Advances and Answers in Pediatric Health

Why Hearts Fail
Children’s Hospital Colorado doctors are working to uncover the exact mechanisms that lead to heart failure in single ventricle patients to slow disease progression. The team hopes to one day help children avoid heart transplants altogether. P.4

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With the launch of its new Precision Medicine Institute, Children’s Colorado is building infrastructure that it hopes will redefine what medicine looks like in the future.
A letter from a fellow questioner at Children’s Hospital Colorado

Dear colleagues,

When a child arrives at an emergency department with abdominal pain, providers often perform an X-ray, see stool in the intestines, blame the discomfort on constipation and send the patient home. While common, this approach is a leading reason why appendicitis — which isn’t detectable via plain radiography — gets misdiagnosed. There’s no doubt that diagnostics can be lifesaving in emergency care, but too much testing can also lead to unnecessary, inaccurate results that may do more harm than good.

How, as pediatric care providers, can we practice research-driven emergency medicine that improves diagnoses while minimizing risk?

A new list, developed in partnership with an organization called Choosing Wisely, is the first of its kind to offer guidance on this ever-important question. Created by a multinational taskforce of emergency medicine professionals at the American Association of Pediatrics, these recommendations are also the first to be endorsed by organizations from both the U.S. and Canada. Our list is based on rigorous published scientific data. It highlights eight common pediatric conditions associated with high diagnostic rates in emergency departments and offers data to help providers avoid these tests.

Having spent the last two decades researching evidence-based emergency medicine, this collaboration leaves me with a great sense of encouragement for what lies ahead. Not only will this list support providers navigating emergency care, but it will also reduce patient harm caused by excess radiation, prolong hospital stays and false-positive test results in a world where families face crowded emergency rooms, skyrocketing costs and pervasive uncertainty.

As we prepare to share our methods with colleagues across North America, I’m hopeful that this list will help us all create a healthier and less burdensome future for every child.

Best regards,

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Medicine for the Future

NEUROLOGY
Children’s Hospital Colorado is partnering with the GRIN2B Foundation to open a new center focused on developing a standard of care for patients with genetic conditions related to ionotropic glutamate receptors, known as GRI disorders. This will be the first GRI Center of Excellence in North America. These GRI variations cause a range of neurodevelopmental disorders with symptoms such as low muscle tone, gross and fine motor disabilities, seizures and limited speech.

The team’s research efforts focus on genetic sequencing and personalized care. Kristen Park, MD, who serves as the Center’s director, says that while more still needs to be explored about these rare conditions, this area of medicine has grown significantly over the past several years.

“It’s snowballed into this big path of discovery,” Dr. Park says. “At our hospital, as we’ve taken up genetic testing as a big part of diagnosis and management for epilepsy in the pediatric population, we have identified more and more kids [with these GRI conditions].”

Now, the Center will take those efforts to the next level and formally bring together a multidisciplinary team of specialists from a nurse coordinator, neurologist and genetic counselor to a developmental pediatrician, speech therapist and social worker. The Center will begin seeing patients with these rare genetic variations in May 2023, thanks to a generous donation from the GRIN2B Foundation.

“The Center is starting to make connections, centralize treatment and provide families with expertise if they live in an area where they did a genetic test, but they don’t understand that result,” Dr. Park says. In addition to providing comprehensive, multidisciplinary care to GRI patients, the Center will also participate in a natural history data collection effort and collaborate on groundbreaking clinical research as experts seek to understand more about these rare conditions.

“To me, the best thing about it is how many people are coming together from so many different places to make change and progress happen,” Dr. Park says. “You have the scientist in the lab, the clinicians who are caring for patients face-to-face, families who are raising money, awareness and connecting people so we can get all this data. We have a lot of investment from people to make this happen, and I think that is the way of medicine for the future.”

OPHTHALMOLOGY
Children’s Hospital Colorado is now home to the first pediatric genetic eye disease clinic in its seven-state region. Emily McCourt, MD, will oversee research and treatment at the clinic as the inaugural Ponzio Family Chair for Pediatric Ophthalmology.

Now, children with rare eye diseases can visit a range of specialists, including ophthalmologists, retina dystrophy specialists, geneticists and genetic counselors at the same visit. Unting these experts in a single location isn’t just convenient for families, it also fosters communication that’s essential for advancing research.

“The endowed chair gives us the ability to have a collaborative clinic,” Dr. McCourt says. “It sets the groundwork for customized gene therapies and other innovative ways to diagnose and treat genetic eye disease. Combining our knowledge and treating patients together creates a deeper understanding of these conditions, which is essential to preventing and curing blindness in children.”

When the endowed chair was finalized in January 2023, Dr. McCourt and her team established an inherited retinal disease registry in collaboration with the University of Colorado School of Medicine’s Division of Ophthalmic Epidemiology. The registry, which is poised to be the largest of its kind in an academic setting, will assist researchers in understanding which inherited diseases, such as retinitis pigmentosa, are more common in Colorado — and how they can best be treated.

In the few short months that the clinic has been seeing patients, the team’s work has already proven life-changing. On their first day, Dr. McCourt’s team diagnosed a rare, yet treatable genetic condition.

“We made a diagnosis that could save a child’s life,” Dr. McCourt says. “This added to the momentum and excitement we have about seeing children with genetic eye diseases as a collaborative team.”

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Advancing a Vision

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A team of doctors at Children's Hospital Colorado's Heart Institute is working to uncover the exact cause of why some children's single ventricle hearts fail after surgery and identify potential therapeutic drugs to stop that progression.

UNCOVERING ANSWERS

When Dr. Garcia arrived at Children's Colorado nearly eight years ago, Dr. Miyamoto saw an opportunity to bridge the world of basic science and clinical translational research for single ventricle heart disease. At the time, researchers knew that adults with heart failure typically have mitochondrial dysfunction, where the energy factory of the cells is not functioning properly. But that was never proven true for single ventricle pediatric patients — until now.

"Until recently, very little was known about the transition to heart failure in this unique population," Dr. Garcia explains. "But over the past several years, our lab and others have really characterized what happens at a molecular level."

Dr. Garcia has worked her entire professional career to identify mechanisms of heart failure progression and to assess if there is mitochondrial dysfunction in these failing single ventricle hearts. And according to Dr. Miyamoto, Dr. Garcia's latest paper, published earlier this year in Journal of the American College of Cardiology, is the first to show proof of this. Her team found that failing single ventricle hearts have dysregulated metabolic pathways and impaired mitochondrial function. They also found an intermediate metabolic phenotype in single ventricle hearts prior to the onset of heart failure, suggesting even nonfailing single ventricle hearts are vulnerable to metabolic dysfunction and eventual heart failure (1).

SUPPPORTING THE RESEARCH

These kinds of studies are possible thanks to the cardiac tissue biobank on the CU Anschutz Medical Campus. This is an essential tool for pediatric researchers studying heart failure because they are not able to conduct many of the invasive studies researchers perform to study heart failure in adults, such as heart muscle biopsies. Once a child needs a heart transplant, the researchers get permission from the families to take part of the diseased heart for this biobank. The challenge with mitochondrial studies like the one Drs. Miyamoto and Garcia have been working on is timing.

"These mitochondrial studies have to be done in the moment, because once you freeze the mitochondria, they burst and they aren't going to function anymore," Dr. Miyamoto says. "Some of these studies need to be done in the middle of the night or the middle of the week. If it's Christmas Day, it's done on Christmas Day."

Once the team is notified that a heart transplant is taking place, they spring into action to complete their mitochondrial studies immediately. They then freeze the rest of the heart tissue to study later.

"That freezes that piece of tissue in time. So, it preserves things like enzymes, proteins and genes so we can go back and look later," Dr. Miyamoto says.

IDENTIFYING PROMISING THERAPEUTIC TARGETS

With this understanding of the mitochondria’s role in heart failure for single ventricle patients, Drs. Miyamoto and Garcia and their team have turned to studying different, promising therapeutic options that target the mitochondria’s function.

"This is highly impactful, because there are now drugs that target the mitochondria," Dr. Miyamoto explains. "If this is one of the reasons the heart is failing, then there are therapies that can target that mitochondria and hopefully help the mitochondria function better."

Along with their collaborator, Denver Health’s head of cardiology Brian Stauffer, MD; Drs. Miyamoto, Garcia and Chatfield have identified the drug elamipretide (which is not yet FDA approved for any indication in the U.S.) as a helpful option to improve mitochondrial function in a failing heart. In addition to this drug, Dr. Miyamoto's current R01 grant is looking into a drug called sildenafill, which could also improve mitochondrial function in this population.

"We need to think about different targets of therapy and identifying different drugs that work in our [pediatric] population and not just assume that all these drugs that are great for adults with heart failure are going to help children," Dr. Miyamoto says.

The location of Children's Colorado on a major medical campus with researchers studying the entire lifespan on all corners of campus offers a unique opportunity for collaboration. Dr. Miyamoto says all this work would not be possible without the valuable collaboration with adult cardiology colleagues on the CU Anschutz Medical Campus who started this group with her back in 2007. Kika Sucharow, PhD, a molecular biologist, and Dr. Stauffer. Dr. Chatfield is also on the pediatric team as one of Dr. Miyamoto's mentees, and she is an expert in cardiac genetics and mitochondrial function, who plays a key role in bringing these research studies to life. She has also been essential to the team’s research on the drug elamipretide and mitochondrial function over the years.

ADVANCING DISCOVERY WITH A MULTIFACETED APPROACH

Pediatric cardiologist Dr. Nakano collaborates closely with Drs. Miyamoto and Garcia and is continuing to push this research forward with a $2.4 million award from the Department of Defense (DOD) to study a specific kind of single ventricle heart disease.

"This is a big step forward for the field of single ventricle heart disease," Dr. Nakano says. "It’s allowing us to take a closer look at what’s happening inside the mitochondria and to test potential therapeutic targets that could help prevent heart failure in this group of patients."

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why hearts fail continued

hydropic left heart syndrome (HLHS). HLHS is a condition where the left side of the heart is underdeveloped and nonfunctional. This study generates heart muscle cells from circulating white blood cells in HLHS patients, known as human induced pluripotent stem cell-derived cardiomyocytes.

Dr. Nakano will explore three different areas with the DOD’s Investigator-Initiated Research Award funding. The first area is focused on better understanding the changes in HLHS heart muscle cells that predispose them to failure, which could ultimately help delay or erase the need for a heart transplant. Next, the study will investigate the effects of having low oxygen levels for an extended period of time, as many single ventricle patients are exposed to low oxygen for the first years of their life. The third part of this research focuses on better understanding the changes in HLHS heart muscle cells that predispose them to failure, which could ultimately help delay or erase the need for a heart transplant.

Over the years, these Heart Institute doctors have shifted their collaborative efforts are accelerating our understanding of why and how these young hearts fail for the smallest patients. 1. Garcia A, Toni L, Miyano C, et al. Cardiac Transcriptome Remodeling and Impaired Bioenergetics in Single-Ventricle Congenital Heart Disease: J Am Coll Cardiol Basic Trans Science. 2023 Mar 6;8(5):258–279. https://doi.org/10.1016/j.jacbts.2022.09.016.

Their collaborative efforts are accelerating our understanding of why and how these young hearts fail for the smallest patients. 1


why and how these young hearts fail for the smallest patients.

Clearing the Airways

PULMONOLOGY

Primary ciliary dyskinesia (PCD) is a rare genetic disorder that impairs the functioning of cilia, hair-like structures that line the airways. It affects the movement of mucus, leading to chronic ear, sinus and lung infections. Patients with PCD suffer from respiratory problems such as coughing, wheezing, shortness of breath and bronchiectasis. Until now, treatment has focused on managing the symptoms of the disease. But a recent study published in the Annals of the American Thoracic Society has uncovered new information that could lead to better therapies for the disorder.

The study, led by Scott Sagel, MD, PhD, a pediatric pulmonologist at Children’s Hospital Colorado, and made possible by the National Institutes of Health-funded Genetic Disorders of Mucociliary Clearance Consortium and the Colorado Clinical and Translational Sciences Institute at the University of Colorado School of Medicine, investigated the relationship between airway inflammation and lung disease in children with PCD.

Using a multicenter cohort of children with PCD, researchers focused on three areas of investigation: if measurements of airway inflammation are linked to lung function, bronchiectasis and airway infections; differences in inflammatory measurements between categories of ciliary ultrastructural defects; and sputum inflammatory measurements in children with PCD compared with children with cystic fibrosis (CF) — a similar lung disease.

The findings of this study are significant, as they pave the way for better treatments for a rare disease that has thus far had few disease-specific options. By identifying the role of airway inflammation in lung disease for children with PCD, researchers can now test anti-inflammatory drugs to treat this aspect of the disorder. This is a promising development for the PCD community, and it demonstrates the value of investing in research into rare diseases. 2

Their collaborative efforts are accelerating our understanding of why and how these young hearts fail for the smallest patients.

Their collaborative efforts are accelerating our understanding of why and how these young hearts fail for the smallest patients.


Why Hearts Fail continued

Cardiac tissue sections from a normal pediatric subject (left) and a subject with single ventricle congenital heart disease (right), stained for nuclei, cardiomyocytes, fibroblasts/vessels and T lymphocytes.

SCOTT SAGEL, MD, PHD
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An all-women team of pediatric orthopedic surgeons at Children’s Hospital Colorado is challenging the status quo with their hip dysplasia research. Gaia Georgopoulos, MD, Margaret Siobhan Murphy-Zane, MD, Nancy Hadley-Miller, MD, and Courtney Selberg, MD, are aiming to not only provide the best care, but also create a whole-patient experience that is unique to Children’s Colorado by incorporating education into the treatment process. This is helping babies get the care they need sooner and helping to decrease the need for pain medication post-procedure. Together, this team of surgeons conducts research and cares for kids across the entire pediatric experience from infant diagnosis into early adulthood.

Developmental dysplasia of the hip is a relatively common condition where the hip joint develops abnormally, making the round, upper end of the femur bone sit improperly in the hip socket. The cause is unknown, but believed to be a developmental issue that occurs before or after birth. The most common treatment for infants is the Pavlik harness, a soft splint that supports the baby’s feet all the way up to the shoulders, helping keep the baby’s hips in a proper position. Babies typically wear the harness for 12 weeks and require intense caretaker oversight as the baby’s movement is very limited.

Children’s Colorado’s orthopedic surgery team is constantly evaluating the effectiveness of their protocols to ask themselves: Do infants actually require a full 12 weeks of treatment or are we overtreating patients? How can we make our care optimal for the patients and easier for the parents?

Drs. Georgopoulos, Murphy-Zane and Hadley-Miller have published several recent studies advancing the standard of care for the Pavlik harness and expanding the knowledge on ongoing management (1). The group is making these evaluations by studying the baby’s age, risk factors, bracing ability and more. These types of studies are possible thanks to the hip registry this team is building at Children’s Colorado, where researchers can dive into the data for a clear understanding of what the research shows is effective.

This registry will also allow the team to continue tracking these patients over a longer period of time, opening up opportunities for personalized treatment for this group of patients in the future. “We are continually evaluating our protocols and making changes to make things a little easier for the families — not so many visits or not so many ultrasounds,” Dr. Georgopolous says. “The hip registry makes it easy for us to go back and look at these and other factors, allowing us to ask good targeted research questions that then can be translated into more personalized care.”

The group recently found babies don’t always need the full 12 weeks of the Pavlik harness to make a full recovery, allowing some families to end that treatment earlier or slowly wean off the treatment before the 12-week mark. This approach still offers many benefits without sacrificing long-term outcomes (2).

Another study revealed the importance of the six-month X-ray and ultrasound in the ongoing management of hip dysplasia. They found that these tests are particularly valuable in predicting residual dysplasia in the future, which can lead to an increased risk for osteoarthritis and functional limitations (3).

Dr. Murphy-Zane says, “I think that our manuscripts reflect that you can have a treatment that works really well, but you have to make sure that you’re doing it for the right reasons. And that has been what our papers have focused on. Are there ways that we can make it easier? For sure.”

Outreach is also a key part of the work. Drs. Georgopoulos, Murphy-Zane and Hadley-Miller are doing to improve care for infants with hip dysplasia. The group connects with pediatricians to help educate them on sensitive risk factors for hip dysplasia in babies. “The education has really made a difference in how often we are seeing these kids before things get pretty bad,” Dr. Murphy Zane says. “Our goal is to not do surgery on these kids. Our goal is to see them early enough that we can treat them with nonoperative methods.”

CARE ACROSS THE LIFESPAN

Dr. Selberg is the final piece to the puzzle. Her research and care focuses on teenagers. For teens with symptomatic hip dysplasia, the periacetabular osteotomy (PAO) procedure is one of the main treatments to correct the hip positioning. Dr. Selberg and her team have created a whole-patient experience that is unique to Children’s Colorado by infusing education into the treatment process to limit the need for pain medication post-procedure.

The team offers a hip education class every month for patients with upcoming PAO surgery. The virtual class gathers physical therapists, nurses and physician assistants to help patients understand the nuts and bolts of surgery and what to expect from recovery. This class also provides a unique opportunity for the patients to hear from a former patient to learn more about their experience.

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“Our goal is to not do surgery on these kids. Our goal is to see them early enough that we can treat them with nonoperative methods.”

MARGARET SIOBHAN MURPHY-ZANE, MD

“They want to know what their scar looked like and how it was going back to school,” Dr. Selberg says. “We do a lot of education before surgery, so we can make sure our patients are on board — that they have their work set up and their home environment set up. If it really helps people be more successful with the outcome of their surgery and be happy about it.”

Dr. Selberg and her team have found this is helping patients feel more confident and prepared before surgery. The team is also analyzing the benefits of using a dedicated perioperative team protocol for the PAO procedure, including anesthesia providers specializing in hip procedures and an intraoperative neuromonitoring team. So far, they have found this approach minimizes blood loss, shortens operative time and lowers transfusion rates. Dr. Selberg presented these findings to the Pediatric Orthopaedic Society of North America in 2022.

A FOCUS ON NON-NARCOTIC PAIN MANAGEMENT

The other main focus of Dr. Selberg’s research is looking at ways to implement a non-narcotic pain management routine. Right now, she is conducting a pilot study using the HeartMath device — a small machine that measures heart variability. Participants are trained in perioperative resiliency, providing them with a toolkit of options for coping with surgery and recovery, such as various breathing techniques.

“When they are in the hospital, they can employ some of these techniques for taking control of their breathing, visualizing what options they have to ask for help and getting up to move around,” Dr. Selberg explains. “The first answer is no. ‘They just need more pain medication.’ Setting up the expectation that we have lots of tools in our toolkit for dealing with pain really helps it become very manageable for patients.”

These education opportunities, paired with the research on the benefits of a perioperative team protocol, are setting patients up for success and allowing teenagers to use less pain medication post-operation.

“Those things really distinguish our center for excellence in terms of doing surgery in a safe way and making sure we are minimizing narcotic use and minimizing hospital stay,” Dr. Selberg says. “That’s definitely one of our strengths.”


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Demystifying Acute Kidney Injury

According to an international study of critically ill children, when a patient in the pediatric intensive care unit (PICU) develops severe acute kidney injury, or AKI, they are eight times more likely to die. For Erin Stenson, MD, that statistic — and the fact that more than 25% of kids in the ICU develop AKI — has been a constant driver behind research that aims to identify the disease early and treat it with precision. She recently published a review (1) of existing knowledge on AKI and has a prospective pediatric study underway to examine this issue further.

Acute kidney injury can result from a variety of conditions that might put kids in the ICU, including trauma and respiratory failure. The most common cause though, Dr. Stenson says, is sepsis. When a child develops a bad infection leading to sepsis, the body relies on the immune system to kill bacteria and viruses. One component of this immune response is the complement system, which is normally highly regulated. But an overactive or dysregulated complement system can begin attacking and killing healthy cells as well. This tends to have a pronounced effect in the kidneys, sometimes leading to AKI.

Given this well-studied relationship between complement system activation and AKI in preclinical models, Dr. Stenson is working alongside Children’s Colorado nephrologist Brad Dixon, MD, and other colleagues at the University of Colorado to identify a complement system biomarker that could indicate elevated risk of AKI. Her current research is focused on factor B, a protein that amplifies activation of the complement system. This activation creates a byproduct in the urine, called complement factor Ba, that Dr. Stenson thinks could serve as a canary in the coal mine for AKI.

As part of this, Dr. Stenson is identifying urine Ba levels that signal worse outcomes of AKI, with the long-term goal to trial novel therapeutics that inhibit factor B to treat AKI. This work is critical, as there are currently no treatments beyond supportive care for AKI, and even if a patient survives an episode of AKI, they are at increased risk for issues as adults.

“If we can limit AKI episodes, we can limit chronic kidney disease and thus the need for dialysis or a kidney transplant as these patients age,” Dr. Stenson explains. “It could have a huge population impact in the future.”


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SHORT ANSWER

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ORTHOPEDICS

| CHILDREN’S HOSPITAL COLORADO | 10 |

A Joint Effort continued
Smarter Image

**Q How can artificial intelligence models use personalized medicine to improve outcomes for children with craniosynostosis?**

An infant’s skull is held together by flexible tissues called sutures, which expand to allow bone growth and accommodate a rapidly growing brain. In children with craniosynostosis, sutures fuse prematurely, causing skull malformation and raising risks of elevated intracranial pressure, vision changes and developmental delays. Treatment for craniosynostosis can have varied results because surgeons may not have data that could help them accurately predict patients’ cranial growth. Now, craniofacial surgery experts at Children’s Hospital Colorado are employing artificial intelligence to create personalized, data-driven models that improve outcomes.

Antonio R. Porras, PhD, pediatric plastic and reconstructive surgery research director at Children’s Colorado and assistant professor of biostatistics and informatics at the University of Colorado School of Public Health, leads this work. Dr. Porras’ team uses artificial intelligence (AI) software to fuel photogrammetry, which takes images of a child’s head from various angles. The resulting anatomical representation not only helps diagnose cranial abnormalities sooner, but also helps predict their progression — all with extraordinary accuracy.

“When we get a patient in the clinic now, we have methods that can tell us exactly what part of the cranium is abnormal, by how much it is abnormal and how much less volume the brain has in a specific area of their head,” Dr. Porras says. “And that is extremely important for surgeons to plan their treatments.”

**FORWARD THINKING**

AI modeling is a novel approach for craniofacial surgeons, but the data sustaining this software is years in the making.

A decade ago, Children’s Colorado’s craniofacial clinic co-director Brooke French, MD, launched an image database intended to improve evaluations for patients with craniofacial differences. The database has nearly 1,500 images, including CT images and 3D photograms of craniosynostosis patients before and after surgery. This database was then extended by Dr. Porras’ team to include CT images of patients without craniosynostosis and those with intracranial hypertension, or elevated head pressure — a potential complication of untreated craniosynostosis. Both sexes are represented across the dataset.

“The work of my team was to leverage all the data that Dr. French acquired and build a tool that would inform us toward the best course of action for every patient,” Dr. Porras says. These images provide a wide range of references for comparison that guide artificial intelligence modeling. This helps quantify even subtle anomalies with greater accuracy.

“With this data, we can create a better tool to help us choose the right surgery and timing,” Dr. Porras says. “We can enable our surgeons to take action before there is an actual problem with the child’s development.”

**A PATH TO PREVENTION**

Today, this technology transcends the limitations of previous cranial models in multiple ways. For one, the noninvasive approach may eliminate the need for multiple CT scans to evaluate craniofacial differences, which expose children to harmful radiation and often require sedation.

Instead, these new methods can use fewer CT scans to quantify individual details, such as bone shape, thickness and mineral density. Additionally, they use 3D photogrammetry to create models that account for variability in head shape between the sexes. Both methods help improve surgical accuracy.

Additionally, Dr. Porras and his team can use the tool to predict changes during a child’s life up to 10 years of age, which is when the most cranial growth occurs.

These personalized predictions are the key to preventing complications that can be life-changing for craniosynostosis patients. “We can enable our surgeons to take action before there is an actual problem with the child’s development,” Dr. Porras says. Since these research methods are less focused on a specific pathology and more focused on understanding abnormal patterns of cranial growth at large, this approach to prevention may extend to children with other craniofacial conditions.

Dr. Porras was recently awarded an R01 grant from the National Institutes of Dental and Craniofacial Research, which he will use to build the first quantitative reference for local head volume development in craniosynostosis patients. Specifically, this reference will illuminate the correlations between regions of the head that are underdeveloped, and those experiencing overgrowth — a key metric for planning effective treatment.

This research will also create methods and tools for evaluating, comparing and predicting growth after different treatments, as well as potential relapses, which will help surgeons identify the best course of action.

**CROSS-DEPARTMENTAL COLLABORATION**

The Craniofacial Clinic at Children’s Colorado leads the nation with these AI innovations, but it wouldn’t be possible without such strong multidisciplinary collaboration. Drs French and Porras’s advancements in care are a result of partnerships with the neurosurgery and craniofacial surgery departments at Children’s Colorado, as well as the biostatistics and informatics, medical genetics and craniofacial biology departments at the University of Colorado. This approach was vital not only in creating the computational methods and software, but also fostering ease of use and implementation for clinical teams.

“It’s really hard finding a team that can do all these things together,” Dr. Porras says. “We’ve been very lucky here that we have been able to create a multidisciplinary team between the university and the hospital.”

The goal of this collaboration is to both advance understanding of the developmental mechanisms of craniofacial disease, and to use this knowledge to create tools that surgeons can easily use for faster, more accurate treatment. Currently, Dr. Porras is asking surgeons to try out the tool and provide feedback to evaluate its usability. That way, surgeons can analyze a patient’s head, understand their exact condition and create a plan for treatment — all in real-time.

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How can improved infrastructure for precision medicine increase access to genetic testing and targeted treatments?

At Children's Hospital Colorado, precision medicine has long been a key strategy for rare disease diagnosis and treatment, but access to the powerful tools behind this work has varied across programs and providers. Now, that’s changing. With the launch of the new Precision Medicine Institute, Children's Colorado will build cross-cutting infrastructure designed to improve access to knowledge, resourcing and connectivity for all clinical areas across the organization. The overarching goal is to improve care, particularly for kids with rare diseases.

Among children, rare diseases are troublingly common. In fact, according to Global Genes, a rare disease-focused organization, children are the most affected by these difficult-to-treat conditions, with about 50% of all rare diseases occurring in kids. Of that 50%, roughly 30% don’t live beyond the age of 5. For many kids, effective treatment comes down to how quickly they can get an accurate diagnosis. But pinning down these rare diseases can be an odyssey, and the average time to diagnosis is roughly seven years. During that time, families can endure misdiagnoses, mismatched treatment plans and more questions than answers.

In recent years, however, physicians have landed on a powerful medical framework that is beginning to change these statistics: precision medicine. Using genetics, environmental factors and large genomic data sets, doctors can reach a diagnosis quicker and gain a better understanding of the specific underlying causes of a child’s condition. This, in turn, allows for treatment plans targeted to each patient’s individual needs (including drugs made specially for them) and ultimately improves outcomes.

At Children’s Colorado, this precision medicine effort is led by Scott Demarest, MD, clinical director; Alisa Gaskell, PhD, scientific director; and Gregor Stoddard, administrative director. The trio thinks of the new Institute as a pillar with three key layers: diagnostics, therapeutic options and education. By joining together to direct this work, they hope to maximize the impact of each layer by expanding genetic testing for as many patients as possible, creating robust data sets to ensure that testing leads to diagnosis, and increasing available therapeutic options through drug development and repurposing, as well as broader access to clinical trials.

Importantly, this work is not solely scholarly. While research is a crucial piece of this puzzle, the team views its work as iterative in nature. “We actually think the critical point is the junction of those two,” Dr. Gaskell says. “It’s how implementing something in clinical care can create the opportunities for additional data and learnings that can improve care. Data is only valuable if it is used.”

The Precision Medicine Pyramid

The team likens precision medicine to a pyramid. At the base is access to genetic and genomic testing, which typically depends on everything from insurance to what providers you’re working with and their experience. Through the new Precision Medicine Institute, the team hopes to break down some of these barriers to ensure every patient who could benefit from these tests gets them. One of the key strategies for this is to bring as much of the work in-house as possible so that it can be done quickly and under one roof. This will allow the Children’s Colorado team to maximize the expertise of clinical and technical experts.

“Through the new Precision Medicine Institute, the team hopes to break down some of these barriers to ensure every patient who could benefit from these tests gets them.”

Continued on the following page
“Genetic results are not just individual results. They have implications for the entire family.”

GREGOR STODDARD

“That immediately ties you into a database of knowledge about the implications of that diagnosis to guide our clinicians on providing exactly the right care for that patient.”

Even with tools like whole-exome sequencing, which allows doctors a detailed look at the coding material in a patient’s DNA, not every patient will receive a diagnosis. That’s why, as part of the Institute’s work, researchers aim to improve existing genetic testing options and link clinical care with research to ensure more kids get the right diagnosis and treatment.

When a patient does get a diagnosis, doctors begin by exploring existing therapeutic options. In one recent case, Dr. Demarest was tasked with treating two young girls who had persistent seizures. Typical treatments yielded minimal results. That changed once whole-exome sequencing came into play. Through that testing, Dr. Demarest discovered that both girls had a novel gene change that impeded their ability to process vitamin B6, which the team had been using to lessen their symptoms. By switching to a form of vitamin B that their bodies could easily process (and that could be readily purchased at local health stores), the team was able to completely stop the girls’ seizures, leading to significant developmental gains.

Repurposing existing supplements and drugs, like Dr. Demarest did in this case, represents the middle layer of the pyramid. But sometimes that’s not possible and doctors must move to the tip of the pyramid: novel therapeutics. In some cases that means developing a brand-new drug specifically tailored to one individual’s unique genetic makeup. That work has begun at Children’s Colorado, and the team hopes to see significant expansion as a result of the Institute’s improved precision medicine infrastructure.

EDUCATION ACROSS THE SPECTRUM

In addition to clinical care and research, the Precision Medicine Institute is dedicated to education in multiple forms. That education starts with patients and families, as such information is incredibly personal and can have rippling effects.

“Genetic results are not just individual results. They have implications for the entire family,” Stoddard says. “There is a level of ethical responsibility we have in a consideration of the entire family unit that we want to bring to bear as we’re integrating this into standard clinical practice.”

The team also aims to serve as an educational resource for providers and researchers everywhere, ensuring they have access to information on available tools and how they can be used to pinpoint a patient’s therapeutic needs.

“Education really serves as the glue that makes this all happen together,” Stoddard says. “If you build all the best infrastructure, but people don’t know how to utilize it and it’s not being put into practice, then you’re not getting anywhere.”

HEALTH EQUITY AND GENETIC TESTING

This work has the potential to make a measurable impact on rare disease outcomes, improving and saving lives like never before. But the Children’s Colorado precision medicine team has found themselves asking important questions about whose lives are being impacted and why.

“We mapped the human genome for the first time in 2008 and since then, there’s been a tremendous amount of advancement in this space, but we have oversampled individuals from Western European descent. So, we know a lot of things, but we know them largely about certain patient populations,” Dr. Gaskell says. “We have a moral imperative not only to ensure that when you need genetic testing within our organization, you get it, but also that we are appropriately testing patients of all backgrounds to inform our knowledge base going forward.”

In placing a clear, intentional emphasis on equity and embarking on a dedicated effort to improve access to genetic testing for kids from minoritized communities, backgrounds and socioeconomic statuses, the team hopes to contribute to overarching knowledge. This will not only allow doctors to better treat kids who visit Children’s Colorado, but also help patients across the globe.

“Part of this is increasing our knowledge of minority groups and what their genetics and genomics look like,” Stoddard adds. “In minority groups, we have a much harder time because we just don’t have a strong database behind those patient populations.”

That goal, like the others driving the creation and implementation of the Precision Medicine Institute, is big and will require focused effort. But for Dr. Demarest and the rest of the team, this work is crucial in building an entirely new approach to medicine that will ensure all patients receive the very best care possible. He hopes that one day precision medicine won’t be the “medicine of the future” — it’ll just be medicine.
Less Sugar, Sweeter Futures

Q. Can specific dietary changes reverse serious liver disease in children—and lower NAFLD rates nationwide?

Nonalcoholic fatty liver disease (NAFLD), a common and progressive disease, is on track to become the leading cause of liver transplants among adults. Childhood intervention is essential for mitigating serious disease in future generations, but the nutritional mechanisms contributing to NAFLD have remained unclear. Researchers at Children’s Hospital Colorado recently published findings that illuminate how both the severity of this disease—and its reversal—depend on a surprisingly simple ingredient: sugar (1).

RISING DISEASE

NAFLD, a disease characterized by fat accumulation in the liver, is an obesity-related complication that can increase the risk of high blood pressure, cardiovascular disease and Type 2 diabetes, among other comorbidities. In the United States, this disease now affects 10% of all children and 38% of children with obesity, with Hispanic youth experiencing disproportionately higher rates of NAFLD.

At Children’s Colorado’s Liver Center, director Shikha Sundaram, MD, sees patients with this disease daily. That first-hand experience is exactly why her recent research explores the role of dietary interventions in curbing rates of NAFLD.

“My study suggested that kids with NASH probably take in about 10 more spoons of sugar than kids without the disease,” Dr. Sundaram says. Specifically, among patients with NASH, a bigger proportion of their energy intake came from simple sugars—such as those found in sweetened beverages, rather than those found in fruit.

“Like when we speak to families, we talk about sugar, sweetened beverages, juice, Gatorade, sweet tea and soda, and it’s not unusual for us to hear that a child is taking in two to three of those beverages per day,” Dr. Sundaram says.

This research study is the first to show that sweeteners can directly contribute to the onset and progression of NAFLD, but that’s not all. Their research also proved that in children, reducing dietary intake of added sugars can reverse—and even eliminate—severe instances of disease (and its complications).

DISPROVING MISCONCEPTIONS

While her research focuses on obesity-related liver disease, it also helps clarify a major misconception around obesity at large: It cannot be cured by simply eating less.

“Our data shows that, when comparing the lean kids to those with NAFLD, their total caloric intake is actually very similar,” Dr. Sundaram says. “That speaks, physiologically and biologically, to what’s happening.”

Specifically, the research shows that the onset of NAFLD isn’t about how much a child eats; rather, it’s about how a child’s digestive system absorbs and metabolizes sugar differently than kids without the disease. This understanding sheds light on how NAFLD could be better detected and assessed through biopsies.

THE ROLE OF SUGAR

Sundaram and her team recently published findings that illuminate the nutritional mechanisms underpinning this disease. The study compared 28 adolescents with NAFLD to 15 control subjects with neither NAFLD nor obesity. Participants logged their daily food and beverage intake using the Harvard Food Frequency Questionnaire over a six-month period. The study looked at consumption of both micronutrients (such as vitamins and minerals) and macronutrients (such as carbohydrates, fats and proteins).

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SHIKHA SUNDARAM, MD, MSCI

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A New Era for Vascular Anomalies

Q: How has the field of vascular anomalies evolved to take on the most mysterious conditions?

For generations, pediatricians have relied on a “wait and see” approach when faced with the presence of a vascular anomaly, a functionally impactful birthmark or growth made up of vessels that develop incorrectly. Historically thought of as innocuous blemishes of little concern that fade as a child grows, many lesions can significantly impact a child’s quality of life. Vascular malformations and tumors — made up of abnormal capillaries, veins, arteries and lymphatic vessels — can be invasive, disfiguring and sometimes life-threatening. These vascular anomalies have long puzzled medical professionals, and the patients have lacked any sense of a medical home, creating a fragmented approach to care. Over the past decade, Children’s Hospital Colorado has transformed the treatment of vascular anomalies through a multidisciplinary approach that standardizes care and advances our understanding of these complex vascular conditions. This effort is spearheaded by experts, including Taizo Nakano, MD, medical director of the Vascular Anomalies Center at Children’s Colorado.

A PARADIGM SHIFT

Many vascular anomalies are considered medical mysteries that don’t fit neatly into any specific medical category. Patients and families find themselves shuffled between subspecialties and between diagnoses. The field historically lacked clear terminology and standards of practice, resulting in excessive or incorrect therapies, pushing doctors and researchers to shift their thinking regarding these conditions. Children’s Colorado has collaborated with national and international colleagues to create a new practice from scratch — from developing a new classification system to developing consensus guidelines and establishing the academic infrastructure for clinical trials.

This new multidisciplinary approach to treating vascular anomalies was spearheaded by the collaborative leadership of Annie Kulungowski, MD, of pediatric surgery; Aparna Annam, DD, of the Department of Pediatric Interventional Radiology and Imaging; and Taizo Nakano, MD, of the Center for Cancer and Blood Disorders. “The goal was to create a multidisciplinary medical home for patients with vascular anomalies, bringing experts together from various fields into the same room to expedite more accurate diagnoses and personalized treatment plans,” Dr. Nakano says.

A MULTIDISCIPLINARY MODEL

The Vascular Anomalies Center has collaborated with most subspecialties available at Children’s Colorado to create a comprehensive medical home for patients with vascular anomalies. The core team includes pediatric surgery (general, plastic and ENT), interventional radiology, dermatology, hematology/oncology, physical therapy and genetics. Depending on the location of the lesion, providers in additional subspecialties volunteer time to collaborate, including orthopedics, cardiology, GI, neurology and neurosurgery.

Therapeutically, the role of surgery has decreased over time due in part to the rise of interventional radiology, which often allows for more focal, minimally invasive treatment. “Interventional radiology is now an essential part of the multidisciplinary team, and efforts are made to increase recognition and support for this field within the institution,” Dr. Nakano says. “The recent addition of two new state-of-the-art interventional radiology suites and the recruitment of new faculty have helped interventional radiology keep up with the demands of this growing field.”

This multidisciplinary approach also led to the development of a disease classification system that goes beyond the physical exam, incorporating clinical, radiographic, pathologic and genetic features to define any given vascular anomaly. This system allows for a more accurate diagnosis and targeted, personalized treatment options, ultimately improving outcomes for patients with vascular anomalies.

“We can now describe anomalies by more than just physical appearance. We include radiographic and histologic features and sequence to identify the genetic drivers of these progressive, dynamic anomalies,” Dr. Nakano says. “As a team, we each contribute our skillset to add layers and depth to the diagnosis, which results in expedited and accurate diagnoses and opens the door to more targeted therapy options.”

Although the field of vascular anomalies is rapidly evolving, many conditions have still not yet been thoroughly studied, leaving gaps in knowledge that must be addressed.

INTERNATIONAL COLLABORATION AND INDUSTRY ATTENTION

In collaboration with the Hendren Project, an online global community of pediatric surgeons and urologists, Drs. Nakano and Kulungowski host a “Multidisciplinary Approaches to Vascular Anomalies” webinar series. They originally developed the series to facilitate international discussions regarding the evaluation and management of vascular anomalies, stressing the importance of a multidisciplinary approach. Additionally, they have collaborated with industry to develop an educational curriculum, allowing them to share patient stories and highlight the shift from clinical, radiographic and pathologic thinking to a more genetic-based approach.

In recent years, the field has caught pharmaceutical companies’ attention, leading to advancements in the field’s first interventional trials to develop targeted pharmacotherapy treatment options. One such example is the FDA approval of alpelisib, a drug initially developed for breast cancer that can treat a large cohort of vascular anomalies known as PIK3CA-related overgrowth spectrum, providing hope for patients and families affected by these conditions.

THE ROLE OF LYMPHATICS

The lymphatic system is an extensive and intricate network of vessels that drains the fluid from soft tissues, circulates through lymph nodes and returns to the heart. It plays a vital role in transporting proteins from the gut and is closely intertwined with the body’s blood vessels. Despite its importance, no single medical subspecialty has traditionally taken ownership of lymphatics, leading to a gap in understanding and treating lymphatic-related diseases. However, as we learn more about vascular anomalies, the lymphatic system is now shedding light on this essential and complex system, leading to breakthroughs in the understanding and treatment of vascular anomalies and their effects on other systems.
A New Era for Vascular Anomalies continued

Interventional radiology imaging of an arteriovenous malformation of a patient’s mandible

of various vascular disorders related to the lymphatic system.

A notable example of Dr. Nakano’s collaborative efforts in the lymphatic space is the treatment of children with Noonan syndrome, a developmental condition with overactive germline genetic defects in the RAS/MAPK pathway that affects the entire body. In addition to cardiac and developmental disorders, patients with Noonan syndrome often suffer from lymphatic anomalies in and around their lungs that risk a catastrophic lymph leak. Dr. Katie Chatfield, a cardiologist at Children’s Colorado, worked with the vascular anomalies team to treat the possibility of repurposing a medication called compassionate use access, which required approval from the drug company, the FDA, Children’s Colorado and the patients’ guardians. To date, the treatment has proved successful, helping patients with their lymphatic issues and improving their overall health — including growth, cardiac function and appetite.

The team’s approach to treating Noonan syndrome is moving beyond single-patient trials and toward expanded national collaborations with other subspecialties and institutions. This work has the potential to transform the understanding and treatment of various disorders related to the lymphatic system, opening up new avenues for research and therapy.

“While the ethics and logistics of treating young children and infants with targeted inhibitors are complex, the possibility of significantly improving the development of a child with Noonan syndrome and limiting life-threatening complications is an exciting prospect,” Dr. Nakano says. “This is what makes academics fun. This is what keeps it interesting.”

IMPACT ON PATIENT CARE

The Vascular Anomalies Center has grown considerably in the past decade. Its support staff, including advanced practice providers, nurses and a clinic coordinator, help care for vascular anomalies throughout the greater Rocky Mountain region. With the expanded use of telehealth and taking advantage of the large multidisciplinary clinic space at Children’s Colorado, more patients can be seen, and demand continues to grow. Dr. Nakano and his colleagues’ work has profoundly impacted patient care and how other medical fields may approach similar conditions.

“We have not only given a home to those diagnosed with vascular anomalies but also provided more satisfying explanations and treatment plans for those with previously unexplained conditions,” Dr. Nakano says. “As the field continues to grow and evolve, I hope that more effective treatments and a greater understanding of these rare conditions will become available, improving the lives of countless patients and families.”

TAIZO NAKANO, MD

Medical director, Vascular Anomalies Center, Children’s Hospital Colorado

Taru Hunz, MD, Endowed Chair of Pediatric Hematology

Associate professor, Pediatrics-Hematology/Oncology and Bone Marrow Transplantation, University of Colorado School of Medicine

This year marks the 55th anniversary of the Children’s Hospital Colorado Adaptive Recreation for Childhood Health program, or ARCH, program. For decades, this program has helped kids with physical disabilities gain confidence and strength through sports and outdoor recreation. Though the program — which was one of the first of its kind in the country — began with just skiing, it has since expanded to include golf, biking, climbing, water sports and more. Each year, Children’s Colorado experts and volunteers engage 80 to 100 kids in these activities, offering funding and scholarships to those who need them. The program celebrated its anniversary in April with an event held at the U.S. Olympic and Paralympic Museum.

Children’s Hospital Colorado recently welcomed a new pediatric surgeon, Kristine Corkum, MD. Dr. Corkum is committed to advancing the field of pediatric oncology by standardizing care, eliminating disparities and raising awareness on the importance of addressing infertitlity issues and hormonal dysfunction in pediatric cancer patients. Having completed her residency at Northwestern University, a post-doctoral research fellowship at Lurie Children’s Hospital and a pediatric surgery fellowship here at Children’s Colorado, Dr. Corkum is poised to make a significant impact. Currently, she is spearheading an institutional review of oncofertility care for high-risk solid tumor patients, with the goal of expanding it to a multi-institutional retrospective study to assess adherence to pediatric oncology consultation benchmarks set by numerous medical societies. “I feel very fortunate to have the opportunity to join an amazing, multidisciplinary fertility preservation program here at the University of Colorado and Children’s Hospital Colorado,” Dr. Corkum says.

Kristine Corkum, MD

PEDIATRIC SURGERY

Brandon Nuechterlein, PA-C

2023 Advanced Practice Provider Special Interest Group Lifetime Achievement Award

Brandon Nuechterlein, PA-C, was recently recognized by the American Society for Transplantation and Cellular Therapy (ASTCT) with the 2023 Advanced Practice Provider Special Interest Group Lifetime Achievement Award. The award recognizes a special interest group member who has made a noteworthy contribution to the hematopoietic cell transplantation and cellular therapy specialty field through publications, presentations, mentorship and leadership. The award was presented at the ASTCT 2023 meeting in February. Of his work, one colleague wrote, “Nuechterlein is highly respected at our institution for his outstanding bone marrow transplant care, his tireless quality improvement work, and his dedication to teaching and advocacy efforts.”
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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’s Department of Pediatrics is ranked eighth in the nation by U.S. News & World Report, and is among the National Institutes of Health’s top-funded research institutions.

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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.

Cancer: #8
Cardiology and Heart Surgery: #14
Diabetes and Endocrinology: #4
Gastroenterology and GI Surgery: #4
Neurology and Neurosurgery: #12
Orthopedics: #12
Pulmonology: #6
Urology: #7