Lifting the Fog of Long COVID

A new body of federally funded research is helping pediatric providers and researchers better understand what exactly long COVID is and how we might prevent it. P. 10

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As a qualified treatment center for a new sickle cell disease therapy, Children’s Hospital Colorado is ushering in a new era of care for this debilitating disease.

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An innovative program is helping rural providers overcome resource challenges and improve readiness for pediatric emergency care.
Burnout among healthcare workers reached an all-time high during the COVID-19 pandemic, a trend associated with increased safety events, medical errors and accidents, and a reduction in the quality of patient and family experiences.

In a post-pandemic world marked by uncertainty, how might we prioritize healthcare worker well-being to ensure retention while fostering a sense of purpose?

Research shows that people who spend at least 20% of their time on things most meaningful to them experience less burnout (1). That’s why, rather than focusing on achieving work-life balance, we encourage people to think about life as standing on a wobble board. Something always needs our attention and energy, and those things are constantly changing. Identifying our core values can give us a true north amid this turbulence, which can help us better align our time and energy to find greater satisfaction.

Many obstacles prevent us from using our time and skills efficiently. For instance, online messaging should make it easier to communicate with families, but it can become a frustrating inefficiency when the communication becomes too complex and requires a visit instead. Taking on practice-optimization projects that solve issues like these provides us with an opportunity to enter clinics and work areas to identify and remedy such challenges, thereby reinstating each person’s ability to do work that aligns with their values, scope and expertise.

Organizationaly, we must create a culture that prioritizes well-being. This begins with leaders who reinforce the importance of recognition, empowerment and career development. In our 2023 medical staff survey, we asked respondents to reflect on their leaders, focusing on certain practices proven to reduce burnout. This assessment will help all leaders establish a culture of well-being in their departments.

An important way to minimize burnout among healthcare workers is to create an environment where their personal values can thrive. Although we have a long way to go, we are closer than ever to creating spaces where individual values, systems and culture work in harmony to show all team members how much they matter. Because now, we know that a truly healthy hospital is one that prioritizes the well-being of its healthcare workers as much as its patients.

**REFERENCES**

Whittling the Wait

GASTROENTEROLOGY AND LIVER TRANSPLANT PROGRAM

Only 15% of pediatric liver transplants currently performed in the U.S. are living donor transplants — a number that has remained stagnant over the last decade. As a result, 30 to 40 children across the U.S. die every year because no graft is available.

Amy Feldman, MD, PhD, Medical Director of the Pediatric Liver Transplant Program at Children’s Hospital Colorado, is on a mission to change these statistics. Dr. Feldman recently received a grant for $100,000 from the North American Society for Pediatric Gastroenterology, Hepatology and Nutrition Foundation, which she will use to build a case for the efficacy of living donor liver transplant.

“Our goal is to demonstrate that not only is living donor liver transplant associated with lower pre-transplant mortality and improved post-transplant patient and graft survival, but also that it is cost-effective,” Dr. Feldman says.

With the grant, Dr. Feldman and her research team will use the Pediatric Health Information System (PHIS) dataset to compare hospitalization costs and resource utilization for pediatric liver transplant recipients from 2010 to 2020.

Additionally, the team will use 10 years of institutional data to compare the graft costs associated with living versus deceased donor liver transplant, highlighting the operational and financial implications of transplantation. “We hope that this data will convince payors to approve living donor liver transplant for every child in need,” Dr. Feldman says.

Currently, Dr. Feldman believes there are unacceptable geographic, socioeconomic and racial disparities in access to pediatric liver transplant, specifically living donor liver transplant. For instance, Black and Hispanic children are half as likely to undergo living donor liver transplant compared to white children. Additionally, Children’s Colorado is one of only a handful of pediatric centers experienced in living donor liver transplant.

“Living donor liver transplant is not offered at every center across the country and is not covered by every insurance,” Dr. Feldman says. “If living donor liver transplant was an option for every child, perhaps we could prevent any parent from losing their child on the transplant waiting list.”

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Eosinophilic Insights

Q: How does new research into eosinophilic gastrointestinal diseases illuminate new paths for diagnosis, treatment and understanding?

The journey through the complex landscape of pediatric gastroenterology has recently taken a significant turn with new research into eosinophilic gastrointestinal diseases (EGIDs) — conditions marked by inflammation in the gastrointestinal (GI) tract from the esophagus to the colon. Spearheading this expedition are Laura Quinn, MD, a pediatric gastroenterologist, and her mentor, Calies Menard-Katcher, MD, whose collaborative efforts have led to pivotal insights into the enigmatic world of EGIDs. The two focus particularly on eosinophilic gastritis (EoG) and eosinophilic duodenitis (EoD) — both rare conditions that until recently were poorly understood.

Driven by a deep-seated fascination with the dual roles of the gut, Dr. Quinn embarked on a meticulous journey through the digestive system to better understand the notable rise in allergic diseases over the past decade.

“I just find it really fascinating that your gut is tasked with two opposing jobs — absorbing food and then also keeping out things that are harmful,” Dr. Quinn explains.

Dr. Menard-Katcher, who served as Dr. Quinn’s research mentor, emphasized the serendipity of their work. “Dr. Quinn’s timing coincided really well with larger conversations around consensus and agreement in the eosinophilic GI world and how to define EGIDs,” Dr. Menard-Katcher notes. “This allowed for real-time contributions to the field.”

A SHIFT IN PERSPECTIVE

In the team’s research, published in the February 2024 issue of the American Journal of Gastroenterology, Dr. Quinn employed a broad array of International Classification of Diseases (ICD) codes to ensure a comprehensive capture of potential cases, followed by a meticulous manual review of patients’ charts to identify potential cases of EGIDs (1). This approach distinguished between EoG, EoD and low-grade tissue eosinophilia based on the location and intensity of eosinophil infiltration. Dr. Quinn described the patient identification process as uniquely rigorous, which ensured the integrity and reliability of their findings.

“We did see increased diagnosis rates for eosinophilic gastritis and enteritis as a whole,” Dr. Quinn says. “This either indicates a growing prevalence of these conditions or increases in recognition and detection.”

The revelation of increased diagnosis rates for eosinophilic gastritis and enteritis brought to light by Dr. Quinn and her team’s research marks a pivotal moment in the field of gastroenterology. It also underscores a potential shift in the epidemiological landscape of EGIDs by challenging the conventional understanding that the small intestine is more frequently implicated in EGIDs than the stomach, suggesting a broader spectrum of gastrointestinal involvement. This shift in understanding has the potential to inform more targeted and effective treatment approaches for EGIDs.

Additionally, the team found that patients with EGIDs have different disease patterns over time, and certain characteristics may predict which patients are more likely to relapse or develop disease complications. These findings can help guide individualized treatment approaches in the clinical setting.

INSIGHTS FOR PROVIDERS

By providing a detailed landscape of EGIDs through a decade’s worth of data, the study underscores the potential for advancing evidence-backed treatments for these rare conditions. This forward-looking approach highlights the essential role of ongoing research and underscores the importance of collaboration across various medical specialties, including gastroenterologists, allergists/immunologists, pathologists and laboratory medicine specialists. Such teamwork is pivotal in forging comprehensive...
Advances and Answers in Pediatric Health

strategies for EGID management, contributing to the broader spectrum of patient care and treatment innovation.

Furthermore, their work emphasizes the importance of multidisciplinary efforts in both understanding and managing EGIDs effectively. Recommendations for healthcare providers to maintain a vigilant approach toward patients with a history of allergies and GI symptoms highlight the need for early and accurate diagnoses.

“Identifying EGIDs early, especially in patients with a known history of allergies, is crucial,” Dr. Menard-Katcher says. “It allows for timely intervention and can significantly alter the patient’s treatment trajectory.”

The study’s contributions extend to influencing global research initiatives, such as the design of phase 3 trials for related conditions, showcasing the significant impact collaborative research can have on the medical field. By pushing the boundaries of EGID research and emphasizing a unified approach to patient care, the findings from this study not only enhance our understanding of these complex diseases but also aim to improve patient outcomes through innovative treatment options and a multidisciplinary care framework, such as the Gastrointestinal Eosinophilic Disease Program. •


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Latest Pulse in Cardiac Care

Q: How does a new medical device enhance the quality of life for young patients facing severe cardiac conditions?

In the evolving landscape of pediatric cardiology, Dustin “Dusty” Nash, MD, of Children’s Hospital Colorado, successfully performed the first implantation of an extravascular implantable cardioverter defibrillator, or EV-ICD, at a pediatric center. This minimally invasive ICD system marks a significant leap in medical technology and signals a paradigm shift in treating young patients with life-threatening cardiac conditions. Jordan, an 18-year-old competitive runner diagnosed with long QT syndrome, emerged as the ideal candidate for this first-of-its-kind procedure.

Unlike traditional ICDs that are implanted below the collarbone with the leads threaded through the veins and into the heart, the EV-ICD system is implanted below the left armpit (in the left midaxillary region) with the lead placed under the sternum. This placement helps avoid certain complications associated with transvenous leads, such as vascular injury and vessel occlusion. Dr. Nash’s selection of the EV-ICD for Jordan was guided by a comprehensive evaluation of its benefits over traditional ICDs. The device’s minimal invasiveness and the promise of a quicker recovery period were key factors in the decision.

“Jordan was quite a competitive cross country and track and field runner, so the EV-ICD felt like a good fit because it doesn’t carry the same amount of exercise restrictions after implantation,” Dr. Nash says.

Jordan’s active engagement in competitive running and his recent diagnosis of long QT syndrome, which could potentially trigger a dangerous heart rhythm, necessitated a solution that could address the medical need without significantly hindering his physical activity. The EV-ICD emerged as the most suitable option, promising to mitigate the risk of sudden cardiac events while accommodating his athletic pursuits.

PREPARATION AND EXECUTION

The implantation preparation for the EV-ICD involved intensive training and planning, highlighting the meticulous approach required for such a novel procedure. Dr. Nash and colleagues underwent specialized training, including practice with animal models and cadavers, to master the device’s technical and procedural nuances.

“Collaboration with Medtronic, the developer of the device,
ICD’s significant advantages in reducing downtime but also highlighted the device’s role in enhancing quality of life for patients with serious cardiac conditions. Jordan was able to resume light exercise within two weeks post-procedure, and his experience exemplified the device’s beneficial impact on recovery timelines — a stark contrast to the lengthy and often restrictive recovery periods mandated by traditional ICDs. This expedited rehabilitation process allowed for a swift reintroduction to daily routines and activities, markedly diminishing the psychosocial and physical repercussions commonly experienced during prolonged recoveries. Furthermore, Jordan’s ability to rapidly engage in physical activity without the fear of compromising his recovery or triggering adverse events demonstrated the EV-ICD’s superior safety and efficacy profile.

“The device not only protected Jordan against potential cardiac incidents but also empowered him to reclaim control over his life, providing an overall sense of normalcy amid the challenges posed by his condition,” Dr. Nash says.

**FUTURE DIRECTIONS**

Dr. Nash’s successful EV-ICD implantation not only establishes a new benchmark in pediatric cardiac care but also opens the door to its potential application in younger patients, thereby expanding the horizons of treatment possibilities within pediatric cardiology. The innovative use of 3D modeling in evaluating the suitability of EV-ICDs for various age groups demonstrates a forward-thinking approach to personalized medicine, tailoring interventions to meet the specific anatomical and physiological needs of each patient.

“We’re not planning on jumping right into implantation for a 6-year-old, but with 3D modeling we’re starting to ask whether EV-ICDs are appropriate for 16-year-olds, 14-year-olds and so on,” Dr. Nash says.

This cautious yet progressive strategy reflects a deep commitment to patient safety and the optimization of outcomes. By gradually extending the age range for potential candidates, the team is methodically assessing the risks and benefits, ensuring that the device’s application is both scientifically sound and clinically advantageous.

Moreover, Dr. Nash’s work signifies a crucial step toward inclusivity in treatment options for pediatric patients facing cardiac challenges. Exploring the use of EV-ICDs for younger demographics highlights the ongoing efforts to fill the gap in available cardiac interventions for children, who often face limited options due to their unique anatomical and developmental considerations. It underscores the importance of innovation in pediatric healthcare, pushing the boundaries of what’s possible to enhance the lives of children with cardiac conditions.

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Glimmers in the Dark

Q: How can researchers embrace the unknown in genetic testing — and how might this advance the future of precision medicine?

Sending a sample for genetic testing has often felt like standing before a cave without a flashlight. Why risk walking into the darkness if you may not find your way? These days, however, researchers like Scott Demarest, MD, Clinical Director of the Precision Medicine Institute at Children’s Hospital Colorado, are repositioning the discomfort of the unknown as an opportunity for understanding. Because if there’s one thing his team has learned from its work in genetics, it’s that without more questions, there can be no more answers.

A shift toward this new realm of thought can be traced back to two Children’s Colorado patients, Vina and Lena Gozeh, who suffered from near-constant seizures — almost 100 per day. Dr. Demarest and his team knew that the sisters, who experienced the same symptoms, had a genetic condition. Lena and Vina, born in 2008 and 2011, respectively, had seizures that were similar to those associated with two known mutations in the ALDH7A1 gene that cause vitamin-responsive epilepsy.

These genetic differences cause an inborn error of metabolism that results in an inability to process vitamin B6 — a nutrient essential for maintaining normal development of the brain, immune system and nervous system. As a result, patients with these genetic mutations can experience seizures, as well as impairments to speech and other areas of cognition, until they consistently supplement with vitamin B6. These clues seemed to add up, except for one important detail: The sisters had already been taking vitamin B6 since they were newborns, and their seizures were only partially responsive to the treatment.

When Dr. Demarest sent the sisters’ genetic material to an external lab for whole-exome sequencing, they weren’t a match for the known vitamin-responsive epilepsy mutations. Even though the sequencing captured the gene responsible for Lena and Vina’s challenges, it wasn’t reported. “Since there was no literature that said this variant is associated with disease, there was nothing to report about it,” Dr. Demarest says.

This is one of the greatest challenges of genetic testing — providers notice that there’s a mutation or correlation that is indeed genetic, but they haven’t discovered how or why that genetic difference is causing the symptoms the patient is having, nor how to fix it.

THE MISSING PIECE

In 2017, the external lab contacted Dr. Demarest about promising new findings. Researchers at a different institution had uncovered a new genetic variant that expanded the known group of vitamin-responsive epilepsies. Specifically, the research showed that these patients, who had a mutation in the PLPBP gene, were missing a binding protein for pyridoxal 5’-phosphate, the active form of B6. Patients in the new study had symptoms that looked exactly like the Gozeh sisters.

Dr. Demarest requested a reanalysis of the sisters’ genes, which confirmed that they had the gene-associated disease discovered in the study. He then consulted University of Colorado School of Medicine colleagues Curtis Coughlin, PhD, who researches genetics, inborn errors of metabolism and vitamin B6 disorders, and Johan Van Hove, MD, who studies metabolic disorders.

As experts in the group of epilepsy disorders that respond to vitamins, Drs. Coughlin and Van Hove guided the decision to increase the dose of the vitamin the girls were already taking. When that improved, but didn’t fully eliminate the seizures, they then switched to a more active form of the vitamin, meaning it’s more readily available and can go straight to work regulating neurotransmitters without having to be metabolized. As the sisters’ care team continued increasing the dose of active B6, their seizures continued to lessen until they stopped all together, granting them the ability to begin progressing developmentally.

CONNECTING CARE TO RESEARCH

Fast forward to 2024, and the Gozeh sisters now serve as a case study demonstrating the power of genetic research to change lives. Albeit today, the Precision Medicine Institute has created the infrastructure to uncover such connections more quickly and on a much greater scale than ever before. For instance, the institute, established in 2023, is now home to the Precision Diagnostic Lab, an in-house genetic testing facility.
Looking ahead, the institute intends to create a consent process where patients at Children’s Colorado are enrolled in a genetic research pool whenever they seek a genetic test in clinical settings.

“The system we’re trying to build is that you can answer those questions you have today, but anytime you can’t get an answer, you automatically feed a patient’s information into a research protocol,” Dr. Demarest explains. “It allows for these types of scenarios where we can then learn from every patient, because you can’t clinically act on things you don’t know.”

The combination of having a greater amount of genetic material to test, and testing more of it, will inevitably lead to more discoveries. Shortening the loop between clinical care and research is also important for making genetic testing more accessible to individual patients, whose information may lead to findings that uncover a cure not only for them, but for an immeasurable number of other patients who’ve been awaiting an answer.

### EMBRACING THE UNKNOWN

Despite the many promises of precision medicine, Dr. Demarest explains that genetic testing can feel fruitless for providers, because finding an answer is so rare. Plus, it has historically been challenging to get genetic testing for conditions that don’t have a defined cure. “Even when we get genetic test results, we tell families and we give them an explanation, but it’s not always treatable,” he says.

That, however, is changing rapidly. “The number of times we’re able to treat something — whether it’s because there happens to be a vitamin that’s available that can treat it, or somebody has created a gene therapy for it — is dramatically increasing,” Dr. Demarest explains.

This is exactly why researchers at the Precision Medicine Institute, together with the Clinical Genetics and Inherited Metabolic Diseases Program, are cultivating a new kind of relationship with the unknown. Even if they don’t know what they’ll find, or how they might treat it, a willingness to embrace the darkness now will inevitably light the way for their patients, and for other researchers, in years to come.

“We need to bring genetic testing into clinical care earlier to make discoveries for things that we don’t know,” Dr. Demarest says. “We can’t afford not to take those steps to discover what’s going on.”

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**Furthering novel thinking**

Housed in the Precision Medicine Institute at Children’s Colorado, the Precision Medicine Fellowship invites researchers from any discipline to learn and apply genetic principles, including testing and interpretation of results, to their fields of study. It is overseen by Dr. Demarest and Margarita Saenz, MD.

The fellowship, one of the first of its kind, allows trainees to tailor their work to specific goals. In 2024, the institute’s first fellow will study renal nephrology, an area where genetic testing remains uncommon.

“By using our other clinics and clinical experience, we are going to make sure she’s exposed to some of these novel therapies because the principles are going to be similar when certain programs mature and those become available,” Dr. Demarest says. “It’s only a matter of time until those therapeutics are relevant for renal care, and then she’s going to be on the forefront, ready to handle that.”

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Lifting the Fog of Long COVID

Q: How is data finally shedding some light on the elusive and debilitating condition known as long COVID?

For most of us, the novelties of a once-in-a-lifetime global pandemic have worn off. Many have tucked away their KN95 masks and rapid tests on a high-up shelf. Vaccines are becoming more routine, and teachers barely bat an eye when another student reports a case of COVID-19. Even the Centers for Disease Control and Prevention has downgraded the quarantine and isolation protocols for a virus that, until recently, held the entire world in its strong, deadly grip. But for some children, COVID-19 isn’t just a memory of two rough weeks last summer — it’s a persistent and unyielding daily reality. And for researchers at Children’s Hospital Colorado, it’s these kids who define the next phase of COVID-19.

“Ever since the pandemic, there has been this subset of kids who were just not recovering as quickly as other individuals and that was manifesting in lots of different ways,” says Children’s Colorado infectious disease specialist Suchitra Rao, MD. “This is something that touches many of the providers who work at Children’s Colorado. It manifests as respiratory conditions, as cardiac conditions, as GI complaints, as mental health conditions. It really is something that can affect any organ system. And so, there was a collective need to explore and study this more.”

“The internet for a definition of long COVID, and you likely will walk away confused. It could last weeks, months or years. It might just be an annoying cough that hangs around a little longer than expected, or it could be fatigue so debilitating it impacts school, work and life.

“Ever since the pandemic, there has been this subset of kids who were just not recovering as quickly as other individuals and that was manifesting in lots of different ways,” says Children’s Colorado infectious disease specialist Suchitra Rao, MD. “This is something that touches many of the providers who work at Children’s Colorado. It manifests as respiratory conditions, as cardiac conditions, as GI complaints, as mental health conditions. It really is something that can affect any organ system. And so, there was a collective need to explore and study this more.”

“It’s a new entity, and there’s still so much that we need to understand and learn about long COVID, because even though it’s something that’s rare, it can prevent people from having a healthy existence.”

SUCHITRA RAO, MD

BECOMING PART OF RECOVER

That’s the impetus behind a National Institutes of Health-led research initiative known as RECOVER: Researching COVID to Enhance Recovery. The project has many branches, poking and prodding long COVID from every angle to uncover new information, treatments and leads. For three years, Children’s Colorado researchers have contributed to the pediatric electronic health records cohort of the project through an affiliation with electronic health record network PEDSnet, which receives funding from RECOVER.

Dr. Rao serves as one of the principal investigators for the RECOVER pediatric electronic health record cohort and is the site principal investigator for PEDSnet at Children’s Colorado, coordinating and facilitating several new projects each year that help build a deeper understanding of how long COVID functions in children. This branch of the RECOVER research initiative involves careful examination of multiple sources, including everything from clinical and laboratory data to vital sign and digital health data. And with 8.9 million patient records, their findings hold significant weight.
"We were able to start collecting information on patients who were undergoing testing for SARS-CoV-2," Dr. Rao says. "Then we could start learning about what these patients with long COVID were going on to develop — which kids were getting better, which ones were having persistent symptoms, which ones were having ongoing healthcare needs. And so, we've developed a number of studies to answer different questions around long COVID."

In addition to the electronic health record work, Dr. Rao also is part of another branch of the RECOVER project called MUSIC, which is investigating a rare complication of COVID called multisystem inflammatory syndrome in children, or MIS-C. As part of this, she's following children who have been diagnosed with MIS-C to monitor and report on their recovery, noting any additional long-term issues that arise.

**CHARACTERIZING LONG COVID**

In the first few years of its work with the RECOVER initiative, the Children's Colorado team published 10 papers, with more on the way. One of these studies, published in JAMA Pediatrics, took great strides in characterizing the ways in which long COVID presents in the pediatric population.

The study (1) considered records from 659,286 children tested for SARS-CoV-2 between March 1, 2020, and Oct. 31, 2021. Of those children, roughly 60,000 tested positive for the virus. The team compiled health data for each child for the six months following their test and compared those who had COVID to those who did not. Investigators found that 41.9% of kids who tested positive for SARS-CoV-2 displayed some symptom or condition that can be associated with long COVID, compared to 38.2% of kids who tested negative. This nearly 4% difference indicates that long COVID is indeed a concern among children, says Dr. Rao, who was first author on the manuscript.

"This was a very large cohort, and it showed that long COVID is manifesting in kids and that there are some flavors of it that seem a little bit different to what was being seen in adults," she explains.

Not only did the study show that kids are experiencing long COVID, but it also helped researchers gain an understanding of what that might look like. Some of the most common conditions found in these children included acute respiratory distress, myositis, mental health concerns, teeth and gum disorders, and myocarditis. Researchers also found patterns in symptoms not associated with a secondary condition, such as changes in taste and smell, hair loss, chest pain, generalized pain and abnormal liver enzymes.

What's more, the study helped identify which kids might be most at risk for long COVID. Among the children studied, those who experienced more severe acute COVID illness or who had chronic, complex conditions were at a higher risk of developing long COVID.

The team followed up this study with one that used machine learning to further characterize long COVID and provide a tool for defining and classifying it (2). The wide variety of symptoms and conditions that can manifest as part of long COVID have created a gap in providers' ability to predict which kids might end up with long COVID and to diagnose it when they see it. This, in turn, impacts patient enrollment in pediatric clinical trials and studies, as official long COVID diagnoses in children have been scarce.

The study used a tree-based scan statistic data mining tool to identify diagnoses, medications, procedures and diagnostic test codes that were disproportionately seen in patients with long COVID. Results from the study validated the power of this tool in identifying kids with long COVID — something that is particularly important in a pediatric setting, in which the condition is underdiagnosed due to its tendency to present milder than it does in adults.

**VACCINE EFFECTIVENESS**

Most recently, the team published a study (3) that has made headlines for its insights on the effectiveness of COVID vaccines. By gathering data from 17 different health systems, investigators determined just how invaluable COVID-19 vaccines are for the pediatric population.

This work necessitated a cohesive understanding of a condition notorious for its difficulty to pin down. By using a definition for long COVID developed based on all its previously published research, the team was able to focus on a pool of patients with long COVID and cross-check their records for vaccination status.

Continued on the following page
“During a time when people might be questioning whether to give their children boosters or their adolescents the vaccine, this is good evidence that it would have an impact.”

SUCHITRA RAO, MD

“If you look at all of the data, you’ll see that the vaccine’s effectiveness against long COVID was 35% to 42%,” Dr. Rao explains. “The vaccine’s effectiveness was higher in adolescents than in younger kids, and the effects were stronger within that six-month timeframe of receiving the vaccine. So, it was actually 61% effective within six months, but then it did decrease, indicating that ongoing vaccination is needed.”

These findings have the potential to move minds among providers and caregivers alike, because not only do they show conclusive evidence regarding the value of using vaccines against long COVID, but they also come from the largest national-scale study on vaccine effectiveness in pediatrics to date, with a cohort of more than a million children.

“The main message was that vaccination can be helpful in not just minimizing severe COVID, but also in the prevention of long COVID,” Dr. Rao says. “During a time when people might be questioning whether to give their children boosters or their adolescents the vaccine, this is good evidence that it would have an impact.”

With each new study, the Children’s Colorado RECOVER team has wielded data as the ultimate tool to explain the unexplainable, measure the intangible and lift the fog shrouding long COVID. In doing so, these researchers have helped construct a path for every child and family facing a scary, lingering and uncertain future as a result of this disease.

“A lot of kids are not able to go to school. A lot of adults are not able to continue their work. It’s now turning into this very prominent chronic disease,” Dr. Rao says. “It’s a new entity, and there’s still so much that we need to understand and learn about long COVID because even though it’s something that’s rare, it can prevent people from having a healthy existence.”


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How is gene editing technology allowing for new, curative treatments for sickle cell disease?

For kids with sickle cell disease, curative treatment options have historically been limited by the need for a well-matched, related bone marrow donor. Only a small minority of patients are fortunate enough to have a match in a relative, and unrelated donor transplant is limited by the fact that the disease disproportionately impacts the Black community, which remains underrepresented on donor lists. What’s more, this type of transplant carries a high risk of graft rejection and graft versus host disease. In late 2023, though, the U.S. Food and Drug Administration (FDA) approved two new therapies for patients 12 and up, called Lyfgenia and Casgevy, that allow for autologous bone marrow transplant, which uses the patient’s own, altered cells instead of a donor.

Sickle cell disease is a set of genetic blood disorders in which hemoglobin, a protein within red blood cells, is abnormal. This causes significant changes in the shape and form of red blood cells that lead to severe anemia, pain crises and more. With such limited treatment options, people with the disease are often left to manage a lifetime of symptoms, pain, organ damage and early mortality, or risk the complications of unrelated, or allogeneic, donor transplantation.

Experts at Children’s Hospital Colorado currently care for more than 220 children with this difficult disease, and thanks to the FDA’s recent decision, these patients now have access to new, life-changing therapies. In March 2024, Children’s Colorado became one of the first qualified treatment centers (and the only one in the region) for the newly FDA-approved Lyfgenia therapy. Its providers will soon begin the treatment for children locally, as well as kids and adults from Montana, Wyoming, New Mexico, Kansas, Texas, Nebraska and South Dakota.

The two FDA-approved treatments each take a different approach to helping patients’ bodies produce healthy hemoglobin that forms non-sickling red blood cells. Kids with sickle cell disease typically don’t have major complications as babies. That’s because they make a different type of hemoglobin called fetal hemoglobin, which blocks sickling. As kids with this condition grow older, the BCL11A gene is activated, causing the body to switch from producing fetal hemoglobin to the mutated sickle hemoglobin. Casgevy uses CRISPR gene editing to decrease expression of the BCL11A gene, allowing the body to produce fetal hemoglobin once again. Lyfgenia, meanwhile, infuses a new copy of a mutated HBB gene, which makes beta globin, ensuring the body produces normal non-sickling hemoglobin after treatment.

Because of its large population of patients with sickle cell disease and its longstanding expertise in the field of gene therapy, Children’s Colorado will assume the important task of providing access to these therapies.
“We are considered a high-volume transplant center for patients with sickle cell disease,” says Christopher McKinney, MD, Children’s Colorado hematologist. “We’ve participated in multiple allogeneic and autologous curative therapy trials for sickle cell disease and are usually one of the highest accruing centers. So, we have a lot of experience in transplant for sickle cell disease, as well as the supportive care that goes along with that.”

In particular, the team’s experience with a vital part of the treatment plan, apheresis, sets Children’s Colorado apart. Apheresis involves mobilizing and collecting a patient’s stem cells and is particularly tricky in patients with sickle cell disease.

“After administering a medication to help patients release stem cells from the bone marrow into the blood, we hook them up to a machine to isolate and collect those stem cells. This process is different in patients with sickle cell disease and technically a lot harder to do,” Dr. McKinney explains. “Few centers across the country have experience doing this. Because we have participated in gene therapy clinical trials and have done it for previous patients, we have a substantial amount of experience with mobilizing and obtaining those stem cells, which is important for safely and efficiently obtaining enough cells for gene therapy.”

It can take months and multiple rounds of apheresis to collect enough stem cells for the treatment, and at this point, the journey is far from over. Patients must then undergo roughly three months of red-cell-exchange transfusion while the cells are being manufactured, during which patients get donor blood to keep the number of sickle cells in their blood low and prevent complications. Then, they have four days of high-intensity chemotherapy designed to remove their existing bone marrow and make space for the genetically altered stem cells. After stem cell infusion, patients spend the next four to six weeks getting supportive care in the hospital while waiting for the stem cells to grow. This extensive process requires sickle-cell-specific expertise, experience and equipment to ensure good outcomes — something available at only a limited number of centers nationally.

“It was a total change in my energy level and how I was able to just go about life! I didn’t have to worry about having pain crises every other day or every month.”

XAVIUS HYMES

“A NEXT-GENERATION TREATMENT

In addition to providing treatment and care for kids and adults in the surrounding states, Dr. McKinney and his research team at Children’s Colorado are currently enrolling patients in a new sickle cell disease gene therapy clinical trial through the Ruby EDIT-301 study. Using next-generation CRISPR technology, which allows for greater precision in gene editing, the gamma globin gene promotor is altered to a naturally occurring sequence in patients born with high levels of fetal hemoglobin so that it becomes resistant to the effects of BCL11a, the protein that stops the body’s production of fetal hemoglobin. This increases healthy blood cells and decreases sickle cells.

Preliminary data presented at the American Society of Hematology meeting in December 2023 showed rapid increases in production of fetal hemoglobin and resolution of severe pain crises in all patients. Over the next two years, the team will monitor them to understand whether long-term results match the promise of preliminary data.

A year after his own transplant, 28-year-old Xavius Hymes shared his experience as an early recipient of gene therapy at Children’s Colorado with Colorado Public Radio (CPR). “It was a total change in my energy level and how I was able to just go about life! I didn’t have to worry about having pain crises every other day or every month,” Hymes told CPR.

This is exactly the outcome Dr. McKinney hopes for every child and adult living with sickle cell disease. “This is a really exciting time, because for so long they had so few treatment options,” he says. “I see patients when they’re diagnosed on newborn screens, and their parents are incredibly nervous and scared about what’s going to happen to their child. Now we get to tell them that it is very possible they might not need to live with sickle cell disease forever.”

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A recent collaborative effort between Children’s Hospital Colorado pulmonologists and radiologists, as well as international colleagues, has led to the development of computed tomography (CT) imaging criteria specifically designed for diagnosing pulmonary fibrosis in children. This initiative, detailed in the landmark study (1) published in the January 2024 edition of Pediatric Pulmonology, aims to help providers use imaging to quickly identify pediatric pulmonary fibrosis, allowing patients to get the care they need.

Highlighting the urgency of developing specific CT imaging criteria for pediatric pulmonary fibrosis, Children’s Colorado radiologist Jason Weinman, MD, pointed out the critical nature of this advancement. “Given the advent of clinical trials and subsequent treatment for fibrosis in children, it is critical to identify the patients with fibrosis, especially since many are poor candidates for lung biopsy due to advanced lung disease,” Dr. Weinman says.

The study underlines the distinct manifestations of pulmonary fibrosis in children compared to adults, notably the absence of honeycombing (clustered cystic airspaces) and more diffuse CT findings. This collaborative effort not only paves the way for early identification and treatment of pediatric pulmonary fibrosis but also ensures the inclusion of these patients in vital clinical trials. Emily DeBoer, MD, pulmonologist at Children’s Colorado, emphasizes the impact of the newly developed criteria on research. “The criteria already have influenced the inclusion of pediatric patients in clinical trials,” Dr. DeBoer says. “They have been used to help enroll in clinical trials with further validation planned for future trials.”

This research underscores the need to differentiate between pediatric and adult pulmonary fibrosis, as it is crucial for the transition from pediatric to adult care. “Understanding the differences between adult and peds patterns can help providers prepare for this transition,” Dr. DeBoer says. “This research not only enhances our understanding of pediatric pulmonary fibrosis but also exemplifies the critical role of interdisciplinary collaboration in advancing pediatric healthcare.”


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Road to Readiness

Q: How can pediatric readiness improve emergency care outcomes for children across Colorado?

When a child living in a rural community needs immediate critical care, they’re often hundreds of miles from a hospital that can help them — a distance that can determine their fate. Faced with the decision to either visit a critical access provider or travel for hours to a large hospital with critical care capabilities, rural children experience double the mortality rate of kids in urban areas, according to the Centers for Disease Control and Prevention. Now, a program within the University of Colorado School of Medicine, EMS for Children Colorado, is helping turn these statistics around. With one rural hospital as its model, the team is proving that pediatric readiness efforts can transform an unprepared emergency room into an institution ready to save lives.

THE DECLINE OF RURAL HOSPITALS

Emergency Medical Services (EMS) for Children is a federally funded program that gives hospitals access to medical education and resources so they can implement pediatric best practices in their institutions. Kathleen Adelgais, MD, MPH, has seen the challenges facing rural communities over the past decade directly impact pediatric healthcare.

“There’s been a national closure of hospitals in rural communities, partly because they don’t have enough annual visits to sustain them,” says Dr. Adelgais, who serves as Project Director for the EMS for Children Colorado state partnership program. “Then hospitals must make decisions about what service lines they’re going to keep open.”

Fewer hospital visits are closely tied to population decline in small town America — a rising trend with a range of causes. For instance, a major employer might close, forcing people to move elsewhere. Those who stay often lack health insurance or the extra funds needed to visit a hospital, which means they likely won’t unless it’s necessary (1). Rural hospitals are considered critical access, meaning they’re eligible for federal funding if they don’t belong to a major healthcare system. However, it can be difficult to secure these funds and know how to allocate them appropriately toward improving pediatric readiness.

No matter what causes towns to decline, healthcare workers feel the strain. They often have to drive further to reach clinics with patients while serving multiple roles, putting in more hours across specialties, primary care and the emergency department. “Healthcare providers have to maintain a higher level of scope and do a lot more to maximize their role with limited clinical exposure, because there’s lower volumes of patients overall,” Dr. Adelgais says.

Although 93.7% of children in the United States can travel to an emergency department within 30 minutes, only 33% of children live within 30 minutes of an emergency department that’s pediatric ready (2). “If a child goes to an emergency department and they’re very, very ill, and that hospital is not ready to care for them, it will be difficult to provide the stabilizing care they need before transfer to another hospital,” Dr. Adelgais adds.

RAISING THE BAR IN RIFLE

As part of its work in supporting hospitals, EMS for Children Colorado oversees Colorado Pediatric Preparedness for the Emergency Room, or COPPER — a program that partners with healthcare organizations across the state. Representatives from nursing, respiratory therapy, pharmacy and medical education from Children’s Hospital Colorado, the University of Colorado School of Medicine, Denver Health, HealthOne, UCHealth and other healthcare networks formed COPPER’s steering committee in 2018.

After creating a webpage with pediatric readiness resources, including a Colorado-specific version of the national pediatric readiness in the emergency department checklist, the multi-institutional, multidisciplinary steering committee invited hospitals across Colorado to participate in a pilot of the program, in which they would complete the checklist and application, plus get a letter of commitment signed by their leadership team.

Grand River Health was one independent hospital that became an early adopter of pediatric readiness through COPPER. After
signing up for the pilot program, this independent rural hospital in Rifle, Colorado, scored 51 on the 100-point national Pediatric Readiness Project assessment — an evaluation that asks questions regarding staff credentials, emergency department triage policies, equipment inventory and other hospital policies specifically related to the care of children.

This low score prompted Grand River Health to take action. Its leaders asked for support from the COPPER steering committee, which offered its pediatric readiness resources. Using these guidelines, Grand River Health embarked on a hospital improvement plan that touched every area of its care plan for kids.

For example, Grand River Health’s care teams developed a system using color-coded sticky dots to manage medications and kid-sized equipment. These dots are matched to the child’s height and weight and stick onto their arm band to ensure proper dosing. “As care gets transferred out of the ER to an inpatient team, that information is just a basic part of describing the child in addition to what their diagnosis is, what their age is and what their length-based tape color is,” Dr. Adelgais says.

Grand River Health’s care team also used COPPER resources to better understand when CT scans aren’t needed and how to insert child-sized emergency airway devices.

After the improvement plan, Grand River Health scored a 97.5 on its pediatric readiness score, placing it in the top 10% of facilities nationwide. Members of the COPPER steering committee conducted a site visit in May of 2023 to evaluate Grand River Health’s improvements, ensure pediatric readiness in their emergency department and award them with COPPER recognition.

Grand River Health now serves as a case study that informs how the EMS for Children Colorado program can help other hospitals on the Western Slope better prepare to help children who come to them in critical situations.

**PARTNERING IN PREPARATION**

Such preparedness doesn’t just improve care for children — it levels the playing field for every hospital and patient.

“Pediatric readiness is a rising tide lifting all boats,” Dr. Adelgais says. “Once you start to really pay attention to your policies and procedures, medication safety and patient safety — all the key components of general healthcare for a group of vulnerable patients — it highlights where there are other safety issues at the hospital level.”

For instance, recent research shows that a higher level of pediatric readiness is directly correlated with a reduction in mortality based on race and ethnicity (3).

Additionally, pediatric readiness reduces the health disparities that occur between rural and urban children.

“The data shows that if hospitals are pediatric ready, they are better able to stabilize children until they can get to definitive care. There’s a decrease not just in long-term mortality, but also in short-term mortality,” Dr. Adelgais says.

Continued on the following page
Road to Readiness continued

Findings from 2023 show that injured children who sought care at hospitals with a pediatric readiness score of 88-100 saw a 60% lower in-hospital mortality rate, while the mortality rate among children seeking care for medical conditions was reduced by 76% (4).

Despite these benefits, one of the greatest obstacles preventing a nationwide improvement in pediatric readiness is the siloing of healthcare organizations and the protection of information. Historically, hospitals in the same region have regarded one another as competitors, and therefore haven’t been likely to share their best practices.

Today, however, Dr. Adelgais and her team encourage all hospitals to think of one another as resources that can share crucial information and teach critical skills. Once rural hospitals become pediatric ready, larger children’s hospitals can feel confident referring patients there when volumes exceed capacity. This work also allows rural kids to receive care close to home, which in turn keeps their local hospitals open.

According to Dr. Adelgais, this fosters a win-win situation that gives kids the care they need more quickly: “If we can align on pediatric readiness, we can create a system that’s ready to take care of children anywhere, at any time, with any condition.”

Victory for Retinopathy

The University of Colorado Department of Ophthalmology, working alongside Children’s Hospital Colorado, recently introduced a new tracking system for managing retinopathy of prematurity (ROP) in preterm infants. Integrated with the Epic electronic health record system, this tracker represents an enhancement in the proactive follow-up care for infants at risk of ROP, a condition that could lead to blindness if left unchecked.

Every year, around 14,000 infants in the U.S. are diagnosed with ROP. While the condition is usually mild, the risk of severe outcomes underscores the critical need for timely and effective follow-up care. Traditional tracking methods, often manual and error-prone, fell short of ensuring that every infant at risk received the necessary attention.

The new tool, which is the brainchild of pediatric optometrist Melissa Engle, OD, FAAO, and her colleague Jennifer Jung, MD, automatically tells providers which babies are due for follow-up appointments, greatly reducing the risk of missed opportunities for care. By automating this process, the tracker boasts an impeccable success rate in scheduling accuracy, setting a new standard in neonatal care.

The tracker also enhances the efficiency of care teams by identifying infants who are at risk based on specific criteria, such as birth weight and gestational age, and ensuring they are promptly scheduled for screening. It streamlines the workload for eye care professionals and improves care continuity for infants transferred between facilities, offering a full view of their medical history and prior examinations.

The feedback from the pediatric ophthalmology community has been universally positive, praising the system for its reliability and the significant improvements in the ROP care workflow. As interest in this technology spreads across the country, its impact is set to extend even further. Infants at risk of ROP nationwide will be able to receive the timely and critical care they need to thrive.

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Challenging Dogma with Data

Surgery

Conventional medical wisdom has held tightly to Boyle’s law when transporting patients with a traumatic pneumothorax at altitude. A traumatic pneumothorax occurs when air accumulates between the chest wall and injured lung, resulting in partial or complete lung collapse. Based on Boyle’s law, which describes the effect altitude has on gases in closed spaces, as altitude increases, ambient pressure should decrease, causing a pneumothorax to get bigger and further compress the lung. As a result of this principle, doctors often place a pneumothorax to decompress a pneumothorax before flight — a painful procedure that can delay time to definitive care and cause unnecessary trauma to a child’s body.

Through a retrospective study (1) of more than 400 pediatric patients, Children’s Hospital Colorado researchers, led by pediatric surgery research fellow Nicole Becher, MD, and Associate Trauma Medical Director Steven Moulton, MD, aimed to challenge this notion. “Dogmatic practice has been to place a chest tube before they’re transported, because people are afraid that the pneumothorax is going to expand and hurt the child. And the child’s going to be in a helicopter, where you can’t easily put in a chest tube,” Dr. Becher says. “But that wasn’t based on any data. And so, we said, OK, let’s study it.”

The team’s data set included 12 years of information on every child that was transported to Children’s Colorado with a known pneumothorax and without a chest tube. The research showed that elevation gain during flight and during ground transport over the Rocky Mountains did not cause complications from pneumothorax expansion in any patients. In fact, just five patients experienced expansion, and none became symptomatic or went into respiratory distress.

Additionally, the team found that most kids never even needed a chest tube to recover, because most had small pneumothoraxes that resolved on their own. Only 19 patients required a chest tube after arriving at Children’s Colorado, and in those cases, the children had a medium or large pneumothorax prior to leaving their original location. “The biggest conclusion we can draw from this is if the patient were staying at your institution and you wouldn’t place a chest tube, don’t place the chest tube prophylactically,” Dr. Becher explains. “There’s no need to place a chest tube just because a child is being transported.”

“In fact,” she adds, “please don’t.”

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Exceptional care counts
Here, it all adds up. From the lifesaving studies we design and the boundary-breaking treatments we offer, to the moments we spend brightening a child’s day, every extra second we dedicate to improving care for kids makes a difference. This year, those combined efforts have earned us a spot among the best children’s hospitals in the nation with four specialties ranked in the Top 10. 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.