whole-genome sequencing lab to revolutionize the hospital's capabilities. That, of course, required funding and physical space, but also the creation of a new team of molecular technologists, data scientists and engineers, plus technology and infrastructure to support the work.

In September 2024, the lab opened its doors and began helping even more pediatric patients in an entirely new way. The first differentiator that Dr. Gaskell and her team hoped to put in place was the use of buccal swabs instead of using blood for testing. Because another needle poke and appointment are major barriers to care, Dr. Gaskell's team decided to employ a simple swab of the inner cheek instead and started mailing kits to families' homes, where patients can collect samples from the comfort of their living room. This also allows parents to send the team their own DNA samples, which can help create an even more complete picture of their child's genome.

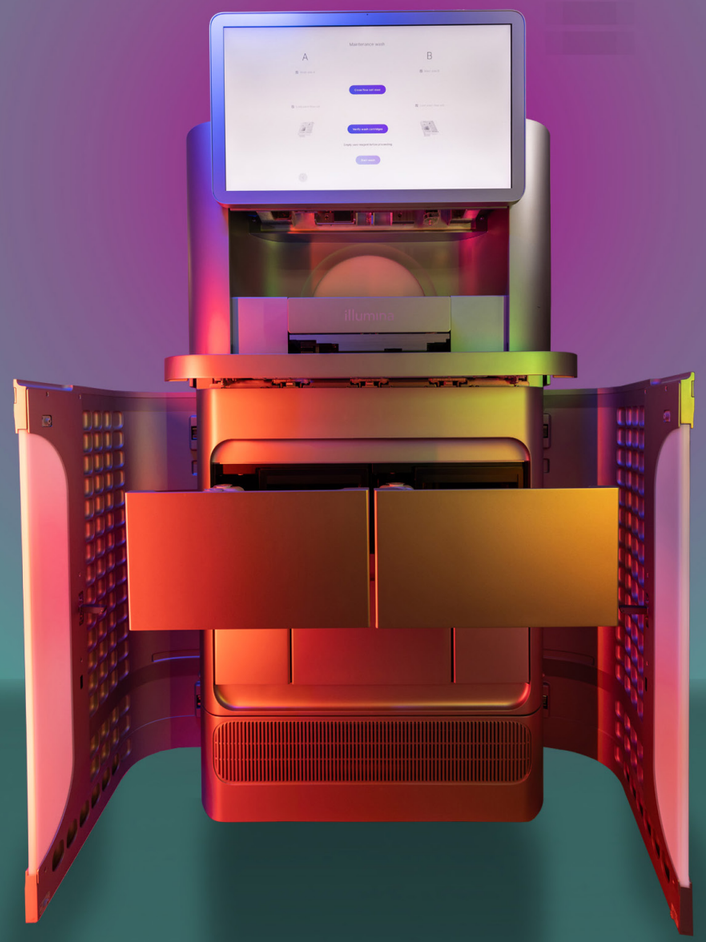
And rather than just collecting a patient's DNA and answering one question, that genomic information is stored and layered into Epic, the hospital's electronic health record system. According to Nicholas Willard, DO, Medical Director of the Precision Diagnostics Laboratory, taking this extra step not only provides patients with information that could help them in the future, but also allows them to contribute to a larger dataset of human genetic information that could help solve medical mysteries now and in the future.

"We may not have the answer or diagnosis today, but because we've set up our program the way we have, there's a high chance that we will be able to provide that for the patient one day," Dr. Willard says. "The desire is to really maximize the likelihood of us finding that answer. And then, by partnering with the research community and making that data totally unidentifiable, we can allow researchers to ask questions in these large data sets too."

HOW WGS WORKS

The amount of information gathered from one genome is staggering — about 250 gigabytes of data are generated in the process. That would take a whole team of people at least a full year to process. At the Children's Colorado lab, specialized tools and equipment allow the team to do it in just a few hours.

Dr. Gaskell likens the sequencing instrument to a satellite, taking pictures of the entire Earth and then working alongside other tools to zoom in and focus on just one house. That large picture of the genome is honed to help researchers understand specific regions with mutations. Those mutations are then matched to known symptoms associated with that change, if any exist. By using algorithms developed internally and by key industry partner Illumina, the team can turn and maneuver the data to uncover important associations between genetic differences and clinical presentation. Parental DNA helps narrow the picture even further by weeding out inherited mutations and dialing in to unique alterations or combinations within the patient's DNA.



"I call it the Rubik's cube," Dr. Gaskell says. "You have this large data set, and rather than going through it one by one, you start pivoting the data and seeing if something makes sense."

But it's not only technology doing the work. The true strength of the Children's Colorado whole-genome sequencing lab is its ability to meld machine learning with the expertise of clinicians, researchers and technologists, who approach data like detectives puzzling through clues.

"It's a tighter network of colleagues that can be brought together that have been now walking alongside each other for a while," Dr. Gaskell explains. "We are talking about gray areas. We are getting really good at identifying an alteration, but in many cases there's no other evidence out there to help us elucidate the impact that alteration has on the clinical presentation, and we don't really know how that alteration changes the function of the gene. It's really good to have a discussion with the clinicians to inform on the significance of that change. When you separate those processes, you're making a decision in a vacuum. Now we're making a decision as a team."

FROM BENCH TO BEDSIDE

In just the handful of months the lab has been operational, hundreds of kids have turned to its capabilities for answers. Dr. Willard says he sees one incredible case after another that may have gone differently without the help of such advanced testing.

In early 2024, a teenage patient with a mass in his thigh visited the hospital for care. Biopsies only revealed spindled cells, which could indicate any number of diagnoses, including a tumor or trauma. Sequencing allowed the team to narrow in on a genetic cause, something that wouldn't otherwise be possible.

In this case, the patient had neurotrophic tyrosine receptor kinase (NTRK) gene fusion. When these gene fusions occur, a cell-signaling gene, which tells cells to divide, can't turn off and on as the body intends. Instead, it is connected to a gene that is always turned on, forcing cells to replicate with no off switch. Thankfully, within just the last five years, researchers elsewhere developed a drug that targets this process and inhibits abnormal genetic events involving NTRK family genes.

Later in the year though, the patient's tumor returned, as it had become resistant to treatment. Through additional sequencing, the Children's Colorado team identified a new mutation that the tumor had acquired to overcome the NTRK inhibitor. Armed with that information, his doctors identified a new drug, already on the market, that the patient could begin taking right away.

"Without this genetic testing, we would not have rendered the appropriate diagnosis," Dr. Willard says. "A lot of places wouldn't be able to catch this genetic event, but we did and there's a very specific drug to treat it."

According to Dr. Willard, this patient's story is far from a needle in a haystack. Every single day of every single week, he hears of new children who benefit from the team's ability to turn the complex and mysterious into the known and manageable.

Continued on the following page

Where Genetics Meet Medicine

Children's Colorado's whole-genome sequencing lab provides endless opportunities for more precise diagnosis and treatment of genetic diseases. One area where the lab's capabilities are already having a significant impact is in pharmacogenomics, a field of study that seeks to understand how a person's genetic makeup influences their response to medications.

"There are specific genes that have implications on how we respond to a drug, whether or not it's effective and whether or not we're able to break it down," explains Elizabeth Fenstermacher, MD, who serves as co-chair of the Genomics Application Governance Committee (AGC) at Children's Colorado. Gene variants can influence drug metabolism across a spectrum: Some patients may be intermediate metabolizers, which means they tolerate lower doses of certain drugs, while poor metabolizers may not be able to take them at all.

For example, some people are born with variants in the genes thiopurine S-methyltransferase (TPMT) and nudix hydrolase 15 (NUDT15), which influence how they metabolize immunomodulator drugs called thiopurines. These medications, such as azathioprine, are used to tamp down the immune system when a patient has a blood-borne cancer or rheumatologic disease. Azathioprine is also an important medication for preventing organ rejection after a donor transplant.

About 1 in 10 people has a gene variation that causes a partial reduction of TPMT activity and about 1 in 300 people has a severe reduction of activity. "If you have variants in those particular genes, you may not break down those medications as well," Dr. Fenstermacher says. "It can be really dangerous — and even fatal — if you were to get standard dosing of those medications."

That's where pharmacogenomics comes in. Testing patients for these gene variants before prescribing thiopurines can prevent potentially catastrophic outcomes and ensure the drugs work as intended.

SETTING SIGHTS ON STANDARDIZATION

The pharmacogenomics team at Children's Colorado and the University of Colorado School of Medicine, which includes pharmacy leaders, laboratory analysts, geneticists and technology experts, began its initiative in November 2024 by incorporating TPMT and NUDT15 variant information into Epic.

"We're starting with these two high priority genes, but now that we've built the framework, we plan to phase in additional genes as rapidly as we can," Dr. Fenstermacher says. Next, the team plans to use scientific literature and guidance from subject matter experts to determine which additional genetic information to include in Epic. Variations with the strongest potential for patient harm will take priority.

This rapid implementation is made possible by Epic's built-in genomics module, which makes it easy for providers to understand their patients' genomic indicators. These are not diseases or diagnoses, explains Children's Colorado geneticist Austin Larson, MD, but rather, differences that could determine how patients respond to medications. "We have the ability to attach genomic indicators to patients' health records, and then the genomic indicators trigger decision support for clinicians dynamically," Dr. Larson says.

This information is all strategically located in the same area where providers would find allergy information, so if they do prescribe azathioprine to someone who's considered a poor metabolizer, Epic will immediately prompt them with a warning — and instructions on what to do next. These directives involve detailed guidance from Children's Colorado's OurPractice Advisory, or OPA, a tool within Epic that allows hospitals to share organization-wide reminders and clinical action items that can support provider workflows. They can also access information on how to proceed in the presence of comorbidities (if a patient also has Down syndrome, for example), and call for extra support if needed.

"You can get a one-click pharmacy consult if you need to talk to a pharmacist about the specific clinical circumstances, learn how much to reduce the dose or determine if a different medication is needed," Dr. Larson says. "Instead of overwhelming providers with a list of 30 things their patient needs, the goal is to provide the genetic information to the right person at the right time with specific actions that they can take."

The Genomics AGC will ensure that providers across the institution are updated and informed of this Epic change, and they will all be invited to learning sessions where they can better understand the drugs they commonly prescribe, and which genetic variants might put their patients at risk.

Looking ahead, the team plans to include pharmacogenomic guidance for all kinds of inherited diseases, from neurofibromatosis type 1 to sickle cell disease. "We're able to push out education across the institution using these OPAs as a way that we make sure everybody is prescribing with the best practices following the most recent clinical guidelines developed with international consensus," Dr. Fenstermacher says. "I think it's really an incredible tool."

Standardizing pharmacogenomic information in patient charts isn't just important for current treatments, but also for nuanced medical needs that may arise in the future. "We can generate new information from the data that we already have and turn on a genomic indicator for all our patients without anyone getting a new test," Dr. Larson says. "We can improve the quality of the data and improve the quality of the decision support, iteratively, on an ongoing basis."

In other words, when used for whole genome sequencing, a single buccal swab at age 9 can continue informing a person's treatment throughout their lifetime.

BROADENING THE CONVERSATION

At the national level, Children's Colorado pharmacogenomics clinical pharmacist Christine Formea, PharmD, is joining broader conversations through participation in the Standardizing Laboratory Practices in Pharmacogenomics (STRIPE) forum, which is part of the American Society of Pharmacovigilance.

"This collaborative community brings stakeholders from across the country together to start thinking about creating standards," Dr. Formea says. "How do we focus resources toward standardization, having common language and understandings?"

At the most recent STRIPE national meeting, Dr. Formea helped moderate panel discussions and was honored with the organization's Double Helix Award, which recognizes leadership in advancing the field of pharmacogenomics.

"My hope is we are able to remove barriers to access and make genetic testing available to all of our patients at a low cost," Dr. Formea says. "There's tremendous opportunity for this program to grow even larger as we incorporate more genes and drugs, and to impact more patients in meaningful ways by providing medical safety and improving patient care." ●

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On Target: Treating Gut Inflammation

Q: Could this breakthrough lead to safer, more effective therapies that reduce immune suppression?

Inflammatory bowel disease (IBD) is characterized by an overreactive immune system causing inflammation in the digestive tract, including the intestines, the body's largest immune organ. Most drugs used to treat IBD are immunosuppressive, increasing susceptibility to infections. What if researchers could create a more precisely targeted treatment without these widespread side effects? Children's Hospital Colorado and University of Colorado School of Medicine researchers believe they have. They're calling it a "refined bullet" — a way to treat IBD without global effects.

In IBD, the immune system is dysregulated causing immune T cells to attack healthy tissues instead of targeting invaders. "The goal is to find ways to turn the overreactive immune system off, but not turn it off too much," explains Edwin de Zoeten, MD, PhD, Director of Children's Colorado's Pediatric IBD Center.

WHERE IT BEGAN

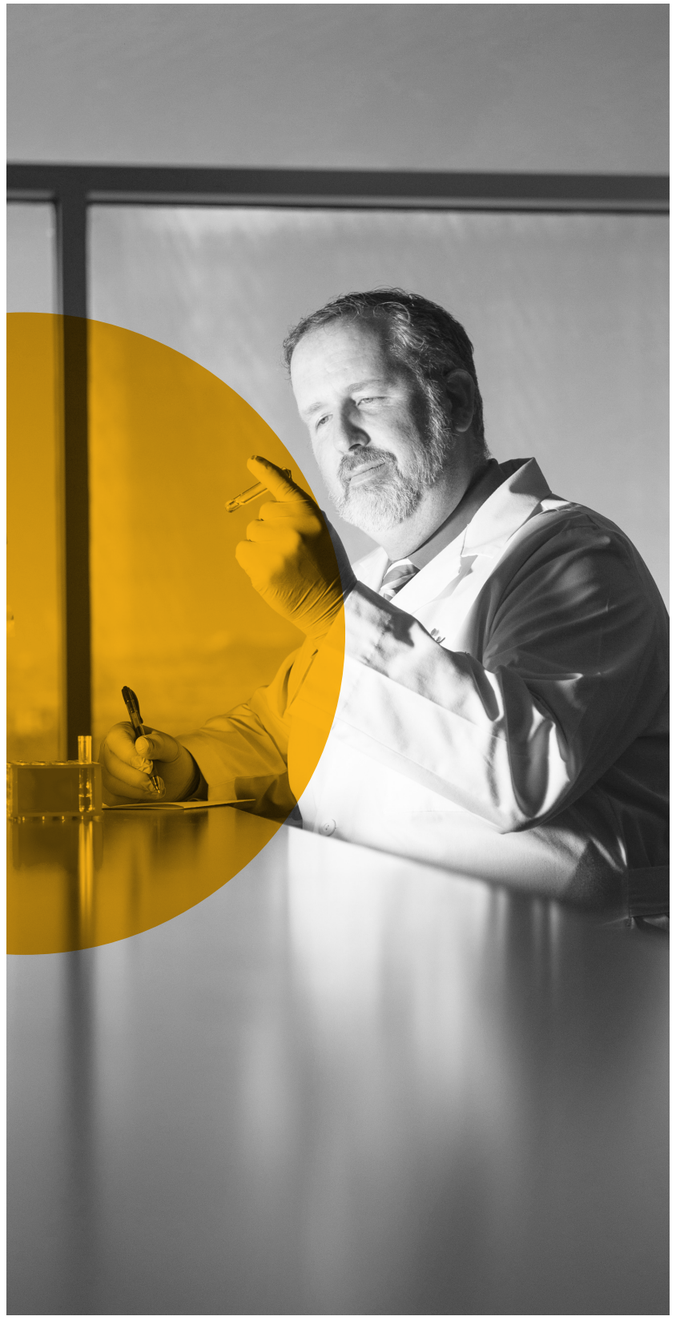
Tissue hypoxia, in which there are low oxygen levels in the intestinal tissues at the site of inflammation, is a defining trait of IBD. The low oxygen acts like a trigger, worsening inflammation. For Dr. de Zoeten, who is interested in cellular stress, hypoxia was the perfect place to begin searching for a better treatment. He and the team of researchers wanted to examine how low oxygen environments impact T cells. Specifically, they were interested in CD4+ T cells — immune cells found in inflamed intestinal tissue — and how these conditions influence immune system behavior.

In individuals with IBD, T cells become overactive and mistakenly attack the body, causing inflammation. Previous research by Sean Colgan, PhD, at the University of Colorado School of Medicine, indicated hypoxia inducible transcription factors (HIFs), proteins that regulate the body's response to low oxygen environments, can help with recovery from inflammation. HIFs help cells adapt to low oxygen by activating genes that promote survival and regulate immune responses. Still, prior studies didn't give clarity on how the hypoxic environment affected the T cells in IBD.

In Dr. de Zoeten's study, the team exposed CD4+ T cells to both a normal and hypoxic environment. They then analyzed these cells for the presence of microRNAs (miRNAs), small noncoding RNA molecules that regulate immune cells. That's where they made a crucial discovery. They identified a miRNA called miR29a, which was produced in high quantities under hypoxic conditions.

THE IMPORTANCE OF MIR29A

MiRNAs help control which genes are expressed and regulate different processes, including immune responses. In this case, they suppress overactive immune responses and promote anti-inflammatory pathways.



Dr. de Zoeten and the team proved the production of miR29a begins with a chain reaction. First, inflammation stimulates hypoxia, which leads to an increase in HIF-2a production. HIF-2a, like other HIFs, plays a role in regulating immune responses. Specifically, HIF-2a promotes the production of miR29a. This domino effect helps regulate the immune response and inflammation, unveiling a pathway not fully known before this study.

After identifying how miR29a production is increased, researchers then looked at the miRNA's impact on inflammation. Using lipid nanoparticles to deliver a miRNA mimetic, a chemically altered miRNA, researchers discovered another key relationship. The preclinical models that received the mimetic experienced less inflammation. The inverse is also true. The models with a miR29a deficiency presented with enhanced intestinal inflammation. Researchers believe by increasing the production of miR29a, they can suppress the overactive T cells, reducing inflammation and improving overall symptoms in patients with IBD.

THE IMPACT OF THIS POTENTIAL TREATMENT

"This concept is really targeting one regulatory pathway. It's upstream from many of the targets that we have currently," Dr. de Zoeten says. "It targets the function of the cell rather than the product of the cell."

Not only do current medications suppress the entire immune system, but the medications also only work for about half of those with IBD. According to the Centers for Disease Control and Prevention, IBD affects up to 3 million people in the United States, with symptoms ranging from chronic diarrhea to abdominal pain and fatigue. In children, this can lead to growth delays, weight loss and other complications.

"The more options and targets we have, the higher likelihood we'll find a medication for every patient that has the disease," Dr. de Zoeten says.

For Dr. de Zoeten, this research is personal. Originally trained as a cancer immunologist, Dr. de Zoeten found a passion for IBD after the loss of his mother, who passed away from complications of the disease. In the decades since, researchers like him have made incredible advancements in the treatment of IBD.

"We don't even use most of the medications [that were] available to my mother. I would say the advances over the last 25 years have been tremendous. They've changed patients' lives for the better," Dr. de Zoeten says.

The fight continues. Dr. de Zoeten and the multidisciplinary team are still looking for ways to refine treatment further, avoiding off-target effects and whole-body immune suppressions. In future studies, they plan to investigate other cell types that may be affected by HIF-2a, the long-term efficacy of miR29a, mimetic therapy and methods to improve delivery.

"It's how do we target the right cell at the right time. It's working with people on campus and across the world to assess the best nanoparticle, the best way to target inflammation. It's a collaborative effort, and it's not just one person," Dr. de Zoeten says.

With groundbreaking discoveries like miR29a, the prospect of targeted therapies offers new hope, ensuring better outcomes for millions living with IBD. ●

EDWIN DE ZOETEN, MD, PHD

Director, Pediatric Inflammatory Bowel Disease Center, Children's Hospital Colorado

Professor, Pediatrics-Gastroenterology, Hepatology and Nutrition, University of Colorado School of Medicine

Zooming Into Focus

Q: How are doctors pushing the limits of technology to more accurately diagnose fetal heart conditions?

Imaging the heart of a fetus is innately tricky, requiring precision and expertise. MRI has the potential to provide critical diagnostic information in fetal heart conditions in addition to standard imaging options, but visualizing the fetal heart with MRI is challenging. That's because the small size of the heart in utero, the fast heartbeat and the normal movement of the baby can make clear images difficult to capture. Clear fetal heart images are crucial to providing families with an accurate diagnosis and a detailed plan for postdelivery care. Over the past several years, the fetal cardiac MRI team at Children's Hospital Colorado has been exploring new technology to find a solution to these challenges and finally achieve a clear, crisp movie of the beating fetal heart, thanks to a special clinician-scientist partnership.

Bringing the images to life required a collaboration between Alex Barker, PhD, Erin Englund, PhD, and cardiac experts Lorna Browne, MD, and Richard Friesen, MD. Since 2019, the team has been working with industry partners on an MRI-compatible Doppler ultrasound device which uses ultrasound to detect fetal heartbeat and transmit this signal to the MRI scanner. Those images are then synchronized to the fetal heartbeat, creating depictions of the moving heart and allowing the team to see complex fetal cardiovascular conditions in exquisite detail. With U.S. Food and Drug Administration approval of this new Doppler ultrasound gating device, the team is working on clinical translation of these methods for accurately diagnosing congenital heart disease and other cardiovascular abnormalities prenatally.

"We are pushing the boundaries of our technology on all fronts," Dr. Barker says.

FOCUSING ON FUNCTION AND FLOW

As this technology is so novel, there was a need to establish normative data on fetal structures, including ventricle sizes and ventricular function, to reliably detect subtle abnormalities. In 2024, the team published the first normative data on fetal heart dimensions and fetal heart function using fetal cardiac MRI (1). This work provides a baseline reference for implementing this new technology into practice.

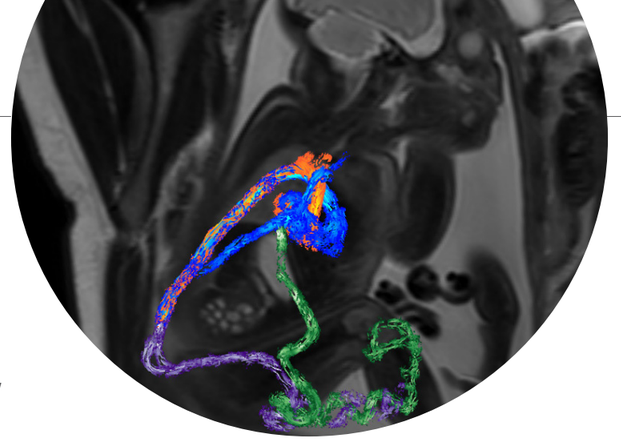
But the team did not stop there. They wanted to see more than just the size of the fetal heart structures to be able to gather the most detailed information possible about congenital heart diseases. They also hoped to be able to visualize and quantify the distribution of blood flow throughout the fetal circulation. To do this, they needed to find a way to use a technique called 4D flow MRI in the fetus. This technique uses a type of MRI that allows doctors to see 3D, time-resolved images of the heart and to measure 3D blood flow through the entire cardiovascular system. Dr Barker was part of the first team to do 4D flow on adult hearts, and over the last eight years, he and his team developed faster sequences to apply this first to small children, and then most recently, to fetuses — where it is revolutionizing how doctors view fetal cardiovascular conditions.

Because it had never been done before in a fetus, the team again needed to establish normative values for fetal blood flow distribution. Dr. Englund, along with postdoctoral research fellow Takashi Fujiwara, PhD, spearheaded the team's most recent publication where researchers applied fetal 4D flow MRI to healthy pregnant patients to quantify the normative distribution of fetal blood flow (2).

"Reliable normative data is an essential step to widespread clinical application," Dr. Browne explains. "In particular, mapping the normal distribution of blood flow in the fetus with fetal 4D flow is a hugely important step because now we can look at the flow distribution in our patients and make better informed diagnoses."

Dr. Englund adds: "It's so rewarding to be a part of this team and to have all the infrastructure in place to be able to make such a huge difference. We'll continue to grow and push the envelope with others jumping on board with us. There's a lot of potential for the future of this."

With a quick research pipeline from idea conception to implementation of new technology, the Colorado Fetal Care Center at Children's Colorado is now the only center in the U.S. routinely performing 4D flow for prenatal patients, and the fetal cardiac MRI team continues to push the boundaries of this technology. The team is now working on even more exciting developments using artificial intelligence and motion correction with international collaborators.



"I've worked on lots of projects over my career as a scientist. I've never been this close to translation so quickly," Dr. Barker says. "It's pretty exciting to be able to take something that we've been working on in the lab and see it actually making an impact. That's what motivates me every day here. It's not just a hypothetical."

BOOSTING DIAGNOSTIC ACCURACY

The main area where the team is seeing a major impact is in diagnosing coarctation of the aorta (CoA), a congenital heart defect that occurs when a baby's aorta doesn't form properly during pregnancy. Current standard technology has limitations when it comes to diagnosing this complex condition, resulting in about a 50% false positive rate, despite best efforts. These false positives have significant implications for families, from impacting maternal mental health and finances, to increasing time spent in the hospital postpartum while teams work to confirm a diagnosis.

"Every modality has its limitations," Dr. Browne says. "When you have these difficult cases where echocardiograms can't be definitive, MRI provides an additional modality and an opportunity to be definitive. That really impacts the counseling of patients and delivery planning."

Providing families with an accurate diagnosis during pregnancy for conditions like CoA allows patients the chance to have clear expectations. Patients who faced the possibility of a CoA diagnosis and now conclusively know their baby does not have the condition, get to deliver at their home hospital with their own care team and bond with baby immediately after delivery. Before this technology, they would have remained unsure if their baby would have this condition until medical interventions and testing after birth.

"This is supposed to be a very exciting time in pregnancy, and then families might get the news that their child has this heart condition, and the excitement turns to anxiety," Dr. Barker says. "Knowing that 1 out of every 2 patients we might be reducing that anxiety motivates me."

And for families with a confirmed CoA diagnosis during pregnancy, the team can make a detailed plan for care postdelivery.

"For some patients it's hard news, but at the same time they are so grateful that we are able to tell them this information, and they know exactly what is going to happen," Dr. Browne says.

STRIVING FOR MORE

The team is onboarding other hospitals across the country to the new Doppler ultrasound gating device and helping them launch similar programs. While they are training others to join in these efforts, they are also focusing on other conditions that could benefit from this type of technology.

"It has a really wide scope of potential applications," Dr. Browne says. "What we're focusing on currently are the conditions where fetal cardiac MRI can make a dramatic difference to patient care such as informing interventions by improving delivery room and postnatal care planning and hopefully improving patient outcomes. It's exciting to be part of such a great team doing such important work." ●

1. Minocha, Prashant K et al. "Reference Values for Fetal Cardiac Dimensions, Volumes, Ventricular Function and Left Ventricular Longitudinal Strain Using Doppler Ultrasound Gated Cardiac Magnetic Resonance Imaging in Healthy Third Trimester Fetuses." Journal of magnetic resonance imaging : JMRI vol. 60,1 (2024): 365-374. doi:10.1002/jmri.29077.
2. Englund, Erin K et al. "Reliability of 4D Flow MRI for Investigation of Fetal Cardiovascular Hemodynamics in the Third Trimester." Radiology. Cardiothoracic imaging vol. 6,6 (2024): e240119. doi:10.1148/ryct.240119.

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"I use a silicone-based, soft adhesive dressing, and patients have liked it. You can shower with it on, and it is low management for the patient. We want to make it easy."

SUMEET GARG, MD

Closing Wounds, Calming Dermatitis

ORTHOPEDICS

Recovering from spine surgery is challenging for anyone, but for a select few kids, it's even more difficult. That's because in rare instances, the wound closure systems many surgeons use as alternatives to staples and sutures can cause allergic dermatitis, an immune response that leads to mild, but aggressive, rashes.

Sumeet Garg, MD, recently wrote a retrospective study (1) on a liquid adhesive wound closure system which combines 2-octyl cyanoacrylate and a self-adhesive polyester mesh. This type of wound closure helps lessen the appearance of scars and reduces the risk of infection, but for Dr. Garg, the rates of dermatitis were too high to continue using it.

"You're recovering from your surgery and then maybe you feel good from the actual surgery after a couple weeks. That's a time when you should be starting to walk more and do more things, and instead you are dealing with this uncomfortable, painful rash," Dr. Garg says.

He stopped using the adhesive several years ago because in a small percentage of patients, it caused significant dermatitis along the surgical site — often a large portion of the back. Instead, his team pivoted to using a similar system that still allows for cosmetic improvements and decreased risk of infection, but without the concern of dermatitis.

"Now I use this silver mesh on the incision that helps with infection and is antibacterial," Dr. Garg explains. "Then, I use a silicone-based, soft adhesive dressing, and patients have liked it. You can shower with it on, and it is low management for the patient. We want to make it easy."

Because the 2-octyl cyanoacrylate wound closure system remains a popular choice, Dr. Garg's study aims to give doctors who still use it a playbook on how to treat dermatitis should the concern arise. His team recommends topical application of medium-potency corticosteroids with antipruritic and vasoconstrictive properties. Additionally, Dr. Garg says doctors should consider using mupirocin ointment on the rash up to three times a day to prevent infection.

Above all though, Dr. Garg urges doctors to share potential risks of the closure system with patients and consider more skin-friendly alternatives, as surgical dressing options are always improving and advancing. ●

1. Miller, Florian, et al. "Dermatitis after spine fusion caused by liquid adhesive (2-Octyl cyanoacrylate)." Journal of the Pediatric Orthopaedic Society of North America, Volume 7, 2024, 100045, ISSN 2768-2765, https://doi.org/10.1016/j.jposna.2024.100045.

SUMEET GARG, MD

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Turning the Page on Treatment

PULMONOLOGY

Every day, tens of thousands of people with cystic fibrosis follow a strict routine, taking multiple daily medications and receiving respiratory treatments. This daily regimen is ingrained into their lives, but a new drug approved by the U.S. Food and Drug Administration (FDA) may help to decrease some of that treatment burden. Children's Hospital Colorado pulmonologist, Jordana Hoppe, MD, is at the forefront of this treatment breakthrough, transforming cystic fibrosis care nationwide.

In December 2024, the FDA approved Alyftrek for individuals with cystic fibrosis. This once-daily CFTR modulator is now available for approximately 90% of people with cystic fibrosis 6 years and older, based on their genetic variants.

Cystic fibrosis (CF) is a genetic disorder that causes severe damage to the lungs, digestive system and other organs. It's caused by mutations in the cystic fibrosis transmembrane conductance regulator (CFTR) gene. The CFTR protein produces thick and sticky mucus in various organs, which can block airways and passageways and cause severe complications. CFTR-modulator drugs, such as Alyftrek, target the defective protein to help improve lung function, lower the risk of respiratory infections, and reduce symptoms and hospitalizations.

Dr. Hoppe led a pediatric study evaluating the safety and efficacy of Alyftrek. The study enrolled 78 children with CF. Before participating in the trial, they were required to be on Trikafta, a current CFTR modulator, for at least four weeks. The participants had baseline assessments before switching to the new medication.

Researchers determined that the new drug is safe for the pediatric population, with most adverse events being mild to moderate in severity and often similar to symptoms of cystic fibrosis.

Not only is the medication safe, but it's effective too. Participants experienced an average decrease of eight points in sweat chloride values, the measurement used to diagnose cystic fibrosis based on the restoration of CFTR function. Through 24 weeks of treatment with Alyftrek, 95% of the participants recorded sweat chloride values lower than the diagnostic threshold for cystic fibrosis (<60mmol/L) and 53% recorded sweat chloride values in the normal range (<30mmol/L).

"To say someone has cystic fibrosis, they have to have a sweat chloride test of 60 or higher," Dr. Hoppe explains. "The percentage of participants that had a sweat chloride below 60, the diagnostic criteria for CF, and below 30, a sweat chloride value that is in the normal range, is higher than the clinical trials of Trikafta."

The international pediatric study ran concurrent with the adolescent and adult studies, allowing a younger group of patients to have earlier access to this new treatment.

"The earlier we are able to start highly effective CFTR modulators, such as Alyftrek, the better the long-term outcomes are going to be," Dr. Hoppe says.

Over the past few decades, cystic fibrosis treatments and life expectancy have improved significantly, thanks to advancements like CFTR modulators. These drugs are absorbed best when taken with a high-fat meal, and eating two high-fat meals daily, as required for Trikafta, can be challenging. Alyftrek helps ease some of the treatment burden for people with CF and their families.

"Anytime we can decrease the amount of medicine someone has to take, it's a good thing," Dr. Hoppe says.

Even with these incredible advances, Dr. Hoppe says there's still more work to do. Around 10% of people with CF are not eligible for CFTR modulator therapy due to their genetic variants. Researchers are committed to exploring new treatment approaches to enhance the health and quality of life for everyone affected. ●

JORDANA HOPPE, MD

Pulmonologist, Children's Hospital Colorado

Associate Professor, Pediatrics-Pulmonary Medicine, University of Colorado School of Medicine

Predicting With Precision

Q: How is microRNA helping doctors better predict the severity of congenital diaphragmatic hernia before a baby is born to create the best possible care plan for survival post-delivery?

Congenital diaphragmatic hernia (CDH) is a rare condition in which the diaphragm doesn't completely develop before birth. It impacts 1 out of 3,000 live births. Even though the Colorado Fetal Care Center at Children's Hospital Colorado achieves better-than-average outcomes for babies with severe cases of CDH, treating these babies remains difficult. In fact, about 50% of babies with severe cases will die from pulmonary hypertension, pulmonary hypoplasia or cardiac dysfunction as a result of their condition. Accurate prognostication for this population is essential, offering an opportunity for in-utero interventions and a tailored care plan post-delivery. Right now, diagnostic tools don't always offer the clarity providers need. Children's Colorado fetal and pediatric surgeon Chris Derderian, MD, is exploring new ways to predict CDH severity with more accuracy, ultimately offering babies the best chance for survival.

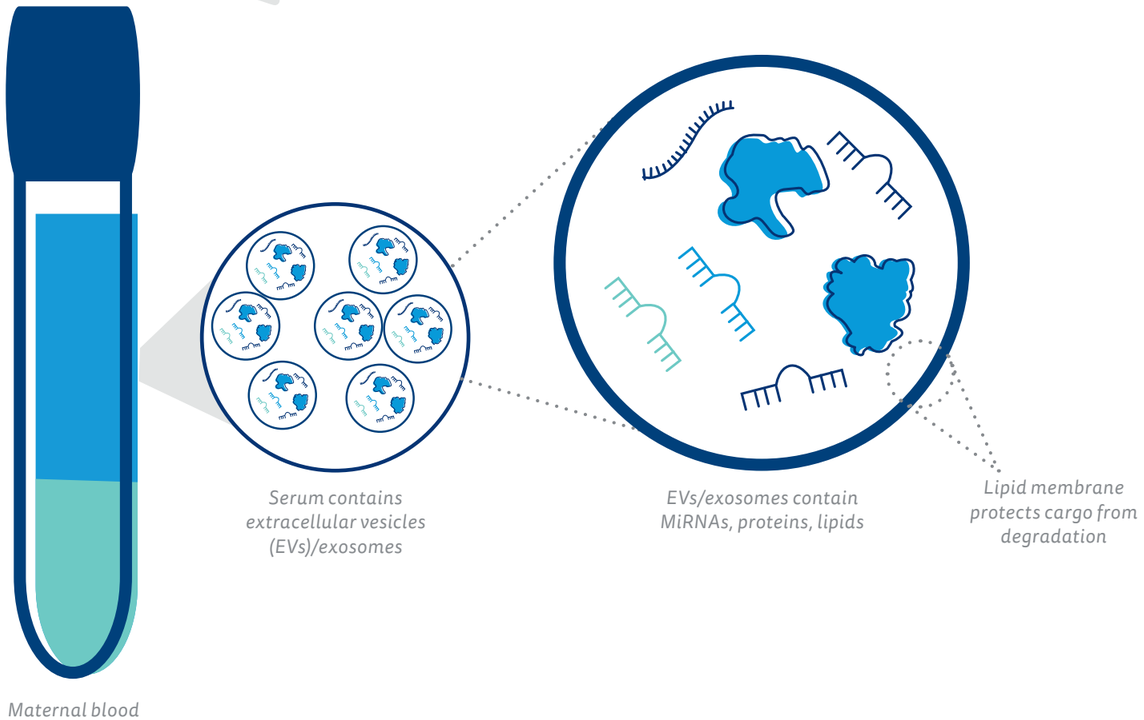
Understanding the severity of CDH in utero is very important for two main reasons. One, it allows the team to better counsel families on what to expect when their baby is born, so they understand survival likelihoods and what a hospital stay might look like after birth. Second, it helps the care team with delivery planning. Some of the most severe CDH cases require a Cesarean section and immediate extracorporeal membrane oxygenation (ECMO) support for the baby. The baby must then have CDH surgery to repair the diaphragm. If the condition is identified earlier enough, doctors may also offer fetoscopic endoluminal tracheal occlusion (FETO) — an experimental surgery performed in utero that can help with fetal lung growth for the most severe cases. Currently, doctors diagnose the severity of CDH through ultrasound and MRI scans, which are limited in their ability to diagnose these complex cases.

"Neither of these modalities are particularly accurate for predicting the need for ECMO or for survival," Dr. Derderian says. "There are opportunities for more accurate prediction."

Three years ago, Dr. Derderian and his team started to explore new approaches to enhance their predictions. For this study, they collected maternal serum samples from pregnant patients, amniotic fluid, cord blood and infant blood samples to analyze microRNA, which help regulate gene expression. Data points also included prenatal imaging predictors through ultrasound and MRI, such as lung volumes, whether the baby needed ECMO post-delivery, and how many babies survived and ultimately were discharged from the hospital. This study involved 11 control patients and 10 patients with CDH, and the team collaborated with the University of Colorado to obtain control samples.

First, the team analyzed the microRNA to identify which had the highest level of gene expression. Then they compared the CDH patients with the control patients using pathway analysis to identify differences that might relate to pulmonary hypertension and pulmonary hypoplasia, pointing at a possible therapeutic intervention opportunity.

Next, the team looked specifically at the microRNA for just the patients with a CDH diagnosis to conduct a biomarker analysis to identify any differences between CDH survivors and nonsurvivors. The researchers found there were a number of microRNAs that were expressed differently between those two groups. Using machine learning random forest analysis, which uses multiple decision trees to reach a single result, they measured the levels of expression for those microRNAs, compared survivors to nonsurvivors and found that they could predict which babies would survive with 100% accuracy. This gives the team a reliable biomarker to use to predict survival for these babies, providing families with a more clear and targeted care plan.



"These findings are promising," Dr. Derderian says. "Because this study was conducted on a relatively small sample size and at a single institution, we now need to validate with later cohorts and across multiple institutions."

Dr. Derderian and his team are also exploring similar research using second trimester serum, rather than third trimester serum, to see if they can replicate this success with the same high degree of accuracy. Those findings would be significant, because they would allow doctors to predict survival at an even earlier point in pregnancy, giving patients access to lifesaving fetal interventions, such as FETO, in hopes of impacting chances of survival.

The team will continue to explore and validate these findings to offer more detailed counseling for babies facing a CDH diagnosis.

CHRIS DERDERIAN, MD
Fetal and Pediatric Surgeon, Colorado Fetal Care Center, Children's Hospital Colorado
Assistant Professor, Surgery-Pediatrics, University of Colorado School of Medicine

Rising to the Challenge

CARDIOLOGY

Pediatric pulmonary arterial hypertension (PAH) is a condition that causes high blood pressure in the arteries of the lungs. Although adults can also have PAH, it presents unique complications in pediatric populations — especially children who are in their first year of life.

For instance, one of the most common types of pulmonary arterial hypertension is idiopathic, meaning there isn't a defined cause. It's also common for PAH to develop because of development-related lung diseases, such as broncho-pulmonary dysplasia and congenital diaphragmatic hernia. This creates the need for advanced and invasive therapies, such as balloon atrial septostomy, lung transplantation and pulmonary-to-systemic shunts, all of which carry risks to the patient.

To better address and account for these differences in age, development stage and pathology among PAH patients, the seventh World Symposium on Pediatric Hypertension created a new, dedicated task force to join their 15 total working groups. This new working group was led by Children's Hospital Colorado pediatric cardiologist Dunbar Ivy, MD. "This World Symposium is held every five years and it's an international group of clinicians who treat patients with pulmonary hypertension," Dr. Ivy says.

For their most recent report (1), the task force held proceedings and defined gaps in care around where further information and research are needed to better support children with PAH. One important area of this consensus discusses how to expand the pool of medications available to providers treating PAH through approval by the U.S. Food and Drug Administration, which currently poses many roadblocks.

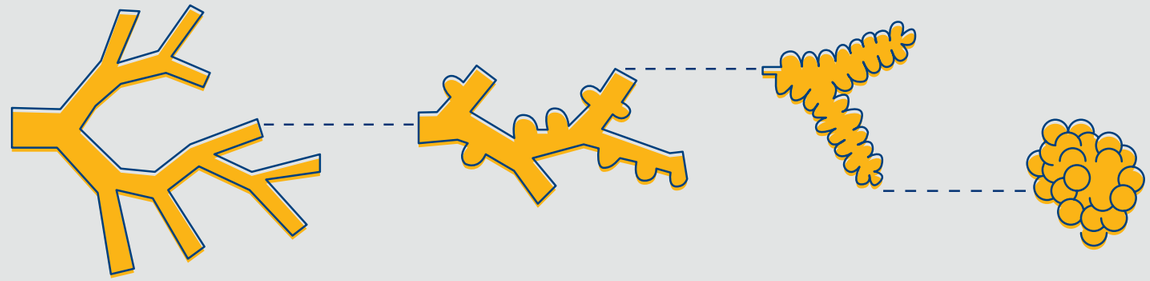
"Our goal is to try to answer all of the questions about imaging and diagnosis and treatments," Dr. Ivy says, "which is challenging, because pediatrics is typically underrepresented in these types of meetings." ●

1. Ivy, Dunbar et al. "Embracing the challenges of neonatal and paediatric pulmonary hypertension." The European respiratory journal vol. 64,4 2401345. 31 Oct. 2024, doi:10.1183/13993003.01345-2024.

DUNBAR IVY, MD

Pediatric Cardiologist, Heart Institute, Children's Hospital Colorado

Director, Pediatric Pulmonary Hypertension Program, University of Colorado School of Medicine



Drawing Connections

NEONATOLOGY

Children's Hospital Colorado neonatologist Erica Wymore, MD, is looking closer at the impact of severe hypertensive disease of pregnancy (HDP), such as preeclampsia, on infants. In particular, Dr. Wymore is exploring the association between HDP and bronchopulmonary dysplasia (BPD) in infants. BPD is the chronic lung disease of prematurity, often requiring long periods of ventilatory support from weeks to months.

Dr. Wymore's most recent study analyzed a cohort of 693 mother-infant pairs. For the purposes of the study, she defined severe HDP as severe preeclampsia, HELLP syndrome or eclampsia. The results showed that infants born at less than 25 weeks' gestation to a mother with HDP had a higher likelihood of developing moderate-severe BPD compared to their counterparts with standard blood pressures — almost two times higher. Babies born at 28 or 29 weeks' gestation did not have the same increased risk.

"We know there is an abnormal sort of vascular process that results in preeclampsia that affects the placenta," Dr. Wymore explains. "We also know in lung disease of prematurity, the blood vessels aren't normal in the baby's developing lungs. Both have a vascular origin story, and this supports that vascular hypothesis."

This research is made possible by a multidisciplinary group based out of the University of Colorado's Department of Ophthalmology where Dr. Wymore is the neonatology collaborator. The team has created a database of maternal and infant data for infants born prematurely.

This new research will allow the team to better counsel families dealing with HDP prior to birth by educating them on their baby's higher risk of lung disease and providing a clearer picture of what to expect during their NICU stay. It also opens the door for more research in the future.

"These findings demonstrate that there's something going on between this vascular disease of pregnancy and the subsequent risk in the fetus, so that's where our basic science researchers can investigate further to find out if there are any targets for therapies to treat these mothers earlier or more aggressively," Dr. Wymore says. ●

ERICA WYMORE, MD

Neonatologist, Children's Hospital Colorado

Associate Professor, Pediatrics-Neonatology, University of Colorado School of Medicine

Bringing ‘Home’ to the Hospital

PULMONOLOGY

When a child in need of long-term respiratory support is able to move from being intubated to having a tracheostomy, their world opens up. They no longer need to be sedated, and they can breathe, speak and eat. But that doesn’t always mean they get to go home. While these kids are medically stable, the logistics of their care remain complex, often requiring home nursing care, specialized equipment, and training for parents and guardians.

For some, getting each of these ducks in a row is manageable, but for others, it’s close to impossible to create the ideal, safe environment for kids with tracheostomies, due to racial and economic disparities, living situations, a nursing care shortage and more. When that happens, patients remain in the hospital under the care of Children’s Hospital Colorado’s Ventilator Care Program. Last year, that program developed an offshoot specifically for these patients: Transitional Respiratory and Airway Center for Kids, or TRACK.

Currently TRACK is home to roughly seven children, including infants, toddlers and young kids. They spend 100% of their time in the hospital and are housed in “neighborhoods” across two different floors at Children’s Colorado, Anschutz Medical Campus in Aurora. The program’s goal is to simulate the home environment as much as possible and help kids reach developmental milestones while they are stuck in the hospital waiting to transition back to life with their family.

“It is trying to make day-to-day life better and less hospitallike,” says pulmonologist Christopher Baker, MD, Director of the Ventilator Care Program. “They get up and they put on regular clothes, and they get out of their bedrooms as much as possible. … We are trying to do our best to meet an important need, but the most important need is that these kids need to go home.”

> “We are trying to do our best to meet an important need, but the most important need is that these kids need to go home.”
>
> CHRISTOPHER BAKER, MD

To bring TRACK to life, the team, which also includes Erica Bracken, Process Improvement Lead for the Children’s Colorado Breathing Institute, visited facilities across the country and met with others via Zoom. From their learnings, they developed routines and roles designed to give kids in the program the opportunity to simply be kids.

On the average day, that might look like waking up, getting dressed, and receiving medication and respiratory treatments. From there, it’s activity time. Every member of the team, including social workers, occupational and physical therapists, music therapists and more, are trained and outfitted with activity plans that help them keep kids active and engaged. In the afternoon, kids might receive more medical care and treatments before jumping into group time to focus on developmental skills and socialization. Right around shift change in the evenings, kids start winding down with baths, pajamas and even bedtime stories. Parents and caregivers are also welcome to join their kids for quality time and activities.

TRACK’s spaces are designed to engage too, with newly created playrooms, rehab spaces and big windows to help kids feel less like they are at a hospital and more like they’re at home, even when returning home is on hold.

The team hopes to one day expand TRACK to a separate location that truly can serve as a surrogate home for these kids, especially as some spend years in hospital care.

This, says Dr. Baker, is not the end goal, of course. Home is the end goal for each and every child. ●

CHRISTOPHER BAKER, MD

Pulmonologist, Director of the Ventilator Care Program, Children’s Hospital Colorado

Professor, Pediatrics-Pulmonary Medicine, University of Colorado School of Medicine

JESSICA DAWSON, MS, RN, CPN

Ventilator Care Program Clinical Specialty Coordinator, Children’s Hospital Colorado

A(:) List

Recent awards and accolades

Melvin Chan, MD

NEPHROLOGY

Immunosuppressive medications play a vital role in helping heart transplant recipients’ bodies accept their new organs. But while some drugs assist a new heart, they can also damage kidney function. That’s where Melvin Chan, MD, comes in. As one of the first graduates from the Pediatric Nephrology Fellowship at the University of Colorado School of Medicine, Dr. Chan is looking into risk factors that affect long-term kidney function and implementing standardized protocols to reduce these risks. Dr. Chan aims to help heart transplant patients with reduced kidney function live longer lives and further use his research to foster multidisciplinary collaboration across all areas of medicine.

Katherine Chin, DDS

PEDIATRIC DENTISTRY

American Academy of Pediatric Dentistry Trustee

The American Academy of Pediatric Dentistry (AAPD) recently named Katherine Chin, DDS, as trustee for the Southwest District. As Chair and Clinical Medical Director of the Children’s Hospital Colorado Department of Pediatric Dentistry, Dr. Chin has used her dentistry expertise to help care for underserved populations, provide multidisciplinary treatment, and help students and residents achieve their full potential. As a trustee for the AAPD, Dr. Chin will be responsible for serving on the educational and financial committees and for reviewing and approving its business. Her appointment as an AAPD trustee lasts three years. In addition to her roles with Children’s Colorado and the AAPD, Dr. Chin is a member of the Colorado Multiple Institutional Review Board and previously served seven years on the Colorado State Dental Board’s Anesthesia Review Committee.

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Connected through care

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

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

The work that sets us apart

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

Here, it's different.