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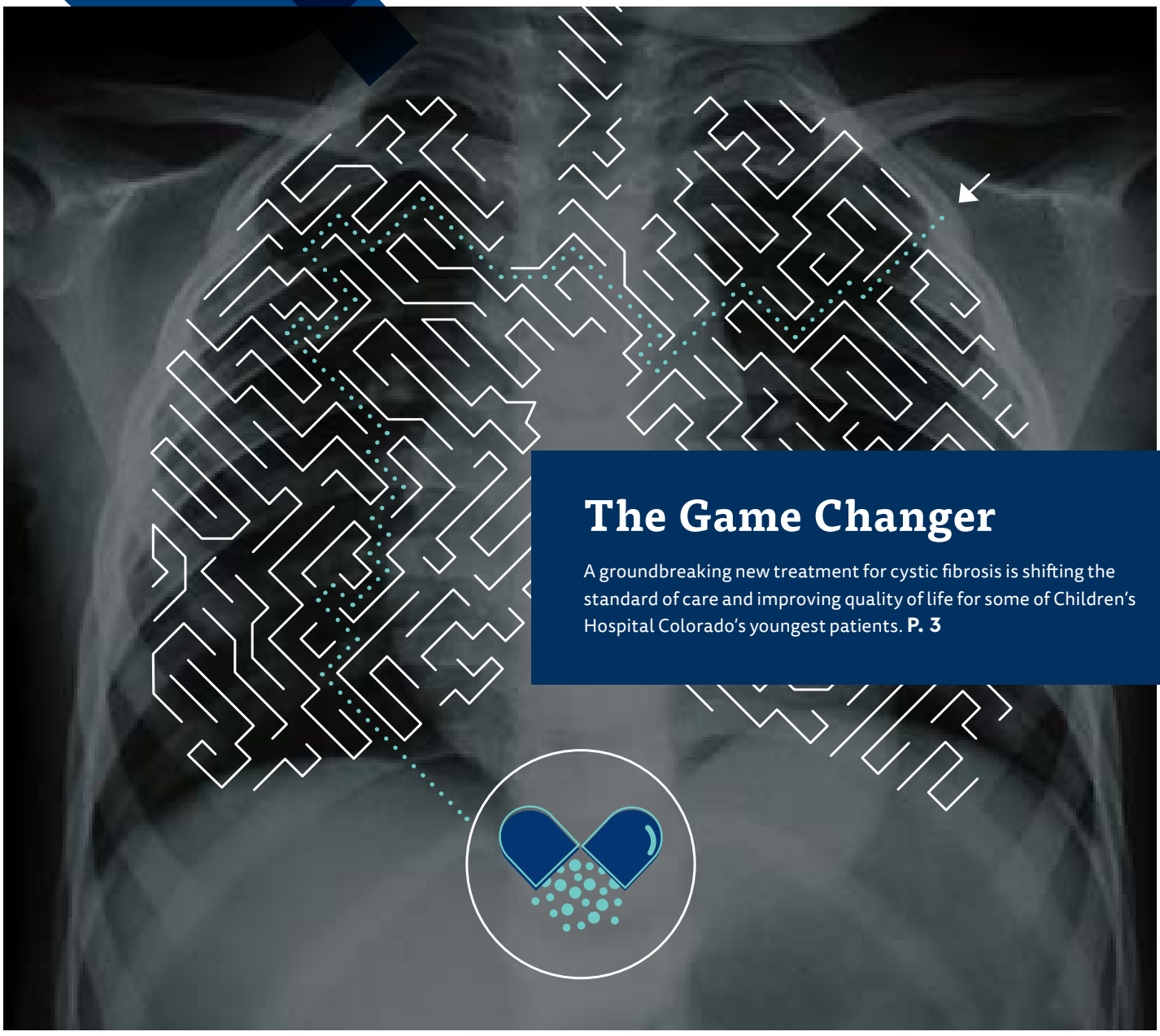
Q: *Advances and Answers in Pediatric Health*



The Game Changer

A groundbreaking new treatment for cystic fibrosis is shifting the standard of care and improving quality of life for some of Children's Hospital Colorado's youngest patients. **P. 3**

Children's Hospital Colorado

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It starts with a Q:

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

Dear colleagues,

Physician scientists have a long history of making important medical breakthroughs. I believe that is because they are uniquely positioned to serve as a bridge, connecting a deep understanding of clinical issues with a natural curiosity for solving complex medical questions. Yet, some in the healthcare field see the physician scientist as a dying breed due to a decrease in emphasis on research in medical schools and residency programs and an increase in demands on time.

How can we better support residents who are seeking to fill this critical role?

At Children's Hospital Colorado, we know that to continue serving as a national pediatric healthcare leader and to truly embody what it means to be a supercenter of the future, we need a robust research component — and that must include physician scientists. For us, that starts with recruiting the best and the brightest to our residency program and building a cohort that represents a full range of interests. We pride ourselves on having a diverse program that includes residents who are focused on everything from research and clinical work to education and health policy.

Then, we support them in realizing their goals. One of the most meaningful pieces of the Children's Colorado residency experience is a mentorship program that yields lifelong relationships and powerful research partnerships. We also have a longstanding focus on individualized education that truly allows our residents to set aside protected time to focus on researching questions they are passionate about answering.

That's because the work our residents set in motion now can have life-changing impacts in the future. Physician scientists don't just think about what they can do to take care of kids today. They think about solving complex healthcare issues for tomorrow's patients. Every year, I'm blown away by the research questions our residents tackle and the difference they make on a national scale.

I know that having a strong group of residents pursuing research as physician scientists makes us better as an institution. They are the lifeblood of our work, and we must ensure that research remains a supported and celebrated aspect of residency programs.

Best regards,

STEPHEN DANIELS, MD, PHD

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

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The Game Changer

Q: How is a groundbreaking new treatment for cystic fibrosis shifting the standard of care and changing the quality of life for younger patients?

When the U.S. Food and Drug Administration (FDA) approved elexacaftor/tezacaftor/ivacaftor (ETI), a new drug combination designed to treat patients 12 years and older with cystic fibrosis (CF), it was a game changer for this progressive, genetic disease. The pulmonary team at Children's Hospital Colorado understood the life-changing impact of this drug and played a significant role in clinical trials to prove its safety and efficacy in even younger children. In April of 2023, thanks in part to data from Children's Colorado, the FDA approved the drug for kids as young as 2 years old — a significant shift and milestone for young children living with cystic fibrosis. But the team doesn't want to stop there.

This new treatment, called a cystic fibrosis transmembrane conductance regulator (CFTR) modulator, helps restore function to the malfunctioning protein that causes CF. This helps the CFTR protein do a better job of moving chloride ions into and out of the cells and better maintains a balance of salt and water in various organs, including the lungs. This treatment provides remarkable health benefits for up to 90% of people with CF who qualify — those with at least one copy of the F508del mutation.

"We know this drug works by reducing the burden of symptoms," pediatric pulmonologist Scott Sagel, MD, PhD, says. "It improves lung function, improves growth and reduces pulmonary exacerbations, which are respiratory illnesses that historically led to hospitalizations of people with cystic fibrosis."

Dr. Sagel worked alongside pediatric pulmonologist Jordana Hoppe, MD, one of the lead investigators in the clinical trial, to help secure approval of this treatment for children as young as 2 years old. They are just two of the many doctors in Children's Colorado's Mike McMorris Cystic Fibrosis Research and Care Center, which is one of the largest and most experienced cystic fibrosis clinical care and research centers in the country.

"Before these drugs, our standard of care really was to treat complications of cystic fibrosis," Edith Zemanick, Associate Director of the Center, says. "We recommended preventative care, like daily mucus clearance, but most of our therapies treated

Continued on the following page

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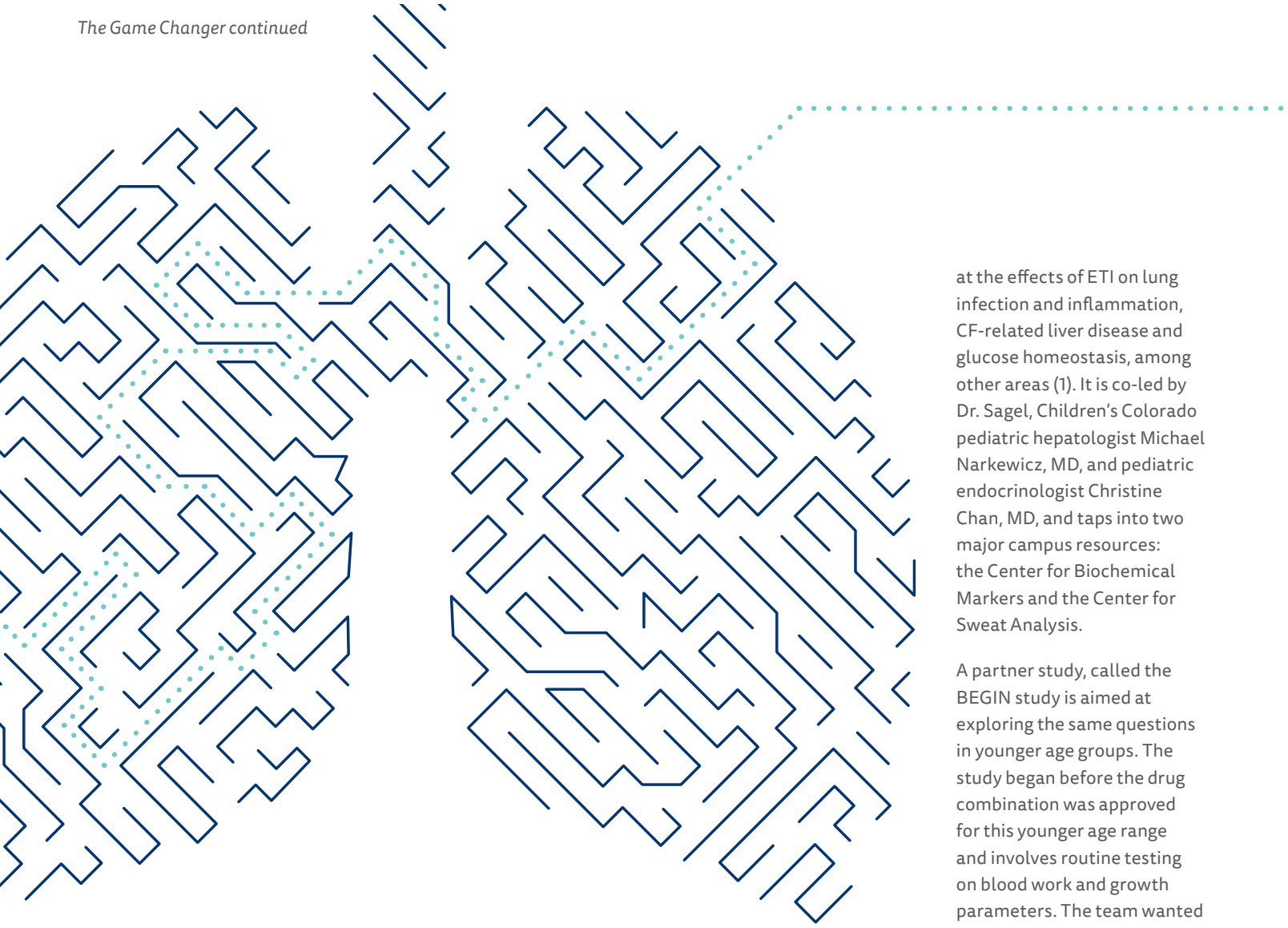
The Game Changer continued



the consequences of CF. The modulators treat the underlying problem, so they get to the cause of all of those consequences."

UNDERSTANDING THE FULL PICTURE

While this treatment is a significant breakthrough, doctors at Children's Colorado and their colleagues across the country are interested in learning how it impacts the whole body for people with cystic fibrosis.

"We don't know all the things that these protein modulators do for people with cystic fibrosis," Dr. Sagel says. "It's a systemic therapy that they take orally and it works throughout the body. How does it change pancreatic function? How does it change liver disease? Does it prevent the progression to diabetes that many people with CF experience?"

Sponsored by the Cystic Fibrosis Foundation, several doctors from Children's Colorado are helping to lead multicenter studies that are looking at the biology of CFTR modulator therapy. One study, called PROMISE, kicked off first for people with cystic fibrosis 12 and older, looking at the effects of ETI on lung infection and inflammation, CF-related liver disease and glucose homeostasis, among other areas (1). It is co-led by Dr. Sagel, Children's Colorado pediatric hepatologist Michael Narkewicz, MD, and pediatric endocrinologist Christine Chan, MD, and taps into two major campus resources: the Center for Biochemical Markers and the Center for Sweat Analysis.

A partner study, called the BEGIN study is aimed at exploring the same questions in younger age groups. The study began before the drug combination was approved for this younger age range and involves routine testing on blood work and growth parameters. The team wanted to have a deep understanding of what was happening before kids started on modulators to better understand the impacts.

Another part of the BEGIN study involves a bronchoscopy study led by Dr. Zemanick, which aims to help clinicians understand what they can expect for patients when it comes to infections and inflammation in the lungs after starting ETI.

"Our hope is that we won't need to see kids as often in clinic, and that they may be able to reduce some of their daily treatments, giving them more time to go to school, play and enjoy being a kid," Dr. Zemanick says. "Kids with CF are at high risk for certain lung infections that we monitor for at clinical visits. Understanding if the chance of infection is lower in kids receiving ETI is going to be really important in informing our care guidelines."

Psychologists at Children's Colorado are also exploring the mental health impacts of this new drug combination in partnership with the Cystic Fibrosis Foundation's National Mental Health Working Group.

SHIFTING THE STANDARD OF CARE

In addition to understanding the impact of ETI on the whole body, doctors are also exploring the shift in the standard of care through a new study, called SIMPLIFY. It asks the question, "What previous typical CF medications can patients stop taking as their symptoms improve with this new drug combination?"

"With cystic fibrosis, we used to do mucus clearance treatments every day, like vest therapy. We would also do mucus-thinning medicines that make it easier to move mucus and cough it out of your lungs. That was the standard of care," Dr. Sagel explains. The SIMPLIFY study investigated the impact of removing one of those pieces — the mucus-thinning medication. Children's Colorado was one site in the multisite study collaboration (2).

The team found there were no significant differences in the group that stopped the mucus-thinning medication, versus the group that continued on the medication. "So, we are now trying to figure out what people with CF do and do not need in terms of their previous standard-of-care therapies and working to reduce the burden of these treatments if they are unnecessary," Dr. Sagel says.

OFFERING HOPE FOR THE FUTURE

"I think the most exciting part is just seeing our patients do so much better," Dr. Zemanick says. "We've always approached CF with a lot of hope, and we expect our kids to do really well. We have many kids who can do all the activities that other kids do, like athletics, but I think this just gives us even more hope for how they'll do going into adulthood."

This hope continues to drive the team of doctors at Children's Colorado who are part of this national effort to improve the lives of children with CF. Their research pushes this work forward in impactful ways from all angles.

"Now for many of our children that are starting therapy at a young age, we expect them to have a near normal lifespan," Dr. Sagel says. "The care model is absolutely going to change. We're going to go from kids with active disease who we were seeing very frequently, every three months, to kids who are doing well."

Children's Colorado is also involved in clinical trials for another drug similar to the recently FDA-approved combination that would be a once-a-day pill instead of twice-a-day. The team is also ready to work on research for future treatments that will help target the 10% of patients who don't qualify for the currently approved modulators due to their specific mutation and push the age range for existing therapies even lower.

"The goal is to be able to start these medicines shortly after diagnosis," Dr. Sagel says. "Certainly, from a therapeutic standpoint, this is our best advancement and biggest breakthrough for cystic fibrosis." ●

1. Nichols, David P et al. "Clinical Effectiveness of Elexacaftor/Tezacaftor/Ivacaftor in People with Cystic Fibrosis: A Clinical Trial." American journal of respiratory and critical care medicine vol. 205,5 (2022): 529-539. doi:10.1164/rccm 202108-1986OC.
2. Mayer-Hamblett, Nicole et al. "Evaluating the Impact of Stopping Chronic Therapies after Modulator Drug Therapy in Cystic Fibrosis: The SIMPLIFY Clinical Trial Study Design." Annals of the American Thoracic Society vol. 18,8 (2021): 1397-1405. doi:10.1513/AnnalsATS 202010-1336SD.

PRECISION MEDICINE

Realizing the Vision

Q: How can a drug designed specifically for one patient help providers extend the benefits of precision medicine to more children?

More than a decade ago, Children's Hospital Colorado ophthalmologist Emily McCourt, MD, diagnosed a young patient with retinitis pigmentosa — an incurable disease that was slowly degrading the girl's vision. Through whole-genome sequencing, geneticists discovered a very specific gene mutation and recently, they developed a very specific treatment to address it. This year, the now-13-year-old patient received her first dose of the drug, tailormade just for her, that aims to stop the disease's progression in its tracks.

The patient was just 2 years old when she first visited Dr. McCourt for issues with night vision. She had seen other doctors for her challenges with balance and insensitivity to pain, but this new symptom added to the puzzle in a troubling way. Dr. McCourt suspected retinitis pigmentosa, in which retinal cells break down over time, and tests confirmed the diagnosis.

"What was remarkable about that first exam was that I could tell she had retinitis pigmentosa, but we don't usually diagnose this in toddlers," Dr. McCourt says. "It's usually diagnosed in teens and young adults, so I knew it was a pretty severe case."

Even with Dr. McCourt's findings, the patient's other symptoms remained a mystery. Over the next several years, she worked to address and track the girl's growing visual impairment, but it would be years until the family got a full diagnosis. That came in 2016, when Children's Colorado geneticist Austin Larson, MD, joined the family's care team. He used results from previously conducted whole-genome sequencing to identify two genetic mutations and offer a diagnosis at last — posterior column ataxia with retinitis pigmentosa, or PCARP.

UNDERSTANDING THE GENETICS BEHIND PCARP

PCARP is rare, but the mutation behind this particular case is even rarer. Most people diagnosed with the condition have mutations affecting both copies of the FLVCR1 gene within the protein-coding region, meaning that their bodies are unable to code for the production of a necessary protein. While the patient has a mutation affecting the coding region of one copy of the gene, the other copy is affected by a deep intronic mutation. Instead of losing its ability to code for the protein altogether, this copy of the gene makes an error in splicing the RNA template for the protein, mistakenly including genetic material that shouldn't be there.

This deep intronic mutation turned out to be the key to a whole new world of options. That's because, while there is nothing that can currently be done for the typical mutations behind PCARP, deep intronic mutations can be treated using antisense oligonucleotides, or ASOs. In 2019, after discussing this experimental treatment option with the patient and her family, the team began working with a lab at Boston Children's Hospital led by Tim Yu, MD, PhD. They were interested in developing an ASO that could bind like a zipper to the specific region of the patient's gene causing the splicing mistake. This would allow the gene to properly code for the typical protein. Researchers tested 15 different versions of the ASO on samples of the patient's cells and found two possible winners that could partially restore function of the protein.

The team then began working with n-Lorem, a foundation focused on providing patients with personalized ASO therapies for free. n-Lorem fine-tuned the ASO design developed in Dr. Yu's lab, funded further preclinical testing to understand possible side effects, and created a lifetime supply of this one-of-a-kind drug. Drs. McCourt and Larson then worked with the investigational drug team at Children's Colorado to secure approval from the U.S. Food and Drug Administration to begin treatment.

STARTING TREATMENT

The ASO isn't a cure. It likely won't reverse the patient's vision loss, and it won't address her other symptoms. What it may do is stop the progression of her vision loss. Since her initial diagnosis, the patient's vision has declined from 20/40 to 20/200, and without

this treatment, her visual impairment will worsen. And with her insensitivity to pain, vision is even more important, as it allows her to identify and properly care for infections or cuts she can't physically feel.

"It's still at a point where she can read with a big magnifier and she can navigate the world," Dr. Larson says. "She has functional vision, and if it can be preserved at this level, that would be a huge difference in terms of her quality of life."

In August, the patient received her first dose of the new drug. It is administered via injection into the vitreous of the eye, as ASOs need to be applied directly to the cells that they aim to affect. She'll initially receive doses every three months before transitioning to a bi-yearly injection.

Along the way, Dr. McCourt will continue to closely monitor her patient's vision to see how well the personalized treatment functions. She'll employ objective visual testing, including visual acuity, light sensitivity, gait analysis and more.

"We don't have any other studies to go on to say she'll need it for five years, or she'll need it for 10 years," Dr. McCourt says. "We know we have enough medicine if she needs it and wants it. The protocol is written in a way that if any member of the team, including the patient and family, think that the injections are no longer beneficial, then we will stop."

BROADENING THE IMPACT

This specialized drug is designed for one patient and one patient only, but its impact could extend far beyond this single child. It's the first instance in which doctors at Children's Colorado were able to bring a patient all the way from genetic diagnosis to specialized medicine, but Drs. McCourt and Larson are confident it won't be the last.

Children's Colorado is driving continuous improvements to its use of genetic testing and tailored therapies through the new Precision Medicine Institute, and Drs. McCourt and Larson teamed up to create a genetic eye clinic aimed at helping more patients like this one. They've already identified another patient with retinitis pigmentosa that could benefit from a similar approach to care.

What's more, through the partnerships and processes created as a result of this one patient's journey, they expect to be able to deliver results quicker and even more effectively.

"The goal is to keep doing this, because each time we do this, we learn a lot about how to diagnose patients earlier in the disease process, our diagnostic capabilities improve and we are learning how to get through this process quicker," Dr. Larson says. "We hope to scale this up and to make it more efficient, to the point where it's practical for more patients."

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Patterns of Promise

Q: Can artificial intelligence models make it easier to predict — and successfully intervene — when kids are at risk of suicide?

Suicide is the leading cause of death among children ages 10 to 14 in Colorado, and the second leading cause of death among teens nationwide. Research has identified many factors contributing to this startling trend — including a history of depression, substance use and family conflict — but societal stigmas, lack of clinical resources and misunderstandings around mental health challenges have made it difficult for physicians to pinpoint the individual circumstances leading to suicidality.

Now, with the help of artificial intelligence (AI), Children's Hospital Colorado psychiatrist Joel Stoddard, MD, MAS, is driving research that could finally predict suicide risk in kids. Dr. Stoddard serves as principal investigator at Children's Colorado's Emotion and Development Lab, which seeks to understand the neurological underpinnings of social emotional challenges in children and adolescents.

In the lab, Dr. Stoddard and his team will use AI to learn which patterns are most likely to lead to a suicide attempt. Then, the AI tool helps the team create models that predict future suicidal thoughts and behaviors as well as the potential interventions that might work best to save a patient's life.

"Pattern detection is really important. You can do it as a human, but it takes a long time — it's like finding the needle in the haystack," Dr. Stoddard says. "We're actually able to predict people's clinical outcomes much faster using data about them, which includes both clinical impressions and computer-derived measures of their behavior."

DIVERSIFYING DATA SOURCES

The models created in Dr. Stoddard's lab are powered by numerous real-world data sources. The first database comes directly from clinical screenings at Children's Colorado, which use the Ask Suicide-Screening Questions (ASQ) to assess suicide risk quickly and effectively with just five questions. Children's Colorado adopted ASQ in 2017, but in 2022, Lauren Wood, PhD, and Shaela Moen, MPH, helped implement another standardized screening for depression from the Hospital Transformation Project — a Colorado state initiative aimed at improving quality of care. These suicide and depression screenings are now conducted during every interaction with patients over the age of 10, and the answers are incorporated into the patient's electronic health record.

Since the AI tool is searching for patterns in data, every bit of clinical information makes its models more accurate. "We're trying to amplify the power of predictive screening," Dr. Stoddard says. "We don't just want to predict what's going to happen in the next month, but also for years to come."

Moen and Dr. Wood have also helped facilitate Children's Colorado's partnership with Zero Suicide — a national framework for improving suicide care and prevention across healthcare settings. Collaborating with Zero Suicide enables Dr. Stoddard's team to access data from the Colorado Department of Public Health and Environment, meaning the AI models incorporate information from real cases of children who've died by suicide. Additionally, Dr. Stoddard and his team are beginning to look at

data from the ABCD Study, the largest long-term study of brain development and child health in the United States, spanning more than 10,000 kids across 21 different research sites. Over the next year, Dr. Stoddard and his team aim to integrate key findings from the ABCD dataset into patients' electronic health records. This data will appear in Epic alongside guidance for following up with patients after they've screened positive for depression and/or suicide — another result of the Zero Suicide implementation by Moen and Dr. Wood.

This will make it possible for a provider to look at a child's chart, instantly assess a complex level of risk based on clinical and nationwide data and view suggested treatment methods tailored to that patient's risk factors. This will result in a level of youth suicide prevention care previously unattainable in clinical settings.

PREDICTING WITH PRECISION

Culling a wider representation of life experiences from a diverse range of data sources is incredibly important for reducing bias and improving accuracy in suicide prevention, all while ensuring that the resulting interventions and treatments are more equitable. For instance, there may be higher rates of suicidality among teens from a certain ZIP code or kids with specific sleep habits — data that might not traditionally be considered in a suicide screening assessment.

"I'm interested in looking at the interactions and the relationships between these predictors," Dr. Stoddard says. "This can help us understand whether there are hotspots or particular risks, and we can understand whether they change over time."

While the team is currently refining algorithms and inputting clinical data manually, the hope is that within a year and a half, it will be so advanced in its learning algorithm that it gathers and learns from every piece of data on its own in real time as clinicians document on their patients.

Future goals aside, Dr. Stoddard's AI-powered predictions are already helping save youth from suicide across the state. "We're using this data and modeling to teach the people who are making policy what's important to consider when screening for suicidality," he says.

In a world where AI is sometimes seen as a threat to important aspects of our humanity, this work shows how it can be used as a positive force to implement policies that save lives, fighting back against one of the greatest public health challenges of our time. "It's not just computers learning — we're integrating the best of clinical screening, a primary form of suicide prevention, with AI," Dr. Stoddard says. "We're helping humans and machines to work together."

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Freckles of the Brain

Q: Are T2 hyperintense white matter lesions in pediatric migraine patients cause for alarm, or could reinterpreting these bright spots on MRIs lead to a revolutionary shift in pediatric neurology?

When pediatric patients present with migraine and headaches, clinicians often recommend magnetic resonance imaging (MRI) scans to rule out more severe secondary causes, such as intracranial masses or vascular anomalies. While these scans rarely show underlying issues, they often reveal incidental findings of nonspecific T2-weighted hyperintense white matter lesions, which appear as small, bright spots in brain tissue. The appearance of these bright spots often adds a layer of complexity, raising red flags, triggering additional tests, causing clinical trepidation and fueling parent anxieties. But what if these lesions aren't connected to migraine or indicative of something sinister? The research, a collaborative effort first authored by Children's Hospital Colorado headache fellow Elizabeth Ackley, MD, and senior authored by neuroradiologist Ilana Neuberger, MD, challenges long-standing perceptions of these lesions.

ANALYZING THE ANOMALIES

Driven anecdotally by experience and the lack of conclusive data in the pediatric population, Dr. Ackley and her team conducted a retrospective cross-sectional study, aptly named Dots and Spots, to compare the incidence of lesions among children with migraine, other headaches and those without headaches (1).

"I started wondering," Dr. Ackley recalls, "whether these bright spots on MRIs were truly indicative of a problem or just incidental findings that we've misunderstood."

The research involved the careful examination of MRI scans from pediatric patients spanning various ages and backgrounds. The study utilized the International Classification of Headache Disorders Third Edition criteria for migraine and other headache disorders. While the team encountered challenges with incomplete medical records, they managed to categorize 248 patients — 144 with migraine, 42 with other primary headaches and 62 with unspecified headaches. Children with known neurological conditions were excluded to eliminate the potential of confounding variables.

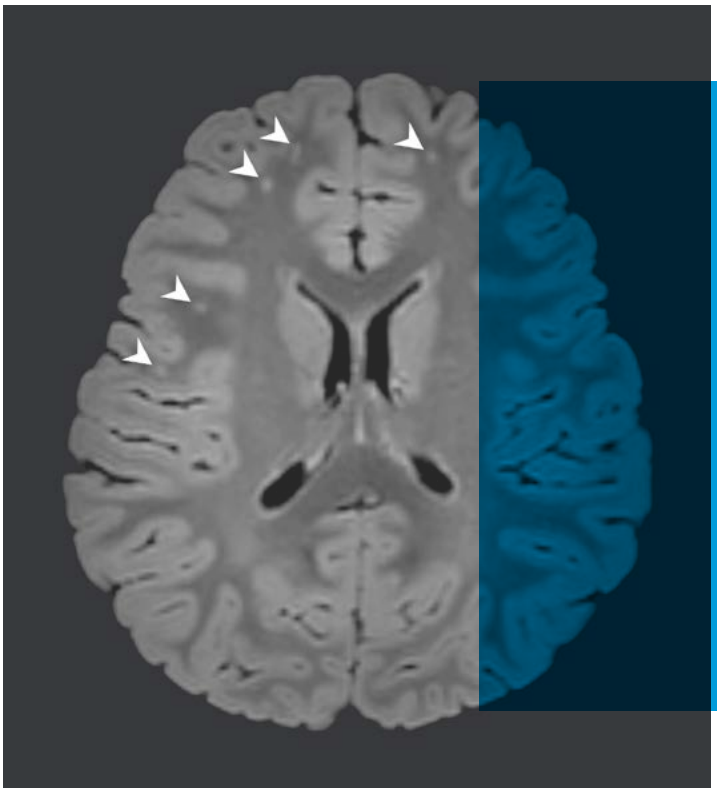
In contrast to adults with migraine, who unequivocally exhibit a higher prevalence of white matter lesions compared to those without migraine, this study revealed no significant difference in the occurrence of such lesions across all groups.

"We found that 40% of all children had these spots, whether they had a migraine, different type of headache or no headache at all," Dr. Ackley says. "Neither age, gender, nor the degree of headache-associated disability had any bearing on the frequency of these lesions. We were expecting no significant differences, and that's exactly what we found."

While there are lingering questions about when and how white matter lesions form — and their connection to migraine in adult patients — the results could have profound implications for medical practice and policy.

IMPACTFUL INSIGHTS

The study's findings have the potential to significantly reduce the number of follow-up diagnostic tests, reducing the risks associated with additional MRI procedures and decreasing healthcare costs. By disentangling the significance of these lesions from the diagnostic process, physicians are liberated to better focus on symptomology and identifying the root cause of patients' symptoms. At the policy level, insurance companies may find it necessary to reevaluate and potentially revise preauthorization requirements for follow-up MRIs that are based solely on the



> "The study reminds us that bright spots on an MRI may just be that — bright spots, not dark omens."
>
> ELIZABETH ACKLEY, MD

presence of white matter lesions, unless there is concern for another neurologic process. It's important to note that white matter lesions can be hallmarks of conditions like multiple sclerosis and leukodystrophy. However, in most cases where concerns for other neurologic diseases are absent, such as in individuals experiencing headaches or those who underwent MRI post-accidents, these lesions may not hold clinical significance.

For parents, the findings are a welcome relief. Hearing that a child has white matter lesions can send parents into a spiral of worry and worst-case scenarios. "The way that I sometimes explain these spots to patients is that they're freckles on the brain," Dr. Ackley says. "I might have more freckles than you, and even though it's technically a sign of a little bit of mild injury to the skin, we don't think of that as being anything dangerous or harmful." By shifting the perspective about the lesions as freckles of the brain, parents can breathe a sigh of relief.

FUTURE OF RESEARCH

While there are still lingering questions, such as the influence of cardiovascular risk factors, Dr. Ackley's Dots and Spots study serves as a compelling argument that, in most cases, these spots probably aren't clinically significant. And while these bright spots on MRIs may no longer be perceived as harbingers of doom, they are still pieces of a larger puzzle that requires continued research to unravel the ongoing mystery of these spots.

In fact, neuroradiologists David Mirsky, MD, and Dr. Neuberger, are collaborating with Dr. Ackley to lead a follow-up study aimed at understanding these lesions from a radiologic perspective.

"Their hope is to reinforce the findings of the Dots and Spots study and put to rest any remaining misconceptions about these MRI features," Dr. Ackley explains. "The study reminds us that bright spots on an MRI may just be that — bright spots, not dark omens." ●

1. Ackley E, Asamoah P, Mirsky D, et al. Dots and spots: A retrospective review of T2-hyperintense white matter lesions in pediatric patients with and without headache. Headache. 2023;63(5):611-620. doi:10.1111/head.14503.

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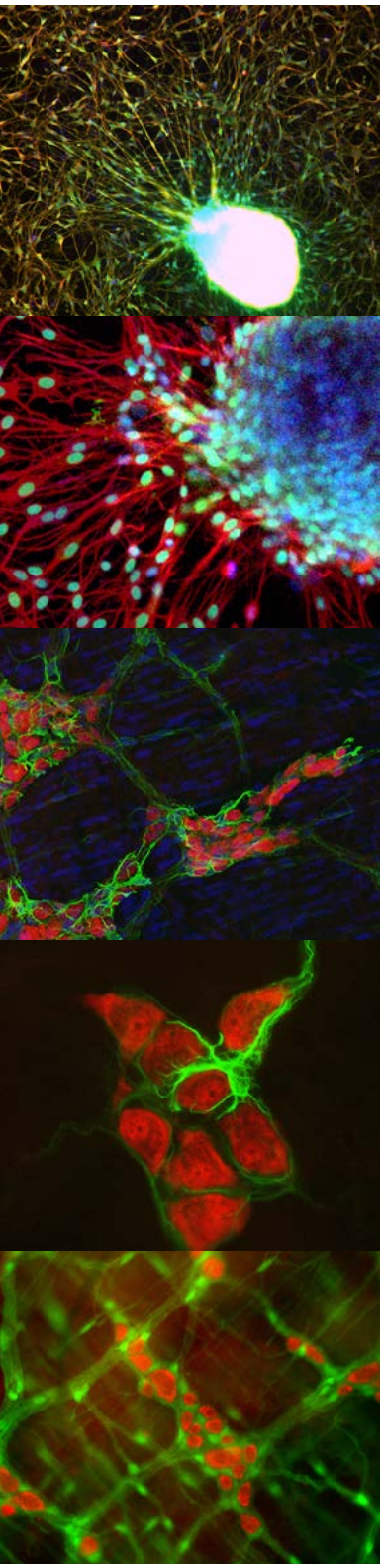

Following a Gut Feeling

Q: How can better understanding the gut-brain connection drastically change our approach to healing a variety of conditions?

Ongoing research from Children's Hospital Colorado exploring the connection between the gut and the brain gives new credence to sayings like "follow your gut" and "having a gut feeling." This work is led by neurogastroenterologist Jaime Belkind-Gerson, MD, who has spent his entire career working to better understand this connection and the impacts of the gut microbiome within and beyond the gastrointestinal (GI) tract.

Researchers have long recognized the importance of a healthy and balanced mix of bacteria in the human gut, but in recent years, they've begun further exploring the ways in which the gut and the brain communicate via the enteric nervous system and the immune system. The implications of this work are broad.

"We have now associated the microbiome with changes in mood, changes in appetite, changes in sleep patterns, in pain thresholds and food sensitivities," Dr. Belkind-Gerson explains. "We've noted that there are changes in gastrointestinal motility and inflammation in the whole body. It's a big deal."

His hope is that one day, doctors will be able to examine a person's gut microbiome and observe concerns with their microbiome diversity or abnormalities in the balance of microbial strains. With this information, he hopes to develop therapies tailored toward restoring each patient's specific microbiome to heal a whole host of conditions, including chronic pain, inflammatory conditions, digestive disorders and even chronic depression.

Until then, his work is focused on growing the base of knowledge related to communication between the gut and the brain. Two studies, both funded by the National Institutes of Health, further explore this connection. The first aims to characterize the gut microbiome in patients with Down syndrome who suffer from gastrointestinal motility disorders, while the second focuses on mechanisms of neurogenesis within the enteric nervous system.

DOWN SYNDROME AND THE GUT

According to Dr. Belkind-Gerson, roughly half of people with Down syndrome develop GI motility disorders in childhood or young adulthood, and the prevalence of GI issues only increases as these patients age. Still, researchers have not yet been able to nail down why.

Dr. Belkind-Gerson suspects a few things may be happening, based on previous research. For example, in mice with Down syndrome (1), researchers found fewer neurons in the gastrointestinal tract, and some studies have shown a relationship between Down syndrome and premature development of Alzheimer's disease.

The first two images show an intestinal enteric nervous system (ENS) culture with neurons and glia forming networks. The next three images show the myenteric ENS (contained within the muscular layers of the intestine) in an animal model. The red cells are neurons and the green ones are glial cells.

"Neurons are kind of master regulators of how things move and feel in the gut," Dr. Belkind-Gerson says. "There are different scientific clues that in patients with Down syndrome, the neurons may not function properly and may perhaps die prematurely, both in the brain and in the gut. We don't know why. So, we assembled a pretty amazing multidisciplinary team to find out."

One member of that team, Kelly Sullivan, PhD, found in a previous study, that people with Down syndrome have an extra copy of a proinflammatory gene called interferon gamma, making them prone to hyperinflammation not just in the gut, but throughout the body. This could contribute to these patients' gastrointestinal motility disorders.

Dr. Belkind-Gerson and his team are now working to bring observations like these to the clinical setting to better understand exactly what's occurring in the body.

"These are all important and interesting observations," he says. "But it's time to actually look and see what's happening to our patients. We're hoping to put all these disciplines together to understand why patients with Down syndrome develop these problems. If it's true to our hypothesis, then it's due to a predisposition to gut inflammation in the GI tract. If so, how can we balance it? How can we prevent it?"

As part of this study, Dr. Belkind-Gerson and his team will study his patients' GI motility and cognitive functioning, while infectious disease expert Dan Frank, PhD, performs microbiome analyses of each patient's stool and Dr. Sullivan carries out RNA-sequencing and metabolomics studies to better understand the associations behind these clinical issues. Over five years, this multidisciplinary team hopes to not only learn more about GI disorders in patients with Down syndrome, but also better understand the connections between GI motility and neurodevelopmental conditions more broadly.

UNCOVERING THE SECRETS OF GUT NEUROGENESIS

It used to be common medical knowledge that each person was born with a certain number of neurons, and once they were gone, they couldn't be regenerated. Over the years, researchers have discovered that this is not true. Instead, investigators found that within specific areas of the brain there is daily neurogenesis, even in adulthood. They found this by using a fluorescent-marked thymidine molecule that allowed scientists to visually see cells replicating in the brain.

Given that there are neurons in the GI tract, and that we see the gut grow as babies age, Dr. Belkind-Gerson has long suspected that neurogenesis happens in the gut as well.

But when gastroenterologists attempted to use the same approach that found neurogenesis in the brain, nothing happened (2). That's because neurogenesis in the gut happens a little bit differently.

"It seems like neurogenesis does occur postnatally in the gut," Dr. Belkind-Gerson says, "but it doesn't happen without an injury. Something needs to happen, and then it gets triggered."

Previous research discovered that this form of neurogenesis happens thanks to various types of glial cells (3), which traditionally support neurons in the gut. Dr. Belkind-Gerson's team found that these glial cells can actually become neurons in the event of injury, through the process of transdifferentiation. Still, researchers don't know how this happens, how robust it is or what exactly triggers the process to begin. And to make matters more complicated, researchers in Japan recently found a new method of neurogenesis in the gut, whereby a type of glial cell that lives outside the gut — Schwann cells — can be recruited to the gut and revert to a precursor cell that then becomes a neuron.

Dr. Belkind-Gerson's second NIH-funded study aims to understand this type of neurogenesis better. The study will use marked Schwann cells and mice with various types of gut injury (e.g., colitis, inflammation and microbacterial perturbations) to attempt to watch and characterize neurogenesis in action. They will then perform GI motility studies to see whether newly made neurons can restore full function to the gut or not.

Dr. Belkind-Gerson says that he's hopeful this research will not only make a practical difference in people's lives, but also help physicians and scientists continue to grow their understanding of the gut-brain connection. This, he says, could unlock entirely new avenues of treatment for some of our most puzzling conditions. ●

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JAIME BELKIND-GERSON, MD

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Pathways to Safer Play

Q: How can new assessment tools improve recovery for sports-related concussions worldwide?

Children and teens who suffer concussions during sports can experience long-term consequences. Fortunately, as public awareness of concussions has grown, so too has research dedicated to their care. The culmination of such research is outlined in the British Journal of Sports Medicine's international consensus statement (1), which sports medicine professionals around the world rely on for evidence-based guidance on concussion prevention, assessment and management. Recently, 36 research papers from Children's Hospital Colorado were accepted for incorporation into this statement and its accompanying literature, including two important tools for improving sports-related concussion management in youth around the globe.

The Children's Colorado researchers behind this work include David Howell, PhD, director of the Colorado Concussion Research Lab at the University of Colorado School of Medicine, and Julie Wilson, MD, the lab's associate director. In October 2022, Drs. Howell and Wilson traveled to Amsterdam to present recent findings at the sixth International Conference on Concussion in Sport, organized by the Concussion In Sport Group. Typically held every four years, the conference unites the world's leading concussion researchers to assess current best practices, discuss recent findings and develop an updated consensus statement. Dr. Howell, Dr. Wilson and three graduate students from the lab successfully proposed a new test that will now be part of the international consensus statement.

"The balance test used up to this point is still in the international guidelines, but it's fairly subjective," Dr. Howell says. "You have people stand on one foot with their eyes closed, and when they try to balance, you judge how many errors they make."

Drs. Howell and Wilson addressed the limitations of the older, more subjective tools with what they named the tandem gait test — an evaluation tool using time-based benchmarking. The tandem gait test is more accessible than other tools because it doesn't require sophisticated gait and balance measurement devices, which can be expensive. It only requires a strip of tape placed in a line on the floor and a timekeeping device such as a smartphone. "The goal is to have somebody walk straight, heel to toe on each step, along the line," Dr. Howell says. "The patient tries to do this as fast as they can, but as you can imagine, a concussion creates some instability and lack of coordination as a result of the injury."

In some instances, healthcare providers can ask patients to walk along the line a second time while simultaneously completing a cognitive task, such as spelling a word backwards.

"Your brain has limits on how much attention it can distribute, and everybody's going to have to slow down a little bit to spell a word backwards," Dr. Howell says. "But post-concussion, we see that people have to slow down even more."

If a patient needs to slow down significantly to process both the cognitive task and the physical task, it could be a sign that they wouldn't do well in a game setting, where they'd have to make quick mental and physical decisions. Now, thanks to the tandem gait test, healthcare providers can reach that conclusion in a matter of minutes.

Compared to some previous tests used to assess concussions, which have about a 60% success rate, the tandem gait test accurately classifies concussions 82% of the time. It began as a graduate school project for Dr. Howell, who, alongside Dr. Wilson, began gathering relevant data from patients in 2019. By evaluating the effectiveness of the new test in the lab against other research-proven tests, they were able to iterate the test until it proved more effective.

"This is a prime example of where research and clinical practice meet," Dr. Howell says.

The tandem gait test isn't the only research from Children's Colorado that was accepted into the international guidelines. The statement also includes a concussion recognition tool that Dr. Howell helped to revise into its current form. This updated evaluation helps nonhealthcare providers, such as coaches and parents, make important decisions in the immediate aftermath of a concussion — including when to remove an athlete from play, when to call 911 and more. Both tests help ensure that kids don't return to sports before they're ready. Research shows that kids and teens

who get back in the game too soon are more likely to experience an orthopedic injury than those who haven't had a concussion, because a concussion can reduce cognitive functions such as reaction time and processing speed.

"There's all of this competing cognitive and motor information that has to process in real-time when playing sports," Dr. Howell says. "If you can't simply do two things at once, you could be at risk for further injury once you actually get back to the field."

Colorado Concussion Research Lab has tested numerous injury prevention strategies as part of their rehabilitation program. "People who go through that program are three and a half times less likely to get a sport-related injury in the year after a concussion than people who didn't go through the intervention," Dr. Howell says. "The goal is to help people return to the things they love doing, but in a safe manner."

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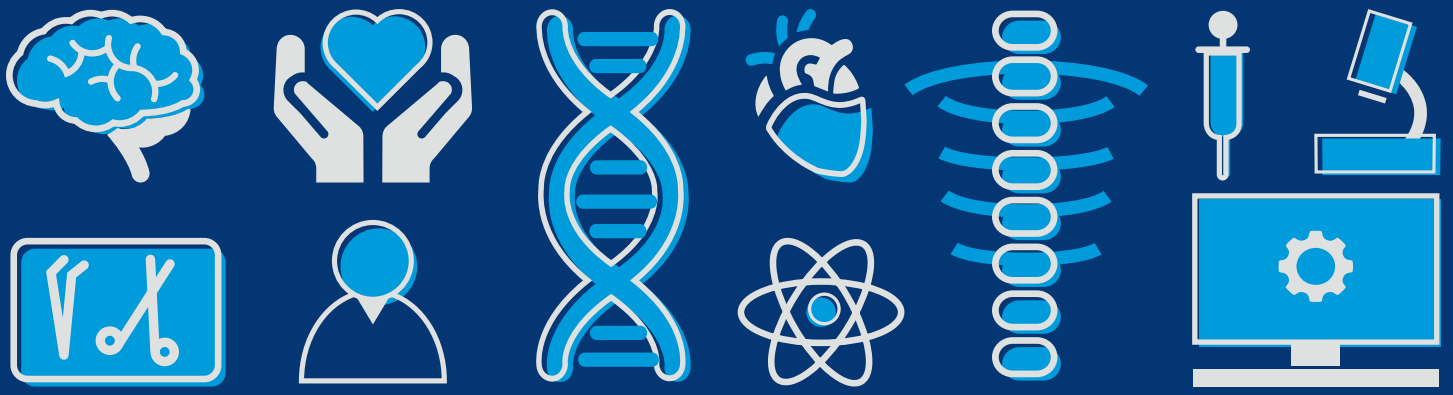
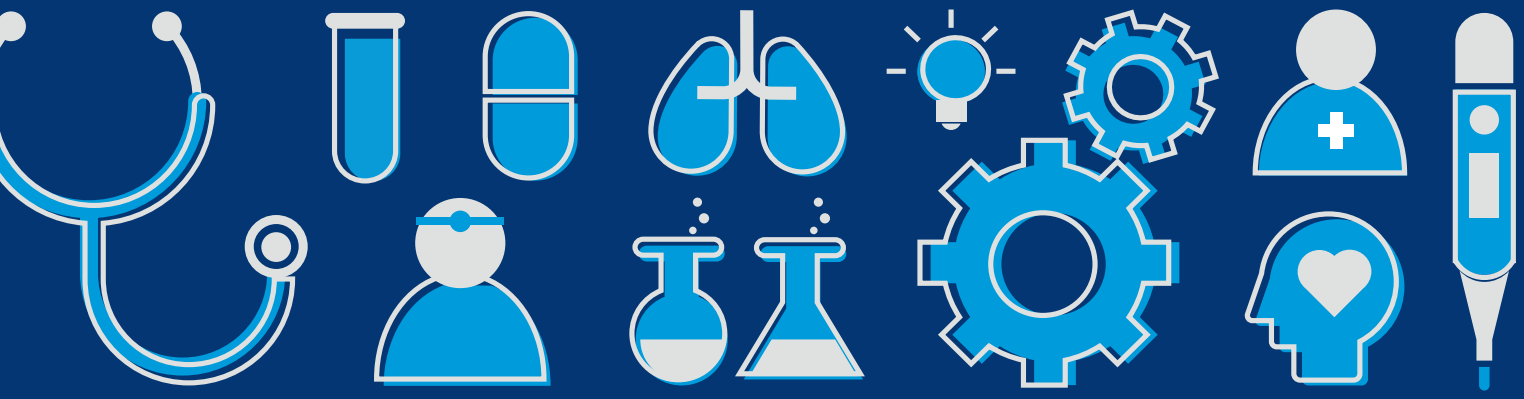


The Advantage of Advanced Treatments

Children's Hospital Colorado researchers don't conduct research just for the sake of gaining knowledge. Instead, their work is focused on bringing that knowledge to the bedside to improve not only the care patients receive, but also their experience. In the pages that follow, you'll learn about three new approaches to treatment that doctors at Children's Colorado are bringing directly to patients to improve outcomes, shorten recovery times and increase patient safety.



Setting a New Pace

CARDIOLOGY

Traditional pacemakers rely on intravenous wires, or leads, to deliver electrical pulses to parts of a person's heart and regulate their heartbeat. While pacemakers are necessary in patients with an abnormally slow heartbeat, their wires can cause a host of serious complications if they become infected, dislodged or fractured. Leadless pacemakers were developed to provide a safer alternative for patients who need their heartbeat regulated in certain situations.

In July 2023, the Children's Hospital Colorado Heart Institute became one of the first pediatric teams in the world to implant the AVEIR Leadless Pacemaker. Children's Colorado's pediatric electrophysiologists Dustin Nash, MD, and Johannes von Alvensleben, MD, implanted the novel leadless pacemaker into an 18-year-old patient's heart. He was the perfect candidate for a leadless pacemaker because he has a severe form of vasovagal syncope — a condition that causes his heart rate to drop rapidly in response to stress.

Now, the leadless pacemaker monitors his heart at all times, but only kicks in to pace his heart rate when it detects a sudden change. Without the movement restrictions and recovery processes that typically come with an ordinary pacemaker, the patient — a collegiate soccer player entering his freshman year — was back on the field acing fitness tests just four weeks later.

The success of this implantation shows great promise not only for pediatric patients with vasovagal syncope, but also for those with intermittent heart block, seizure abnormalities and other congenital heart conditions that don't need constant pacing. Another benefit of a leadless pacemaker for pediatric patients is that they offer a longer battery life, reducing the need for surgeries as the child grows.

In the case of this young athlete, his AVEIR Leadless Pacemaker is expected to last 18 years. And since the device is designed to be removed, his future replacements will continue to be minimally invasive with faster recovery times.

"It was really nice to have this option for our patient rather than the ones that we've traditionally had," Dr. Nash says. "The leadless pacemaker checked all the boxes that we needed." ●

DUSTIN NASH, MD

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The Advantage of Advanced Treatments continued

Pacemaker for the Tongue

OTOLARYNGOLOGY

Obstructive sleep apnea (OSA) is often present in kids with Down syndrome due to low muscle tone and craniofacial features, such as a smaller upper airway or larger tongue, that make it more challenging to maintain an open airway during sleep. For many patients, the first-line treatment — continuous positive airway pressure (CPAP) — is not always effective or tolerable, with long-term adherence rates below 50%. However, there's new hope on the horizon.

Pediatric otolaryngologist Norman R. Friedman, MD, of Children's Hospital Colorado, highlights a breakthrough treatment for OSA in patients with Down syndrome, which is known as upper airway stimulation. This treatment employs an implantable nerve stimulant, which is implanted under the skin of the neck and chest, and works much like a pacemaker for the tongue. When activated, the device stimulates the tongue to move forward, opening the airway to allow oxygen to flow naturally and facilitating breathing.

Recently, the U.S. Food and Drug Administration extended approval for the device to include children with Down syndrome aged 13 and older. The safety and efficacy of the device was evaluated in the STAR clinical trial, which showed significant reductions in sleep apnea events and improvements in quality of life.

While only a handful of children's hospitals currently offer this treatment, Dr. Friedman plans to expand the sleep program at Children's Colorado to treat patients with Down syndrome and evaluate children who still have persistent OSA after undergoing a tonsillectomy.

The device offers a new, innovative approach to effectively managing OSA in young patients, especially those who are not candidates for or cannot adhere to CPAP therapy. It represents a key advancement in sleep apnea treatment and has the potential to improve the lives of patients who previously had limited options.

"This therapy is setting new standards in OSA treatment here at Children's Colorado and beyond," Dr. Friedman says. "We look forward to expanding this treatment to our teens with Down syndrome, as well as the broader pediatric population." ●

NORMAN R. FRIEDMAN, MD

Surgical Sleep Program Director, Sleep Program, Children's Hospital Colorado

Professor, Pediatric Otolaryngology-Head and Neck Surgery, University of Colorado School of Medicine

Mom in Mind

COLORADO FETAL CARE CENTER

A team at the Colorado Fetal Care Center at Children's Hospital Colorado performed the hospital's first fetoscopic myelomeningocele (MMC) repair, joining just a few children's hospitals in the entire country that offer this type of procedure. Fetoscopic MMC repair is a minimally invasive surgery — performed while the baby is still in the womb — that repairs and closes defects in the spine caused by MMC, a severe form of spina bifida. Research shows opting for fetal surgery instead of waiting until after birth results in better motor function for the baby and a 50% decrease in the need for a shunt.

The Colorado Fetal Care Center has offered the traditional open MMC repair procedure for years, but this new surgery places a stronger emphasis on prioritizing the best interests of both the baby and the parent. The surgery also gives the birthing parent the option of a vaginal birth as opposed to only having the option of delivering via cesarean section, which is standard with open repairs.

This procedure is already making a difference for patients. For example, when a New Mexico mother learned at 21-weeks pregnant that her baby had spina bifida, she was immediately referred to Children's Colorado and opted to be the first to receive this new fetoscopic procedure. Pediatric and fetal surgeon Chris Derderian, MD, and a multidisciplinary team performed the successful surgery in August 2023.

"We're excited to be able to offer the fetoscopic approach to give families a choice that benefits both baby and mom," Dr. Derderian says. "One of the really important principles that we support at our fetal care center is that it's a maternal and fetal care center — so not just focusing on the fetus, but also the long-term repercussions for the mother as well."

Children's Colorado is now the only hospital in the seven-state region to offer this leading-edge surgery. ●

CHRIS DERDERIAN, MD

Pediatric and fetal surgeon, Colorado Fetal Care Center, Children's Hospital Colorado

Assistant professor, Surgery-Peds Surgery, University of Colorado School of Medicine

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

Daniel Wood, PHD, MBBS

UROLOGY

Associate Vice Chair of Transitional Care

Urologist Daniel Wood, PhD, MBBS, is the new Associate Vice Chair of Transitional Care for University of Colorado's Department of Surgery in addition to his role as Children's Hospital Colorado's Chair of Adult Congenital Surgery for urology. Dr. Wood's new position will help bridge care between Children's Colorado's adolescent services and UCHealth's adult services on the University of Colorado Anschutz Medical Campus. His area of expertise is focusing on patients who need long-term care following pediatric surgery and working to understand and improve the patient's experience as they transition from pediatric to adult healthcare. This new role will strengthen campus collaboration between surgical programs to ensure continuous care across the lifespan.

Pathology and Lab Medicine

Transmission electron microscopy accreditation

In 2023, the Electron Microscopy Laboratory at Children's Hospital Colorado was granted transmission electron microscopy (TEM) accreditation, elevating its status as one of only two sites in the U.S. accredited to perform ultrastructural studies in diagnosing primary ciliary dyskinesia (PCD). The TEM accreditation comes from the PCD Foundation, a patient-focused organization dedicated to providing resources for people diagnosed with PCD, a rare and debilitating lung disease.

"We're honored to receive this accreditation, as it is a testament to the expertise our lab has developed," says Eric Wartchow, PhD, Electron Microscopy Laboratory Director. "With it, we will be able to provide reliable diagnostic services to an even greater number of centers and patients."

Epidermolysis Bullosa Program

DERMATOLOGY

Center of Excellence recognition

Children's Hospital Colorado's Epidermolysis Bullosa Program was recently recognized as a center of excellence by debra of America, the leading patient advocacy organization for epidermolysis bullosa (EB). The program, led by Anna Bruckner, MD, MSCS, and James Feinstein, MD, MPH, is one of only a handful of institutions providing advanced levels of care for EB, also known as butterfly skin disease. In fact, Dr. Bruckner says the program is gearing up to begin offering the first-ever treatment for dystrophic EB (DEB), a severe form of EB caused by abnormalities or deficiency of collagen VII in the skin. The treatment, which was recently approved by the U.S. Food and Drug Administration in a landmark decision, is a topical form of gene therapy that delivers normal copies of COL7A1 genes to the skin, helping form anchoring fibrils that strengthen the integrity of the epidermis and dermis. Advancements like this are reshaping the future of rare disease treatment and offer significant promise of transformative care and better quality of life.

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BEST CHILDREN'S HOSPITALS U.S.News & WORLD REPORT RANKED IN 10 SPECIALTIES 2023-2024

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.