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Q: *Advances and Answers in Pediatric Health*

The Big Push

Children's Hospital Colorado was the largest trial site for Pfizer's COVID vaccine in children ages 5 - 11. It was also the most diverse. **P. 7**

Children's Hospital Colorado

Affiliated with
University of Colorado
Anschutz Medical Campus

It starts with a Q:

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

Dear colleagues,

A few weeks ago, I was participating in a town hall promoting COVID vaccines within the Black community when someone asked me, "Why should the Black community trust these vaccines?" I answered honestly: I personally feel that, for the Black community, there are very valid reasons to distrust this process.

As researchers, we face a conundrum. We know that medical research in this country has historically centered on white men. We know it's not representing everyone we serve. And the research that has focused on people of color has frequently been exploitative. We have a lot of work to do around trust.

I'm privileged to help lead Children's Hospital Colorado's efforts in diversity, health equity and inclusion. As part of that mission, we're bolstering the data we need to understand our population demographics: race, ethnicity and preferred language. Only through measuring disparity can we intervene and drive real and sustainable change.

When we served as the largest global trial site for Pfizer's COVID vaccine in children ages 5 to 11 — a massive effort that enrolled 250 kids in just 10 days — our priority was to make sure we were representing our community, not only in terms of race and language, but also ability and neurodiversity (see "Shaping the Protocol" on p. 7).

I firmly believe our COVID vaccines are safe and effective in children of all races and ethnicities. And as I stood before that town hall audience a few weeks ago, I said that too. But it'll take more than just saying it.

When we take on the mantle of medicine, we make a promise: First, do no harm. As care providers, we have not lived up to that promise. As long as members of our communities remain disenfranchised, ignored or underserved, we've failed to do our job.

I believe we can do it — and not just for future generations. If we do this work, I truly believe we can make an impact here and now.

I hope you'll join me.

Best regards,

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Hot Button Issue

GASTROENTEROLOGY & RADIOLOGY

According to the National Safety Council, roughly 3,500 people swallow button batteries in the U.S. each year. Once they become lodged in the body, they can cause serious damage, such as vocal cord paralysis, mediastinitis and aortoesophageal fistula, which is typically fatal.

Using radiography to determine button battery location ahead of removal has long been common practice, but this approach falls short in its ability to detect the level of injury inflicted. Since 2012, Children's Hospital Colorado has remedied that shortcoming by employing MRIs after battery removal to provide more information and reduce complications. A recently published retrospective study (1) conducted by Children's Hospital Colorado researchers uses data from the six-year period between 2012 and 2018 to understand the lessons of that practice and share them with the broader medical community.

The study found that using MRIs to determine severity, location and evolution of soft-tissue injury was critical in guiding clinical decisions and in helping Children's Colorado's medical team understand key patterns in button battery injury. For example, researchers found that the most severe complications occurred when the battery lodged in the cervical esophagus. What's more, MRIs played an important role in determining safe patient discharge.

"Providers who care for these children after battery removal are left to decide how long they stay in the hospital and when it might be safe for them to begin eating, knowing that they continue to face a risk of fatal aortoesophageal fistula for up to several weeks," explains Robert Kramer, MD. "Use of these noninvasive imaging tools helps to better define that risk, as well as monitor improvement over time to better inform these decisions."

According to Dr. Kramer, this research can make an impact beyond Children's Colorado. He hopes to see the results of this study lead to standardized care for button battery ingestion across institutions, with the goal of decreasing both morbidity and mortality risks.

1. Grey, Neil E O et al. "Magnetic resonance imaging findings following button battery ingestion." Pediatric radiology vol. 51,10 (2021): 1856-1866.

ROBERT KRAMER, MD
Co-Medical Director of Digestive Health Institute,
Director of Endoscopy, Children's Hospital Colorado
Professor of Pediatrics-Gastroenterology, Hepatology and Nutrition, University of Colorado School of Medicine

Gaming the System

CHILD LIFE

In September 2021, Children's Colorado partnered with Child's Play Charity to host a conference exploring virtual reality, extended reality and gaming in a medical setting. The Pediatric Gaming Technology Symposium was the first gathering of its kind in this emerging field.

The two-day virtual conference drew a global audience of professionals and included discussions of gaming specialties at other hospitals, 3D printing, physical therapy interventions and more. It opened with a keynote address by Jane McGonigal, a video game designer whose therapeutic games have made significant waves. She created a game called SuperBetter, which gamifies various therapies, and shared the many benefits of using this technology in the pediatric space. In addition to attending a wide variety of discussions, participants benefited from a virtual social space which allowed them to interact via avatars and continue the conversation outside formal sessions.

Attendees also met with various other experts, including Abraham Homer, Children's Colorado's gaming technology specialist, who presented about using virtual and augmented reality for pediatrics.

When Children's Colorado brought Homer into its community back in 2019, it became the first pediatric hospital to fill such a role. Under Homer's lead, Children's Colorado has found new applications for gaming, such as virtual reality for procedures like lumbar punctures in lieu of anesthesia and augmented reality in the burn clinic. More projects are underway to grow the program in house, but Homer says he also hopes to help centralize gaming knowledge and build a strong foundation for the future beyond Children's Colorado. The symposium helped move this goal forward.

"In healthcare everything is very formalized, but for gaming techs it's just so unprecedented that there's not really a good roadmap," Homer says. "I think for the game techs themselves, the symposium really solidified that we are a big community, and we are all here to help each other. They are not on an island doing this work alone."

ABRAHAM HOMER
Gaming Technology Specialist,
Children's Hospital Colorado

A Fantastic Voyage

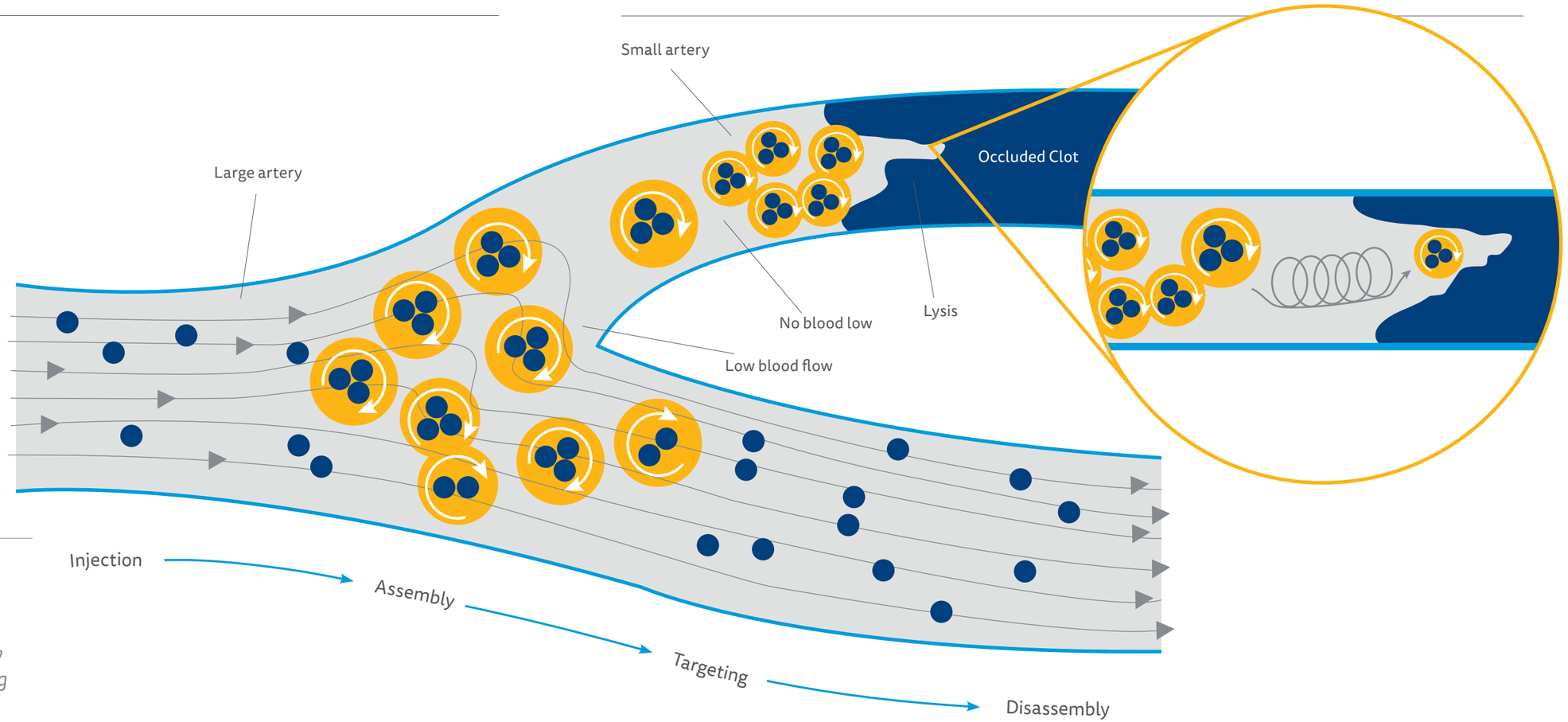
Q: Could tiny magnetic "microwheels" be the latest breakthrough in treating strokes?

In more than a quarter of stroke patients, conventional treatment options are ineffective at breaking up blood clots. Keith Neeves, PhD, is working to change that through a potential new treatment dubbed "microwheels." These rotating clusters of magnetic beads that can be guided toward clots using magnetic fields have already produced impressive results in animal models: A clot that might have taken an hour to break up now takes about a minute.

In the 1965 film "Fantastic Voyage," a group of scientists shrinks to microscopic size to navigate a tiny submarine through a defected soviet spy's vasculature, saving him from a massive stroke by using lasers to break up a blood clot in his brain.

"That's the origin of this idea," says bioengineer Keith Neeves, PhD.

Inspired by the film, Neeves has spent the last eight years working with a cross-disciplinary team of mathematicians, biologists, clinicians, nurses, engineers, students and postdocs to find new approaches to treating strokes that occur in small blood vessels. Instead of a shrink ray and lasers though, Neeves employs tiny magnetic beads that, when exposed to a rotating magnetic field, form what he calls "microwheels."



Neeves hopes that one day these magnetic beads — made of plastic and iron oxide and roughly the size of a blood cell — can be injected into a patient's blood stream and directed toward blood clots. Once in their wheel configuration, the particles act as a swarm, and by altering the magnetic field, Neeves can control the swarm's behavior.

"Over the years, we've figured out ways to manipulate that magnetic field to make the wheels do all kinds of different things," Neeves explains. "We can get them to roll in any direction and there's some modes where they're good at climbing walls. There are other modes where they're good at penetrating into surfaces and there are modes where they roll really fast."

The magnetic field is powered by copper wire repurposed from audio speakers, which is wrapped around cylinders that Neeves can control with a simple joystick. As he moves the field, the swarm of microwheels follows suit.

EXPANDING ACCESS AND CARE

This accessible, affordable technology could have any number of applications, but Neeves and his team are currently focused on using the microwheels to dissolve stroke-inducing blood clots. According to Neeves, stroke treatment has long been stagnant and relies heavily on just one FDA-approved drug with significant side effects. Strokes can also be treated using thrombectomy catheters, which are inserted into blood vessels to manually rip a clot out. To access this treatment though, patients must be lucky enough to live near a hospital that has the necessary suite of tools and expertise.

What's more, 25 to 30% of strokes occur in small blood vessels, which are difficult to reach with catheters and often don't get enough blood flow to successfully deliver clot-busting pharmaceuticals. This is a problem in children with strokes too, whose blood vessels are much smaller than their older counterparts.

That's where Neeves' science-fiction approach could one day make all the difference. With its use of recycled audio materials and its simple infrastructure, it could expand access to care, and its medical benefits are twofold.

"It's not just dumping the drug there at the side of the clot. It actually drives into the clot because we have this mechanical force that allows us to penetrate," Neeves says. "And so rather than dissolving something just at the surface like sandpaper, what we do is we actually drive them in, and it dissolves the clot from the inside

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A Fantastic Voyage continued

out. It gets a Swiss cheese conformation and the rate at which we can dissolve the clot is much faster."

A PRODUCT OF COLLABORATION

So far, this technology has only been tested in animal models, but the results are promising. Neeves and his team have decreased clot-busting time using a combination of microwheels and thrombolytic therapy by a factor of 50 over thrombolytic therapy alone.

This outcome, Neeves says, is the product of dozens of people in a variety of fields coming together in one cohesive space to solve a pressing, though underappreciated, problem. This collaboration is only possible at places like the Anschutz Medical Campus, which, in addition to housing Children's Colorado, also includes the University of Colorado School of Medicine.

"Being on this campus, being able to leverage the different facilities we have, and just the human capital is unique," he says. "There are only a handful of places in the country where you can do this kind of work." ●

KEITH NEEVES, PHD
Professor, Bioengineering and Pediatrics, Section of Hematology, Oncology and Bone Marrow Transplant, University of Colorado Denver

Neeves' microwheels are just one example of how his work contributes to the scientific understanding of blood disorders. Two additional projects have the potential to improve patient outcomes and make major waves.

Organ on a chip

When it comes to running new tests and experiments, most researchers rely on animal models. But a new scientific movement takes human-derived cells and grows important features of an organ in a lab. In Neeves' case, this means taking endothelial cells, which line human blood vessels, and growing them inside tubes the size of a human hair.

"We can grow them inside of these little tubes and then apply different kinds of insults to them, run blood through them and watch clots form," Neeves says. "You can see these clots forming at the cellular scale, which is hard to do inside of an animal or inside of a person. And then we have total control over everything."

The goal of this work is to eventually achieve personalized medicine. One day Neeves hopes that he can recreate an individual patient's exact situation through this process and test different treatments to determine the best option for them.

Mathematical models of clotting

Working with applied mathematicians at Colorado School of Mines and University of Utah, Neeves has created mathematical models that allow him to run 100,000 clotting simulations in just a few minutes. Neeves says the idea is that if they can build strong mathematical models, they can use the information as a screening tool to better understand how the composition of someone's blood might affect its ability to clot or not, particularly in the case of hemophilia.

"You can think about it as having hundreds of knobs on a control panel and then randomly turning them all," Neeves explains. "The model pulls out these key tweaks and says, 'If you turn this knob and this knob, then we get this really interesting and maybe counterintuitive result.'"

Using statistical methods, Neeves' team extracts the most interesting findings and uses experimental methods to verify them. The results go right back into the model, making it better and smarter over time. Most recently, this approach alerted Neeves' team to a possible novel modifier of bleeding in hemophilia. They validated that via experimentation and are now diving into whether that finding is a potential therapeutic target.

Shaping the Protocol

Q: Could a massive study of a COVID-19 vaccine in children also reflect the populations most at risk?

Children under 18 years old generally have milder disease than adults, but they carry COVID just as effectively, making up 20.8% of COVID cases and 22.2% of the U.S. population at large. In mid-December 2021, children were contracting COVID at a rate of nearly 200,000 new cases per week (1). They're a crucial segment of the population to vaccinate.

In 2021, Children's Hospital Colorado played a central role in the effort to clinically validate Pfizer's COVID-19 vaccine for children, enrolling 252 participants altogether. It wasn't just the largest study group, at 11% of the study population worldwide. It was also, very intentionally, the most diverse.

Clinical trials are rarely a big draw for the general public.

"Typically at a pediatric academic institution we're engaged in trials for rare disease, and it's a specific medication or device," says Erin Sandene, director of research operations at Children's Colorado. "You don't often have people champing at the bit to be part of a research study."

For its phase 3 trial of the Pfizer vaccine — the first to receive emergency authorization for use in children ages 5 to 11 from the Food and Drug Administration — Children's Colorado received more than 5,000 initial applicants.

"That's huge," Sandene says.

The slew of public interest presented an opportunity: For Pfizer, it was a chance to capture a large amount of pediatric data and lead the pack in making its vaccine available to the public. For Children's Colorado, it was a chance to be part of something bigger, but also to advance a strategic priority that had been gathering steam all year: the effort to bring better representation to clinical research.

COVERING ALL THE BASES

Pediatric infectious disease specialist Eric Simões, MD, has been leading clinical trials for decades. As a key player in the World Health Organization's effort to help manage common pediatric conditions in low- and middle-income countries, he specializes in the prevention of long- and short-term effects of respiratory syncytial virus, or RSV. In fact, it was his role as primary investigator in a Pfizer RSV prevention trial that led to Children's Colorado's designation as a supersite for its COVID vaccine trial.

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11%

Of the total pediatric cohort for the Pfizer COVID-19 vaccine trial across the globe

Shaping the Protocol continued

"They were asking questions about study design for the vaccine, and I helped with some of that," he recalls. "And then they asked me if I wanted to do a large study here. They proposed 500 subjects. Immediately after I got off the phone with their Senior VP, I talked to Erin."

"We're talking about a randomized, blinded trial — it's a lot more complicated than just here's your shot," says Sandene. "There are a lot of moving parts, making sure you're not unblinding, dispensing drug or placebo. It's a huge amount of required documentation and regulations to consider. There's no way one person could do it all."

The team ultimately committed to enrolling 250 children to the trial — a massive effort in itself, representing 16% of the total enrolled population in the U.S. The project team included a 23-person staff, including a process improvement specialist, a project manager and an external vendor to help with scheduling. The goal: to enroll 25 children per day over the course of 10 days, eventually enrolling 252 children total. Pfizer agreed to pay the salaries of the staff necessary to support the effort.

"That's kind of unheard of," says Sandene. "Pharma companies usually see that kind of thing as a cost of doing business. But in this case, there were a lot of bases to cover."

"I've been doing clinical trials for years," says Chief Quality and Outcomes Officer Lalit Bajaj, MD, MPH, who served as executive sponsor for the trial. "Never have I been involved in something this quick, under this much scrutiny, involving so many people."

RECRUITING FOR REPRESENTATION

The ZIP codes surrounding Children's Colorado's Anschutz Medical Campus, where the study would occupy a wing of the Outpatient Pavilion, are both racially and economically diverse. The team felt the study population should reflect that demography.

"We wanted to enroll populations that often get excluded from studies like these," Sandene says.

Dr. Simões and team centered recruitment efforts on pediatric practices that care for medically underserved communities from Longmont to Colorado Springs. Chief Administrative Officer and General Counsel Michelle Lucero personally handed out materials in Spanish. And once the applications were in, Dr. Simões and team created a survey to ask applicants to self-identify their demographics. They used statistical methods to randomly select numbers that reflected the Colorado population.

And ultimately, they enrolled a population that was more than racially and ethnically diverse. They enrolled patients with autism spectrum disorder, Down syndrome, mental health challenges. They enrolled monolingual speakers of Spanish and Korean. They brought on interpretation services and a full-time child life specialist to help participants feel comfortable and informed.

"Dr. Simões was adamant," adds Sandene. "He really influenced Pfizer in the view that we needed representation that met or exceeded our local demographics, because those were the populations that were most adversely affected by the pandemic. We helped shape Pfizer's protocol."

They also helped shape future protocols at Children's Colorado. A pilot program built into the electronic medical record will collect cultural data moving forward, so research teams can better understand what their communities look like and work to correct disparities between clinical and research populations.

"I'm optimistic this isn't going to be a decades-long effort," says Dr. Bajaj. "In the next two or three years, we're going to get better at this."

16%

Of the pediatric cohort in the U.S.

Most

Diversity of any enrollment site

THE AMAZING PART

One of the most surprising aspects of the study itself was just how effective Pfizer's vaccine was in children.

"We were giving one-third the dose as in older children and getting the same immune response," Dr. Simões says. "The study was actually not powered to show efficacy until 6 months out, but we were able to show efficacy by three months. That's the amazing part."

As the Delta variant surged, just three children in the vaccine group contracted COVID-19. Infections in the placebo group increased steadily.

The data were clear: Pfizer's COVID-19 vaccine was safe and effective in children ages 5 to 11, and it received emergency use authorization from the FDA on Oct. 29, 2021. Less than two weeks later, the team published their preliminary results in the New England Journal of Medicine (2).

The trial continues. The team followed participants through December, when they received a final blood draw to test for undetected infections and immune response. They'll continue to follow for another year and a half. Currently, they're gearing up for a modification of the trial beginning in February 2022, administering booster doses to participants at least 6 months from their initial dose to study their immune response.

Meanwhile, immediately following emergency use authorization, Children's Colorado partnered with the Colorado Department of Public Health and Environment to stand up vaccine clinics at Children's Colorado locations and through general pediatric practices in Children's Colorado's Pediatric Care Network. As of Dec. 7, 2021, those clinics had administered more than 22,000 doses, and that number continues to rise.

The study was so successful that the team was approached by Moderna to conduct a trial of similar proportions, although the team ultimately decided it was too much to absorb. That study eventually took place next door at the University of Colorado School of Medicine.

"One lesson we took from this is that staff hired under our Research Institute are usually committed to projects. We don't have reserve staff that we can mobilize when something like this comes up," says Dr. Simões. "We did it. We got the nurses, the research coordinators, the pharmacists. Everyone was fabulous, and we found the space. But one thing that would help in the future is having a core of uncommitted staff to take on something like this. I hope we can build that." ●

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The Case for Two

Q: Would kids diagnosed with MIS-C do better with more aggressive treatment up front?

More than 50 years after Kawasaki disease was first described, nobody knows quite what causes it or why it happens in previously healthy children. The same is true of multi-inflammatory syndrome in children, or MIS-C, which investigators linked to SARS-CoV-2 infection in early 2020. It was clear right away the two conditions had a lot in common, and so it made sense to treat them in much the same way. But Kawasaki disease experts like pediatric cardiologist Pei-Ni Jone, MD, and pediatric infectious disease specialist Samuel Dominguez, MD, quickly noticed a key difference: kids with MIS-C were sicker.

In April of 2020, healthcare systems around the world faced a steep and urgent learning curve: COVID-19 was spreading rapidly, and much about it remained unknown.

Some of the most pressing questions in pediatrics revolved around MIS-C, a severe complication that, while rare, came with some familiar hallmarks — at least to those who knew what to look for.

"Rash, red eyes, red lips, diarrhea, common things we see in Kawasaki disease," says Dr. Jone. "Both are a hyperimmune response to trying to fight infection."

But there are established courses of treatment. As in Kawasaki disease, patients with MIS-C responded to intravenous immunoglobin, or IVIG, a blood product containing thousands of antibodies. Drs. Jone and Dominguez, who'd run a Children's Colorado Kawasaki Clinic together since 2011, started doing MIS-C rounds in spring of 2020, bringing together the infectious disease and cardiology teams to talk through each case every day at 9 a.m.

In many cases, they found, IVIG wasn't enough.

"We needed to adapt," says Dr. Jone.

CATCHING IT EARLY

By fall of 2020, it was clear that, when it came to MIS-C, time was of the essence.

"Patients with MIS-C have higher levels of systemic inflammation and more often decompensate," says Christina Osborne, MD, "which puts them at risk for requiring admission to intensive care."

"They can get myocarditis and very low blood pressure. The heart function goes down, the coronary arteries dilate," adds Dr. Jone. "That's not good. Some will get a kidney or liver disorder, their blood pressure gets so low. Some go into shock."

Dr. Osborne, a former fellow in pediatric infectious disease and current fellow in critical care with a research interest in coronaviruses, took on the task of creating a protocol for identifying MIS-C early, with input from infectious disease, hospital medicine, critical care, cardiology, rheumatology and emergency medicine. The protocol combined recommendations from the Centers for Disease Control

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IVIG vs dual therapy	IVIG alone	IVIG + infliximab
Required additional therapy	65%	31%
Developed left ventricle dysfunction	20%	4%
CRP fall at 24 hours	0%	-46%
CRP fall at 48 hours	-5%	-70%
Median length of stay	3.3 days	1.8 days

The Case for Two continued

and Prevention and the World Health Organization, among others, but went a step further.

Children's Colorado's protocol was the first in the nation to include routine echocardiography for every suspected case, crucial for catching cardiac inflammation.

INFLIXIMAB VERSUS STEROIDS

Starting in December of 2020, the team also added, for the sickest patients, another intravenous therapy to the IVIG regimen: infliximab, a lab-grown antibody that blocks the production of tumor necrosis factor alpha, or TNF.

"We had four initial criteria: If they were in shock, they needed pressure support, they had dilated coronary arteries and they had ventricular dysfunction, we'd give them infliximab," says Dr. Jone. "But when we looked back in February 2021 at the 72 patients we'd treated since December 2020, we realized only 20 had received IVIG alone. The rest had gotten dual therapy."

What's more, the 52 patients who'd received both therapies had better outcomes. They recovered faster. They required less additional therapy. In fact, a retrospective study the team published in Pediatrics showed patients who received dual therapy did better by every measure (1). The data was so strong the team has since implemented dual therapy into the protocol for every patient diagnosed with MIS-C.

It's a departure from convention, not only in aggressiveness but also in protocol. Most centers have employed steroids as a second course of treatment to IVIG; the New England Journal of Medicine published a study in the summer of 2021 showing an association between treatment with IVIG plus glutocorticoids and lower risk of cardiovascular dysfunction (2). But another study, published in the same issue, concluded there wasn't any difference (3).

Dr. Jone believes TNF blockers are a more intuitive treatment either way: The course of steroid treatment lasts six weeks. Infliximab requires just one intravenous dose. ●

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Decoding COVID Fracture Patterns

For children, the COVID-19 pandemic's early days included remote learning, extracurricular cancellations and new routines. Researchers have noted several impacts of these lifestyle shifts, but a recent Children's Hospital Colorado study has illuminated another outcome.

A team of researchers, including Children's Hospital Colorado orthopedic surgeons Gaia Georgopoulos, MD, and Nancy Hadley-Miller, MD, aimed to understand pediatric fracture patterns that emerged during Colorado's initial stay-at-home order, from March to late May 2020. Among the study's findings is new data showing that patients had 26% fewer fractures relative to the same period in 2019 and 23% fewer than in 2018. Additionally, nearly 30% of patients waited five or more days to seek treatment (1).

The authors noted a few possible reasons for the observed drop in fractures, including that no patients reported fractures as a result of snow sports. In fact, participation in all sports dropped dramatically during the early months of the pandemic.

Though fractures overall went down, one fracture type rose. The study's findings corroborate previous research conducted at Johns Hopkins University School of Medicine (2), noting an increase in nonaccidental trauma, or child abuse, during the early stages of the pandemic. To address this growing concern, the authors recommended seeking new prevention strategies, such as frequent telehealth visits, increased provider and family education to build awareness around abuse, and helping families find new stress outlets.

Nonaccidental trauma might help explain another of the study's findings: Patients with fractures were significantly younger than in past years. But while the average patient age went down, the age of patients with high-energy fractures went up, likely due to increased homebound recreational activities such as skateboarding, jumping on a trampoline, scootering and biking.

As the pandemic continues to impact children's lives, the study's authors recommend better patient and parent education, heightened preparedness for high-energy fractures, continued encouragement to seek care in a timely manner, and an eye toward possible child abuse. ●

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What the Team Says Is Broken

Q: Could a systematic team effort drive down cardiac arrest rates in the CICU?

In 2017, a group of investigators in the Pediatric Cardiac Critical Care Consortium, or PC4, looked at retrospective cardiac arrest data from more than 15,000 cardiac intensive care unit encounters. Their findings on outcomes were startling: The survival rate for patients who did not have a cardiac arrest in the CICU was about 98%. For patients who did have a cardiac arrest in the CICU, that number dropped to 53.2% (1). Pediatric cardiologist Carly Scahill, DO, MSCR, and nurse practitioner Kimberly DiMaria, CPNP-AC, took notice.

"It made us aware of how important cardiac arrest prevention is, not just for morbidity, but for survival," Dr. Scahill says. "It also made us dig into our own data to see where we were."

Knowing where they stood felt particularly important for Dr. Scahill, DiMaria and the team at Children's Hospital Colorado's Cardiac Intensive Care Unit. They, too, were members of PC4, a national collaborative of centers dedicated to clinical data-gathering and continuous improvement. But the first look was a painful one.

At the time of the paper's publication in Pediatric Critical Care Medicine, the national average of cardiac arrests within CICUs was 4.8 per 1,000 patient days. Children's Colorado's average was closer to 5.5, and it was climbing.

"We knew we needed to figure out why," Dr. Scahill says.

LINKING UP EFFORTS

At the time, the team already had several measures in place around cardiac arrest. They had a strong simulation program and a strong nurse education team, and they'd already begun implementing PC4's cardiac arrest bundle.

"There were pockets of work around how to respond to these events but not actually how to reduce the rate," says DiMaria. "The data was a call to action."

Dr. Scahill and DiMaria brought together a group of a dozen team members to figure out a plan: the Cardiac Arrest Reduction and Excellence (CARE) program, aimed at both improving resuscitation response and minimizing the incidence of cardiac arrest. That effort has since grown to nearly 40 team members spanning the CICU and the cardiac step-down unit.

The process starts with debriefing every event and issue with the entire CARE team, which includes representatives from every ICU discipline, from pharmacists to fellows to respiratory therapists. Together, they figure out what could have gone better and then come up with education programs, simulations and process changes to make it go better next time.

"And we send out a dissemination flyer afterward," says Dr. Scahill, "which lets every member learn the lessons that came out of the debrief, even if they weren't involved in the code."

> **"We've taken all these different ideas and made a comprehensive, integrated program that's designed for the needs of our unit."**
>
> KIMBERLY DIMARIA, CPNP-AC

The six arms of CARE

Dr. Scahill, DiMaria and the team designed the CARE program with six basic pillars that strengthen and reinforce one another:

1. A three-tiered in-situ simulation program to practice high-risk, low-frequency emergency skills and reinforce team dynamics
2. Resuscitation-focused educational forums to improve recognition of early signs and increase awareness of best practices
3. A comprehensive cardiac arrest prevention bundle
4. A formal code debriefing process
5. Dissemination of code-related updates to team members in the form of flyers, a lecture series and bedside visits
6. A resiliency program to increase work satisfaction and belonging and decrease burnout

CARE IN ACTION

In 2019, a code went south when CICU team members couldn't locate an essential piece of emergency equipment: an intraosseous access device, most often used by emergency medical clinicians and field medics when intravenous access isn't possible. The device had recently been moved, but the debrief also revealed that many team members not only didn't know where it was, but they also weren't comfortable using it.

In response, the team created education programs. They got a simulation going. They set up skills days and built opportunities for hands-on experience. Nurses rolled through the unit and did refreshers. They found a new, more prominent location for the device — a big yellow box — and told everyone where it was in the dissemination flyer.

"Within weeks, a team needed to place the same access, and they could locate the device and place it, and the patient was resuscitated," says DiMaria. "That's both lifesaving for patients and empowering to the team, and it reinforces the importance of debriefing events and fixing issues as they come up."

THE POWER OF THE FIX

Since getting off the ground during the height of the COVID-19 pandemic last year, the CARE program has posted impressive results. The team has started a quarterly lecture series that breaks down data from each cardiac arrest event and illustrates takeaways. They've created a CARE coaching role and recruited a handful of team members into it. And they've put together several new simulations and trainings.

"The interventions themselves are not necessarily novel," says DiMaria. "It's that we've taken all these different ideas and made a comprehensive, integrated program that's designed for the needs of our unit."

And it's worked. Sixteen months out from implementation, Children's Colorado's CICU has reduced its rate to 4.16 per 1,000 patient days, a reduction of 25%. The rates and averages, as assembled by PC4, fluctuate from day to day, but at times Children's Colorado's rate has been the lowest in the nation.

"Never underestimate the power of fixing what the team says is broken," says DiMaria. "That's our motto."

1. Alten JA, Klugman D, Raymond TT, Cooper DS, Donohue JE, Zhang W, Pasquali SK, Gaies MG. Epidemiology and Outcomes of Cardiac Arrest in Pediatric Cardiac ICUs. Pediatr Crit Care Med. 2017 Oct;18(10):935-943

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Associate Fellowship Director, Pediatric Cardiology
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KIMBERLY DIMARIA, CPNP-AC
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Children's Hospital Colorado
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Master Sequence

Whole-exome sequencing is faster and less expensive than it used to be, but it's by no means easy to deploy. Matching a genetic anomaly to a real-life phenotype requires high-powered expertise in both the clinic and the lab — a level of experience few centers have. On the Anschutz Medical Campus, Children's Hospital Colorado clinicians are collaborating with adult medicine colleagues and bench researchers at the neighboring University of Colorado School of Medicine to leverage these powerful tools for families facing an uncertain future with rare disease, from before birth throughout the lifespan.

MICHAEL ZARETSKY, MD

Co-Medical Director, Colorado Fetal Care Center, Children's Hospital Colorado

Associate professor, OB/GYN-Maternal Fetal Medicine, University of Colorado School of Medicine

KESTUTIS MICKE, MS, GCG

Genetic counselor, Children's Hospital Colorado

Instructor, OB/GYN-Maternal Fetal Medicine, University of Colorado School of Medicine

AUSTIN LARSON, MD

Clinical Genetics and Genomics, Medical Biochemical Genetics, Children's Hospital Colorado

Assistant professor, Pediatrics-Clinical Genetics and Metabolism, University of Colorado School of Medicine

Do the right thing

Q: Is prenatal whole-exome sequencing worth the cost?

By the time the Colorado Fetal Care Center at Children's Colorado evaluated them for some mysterious findings at their 20-week ultrasound, the couple had already had one child, a son with a troubling array of symptoms: low muscle tone, developmental and cognitive delay, hyper-extensible connective tissue. He'd never been diagnosed. It was probably a genetic syndrome, but insurance wasn't going to cover diagnostic whole-exome sequencing. That's not unusual.

"Even when really truly indicated, it's rarely covered," says Michael Zaretsky, MD, Co-Medical Director of the Colorado Fetal Care Center. "Which means a lot of families are not getting answers."

And not getting answers can have serious implications, not only on an infant or child's ability to receive appropriate treatment, but on quality of life for families facing the anguish of suspicious findings and an uncertain future.

That's why Dr. Zaretsky and a team of scientists and specialists from all over the Anschutz Medical Campus worked together to form one of the nation's first fetal precision medicine boards.

"We get these cases that have fetal anomalies or suspicious findings where more targeted tests like karyotype and microarray have not provided a diagnosis, and we meet weekly to review them," says Dr. Zaretsky. "We try to determine whether we missed anything or if there are other testing options, and if we ultimately decide to recommend whole-exome sequencing, we coordinate to get it done."

The panel includes maternal medicine specialists, neonatologists, ethicists, genetic counselors, medical geneticists and bench researchers including developmental biologists and craniofacial surgeons on an ad hoc basis. They've been doing it about a year, and more research groups are getting involved all the time.

"It does take a lot of manpower to get an accurate interpretation of the results and to create specific recommendations for care," says genetic counselor Kestutis Micke, MS, CGC. "Even with whole-exome sequencing, there are a lot of uncertain variants. The strength of the committee is having a lot of pairs of eyes."

It's not a magic bullet. Very few centers are doing routine diagnostic whole-exome sequencing, especially in the prenatal space, so the literature is limited, but Dr. Zaretsky estimates the diagnostic yield rate nationally at about 20%. At the Colorado Fetal Care Center, the board's rigorous algorithm and combined expertise has produced a yield of about 40%.

And it's produced some unexpected results. When the couple mentioned above became pregnant again and the 20-week ultrasound presented some unusual findings, the board ultimately decided to recommend sequencing — and in the process diagnosed their older son.

Even so, "There's not a disease-modifying treatment for his disorder," says Austin Larson, MD, the patient's geneticist at Children's Colorado. "Which, unfortunately, is often the case."

That's because, Dr. Larson observes, the impetus for fetal whole-exome sequencing is twofold: lack of a diagnosis and some visual indication that something is wrong — which indicates the disease is both rare and fairly progressed. In one case, he recalls, the diagnosis produced by whole-exome sequencing was sufficiently grave that the family knew their baby wouldn't live more than a few months.

"But they were able to bond with their baby understanding that his life would be limited, and they derived a lot of meaning from that," he says. "Everyone I've talked to, including the family, believed that was the best possible outcome, and it was because of prenatal whole-exome sequencing.

"The truth," he continues, "is that some of these conditions are never going to be treatable. They're the result of an early fetal process that didn't work, body systems that didn't develop, and

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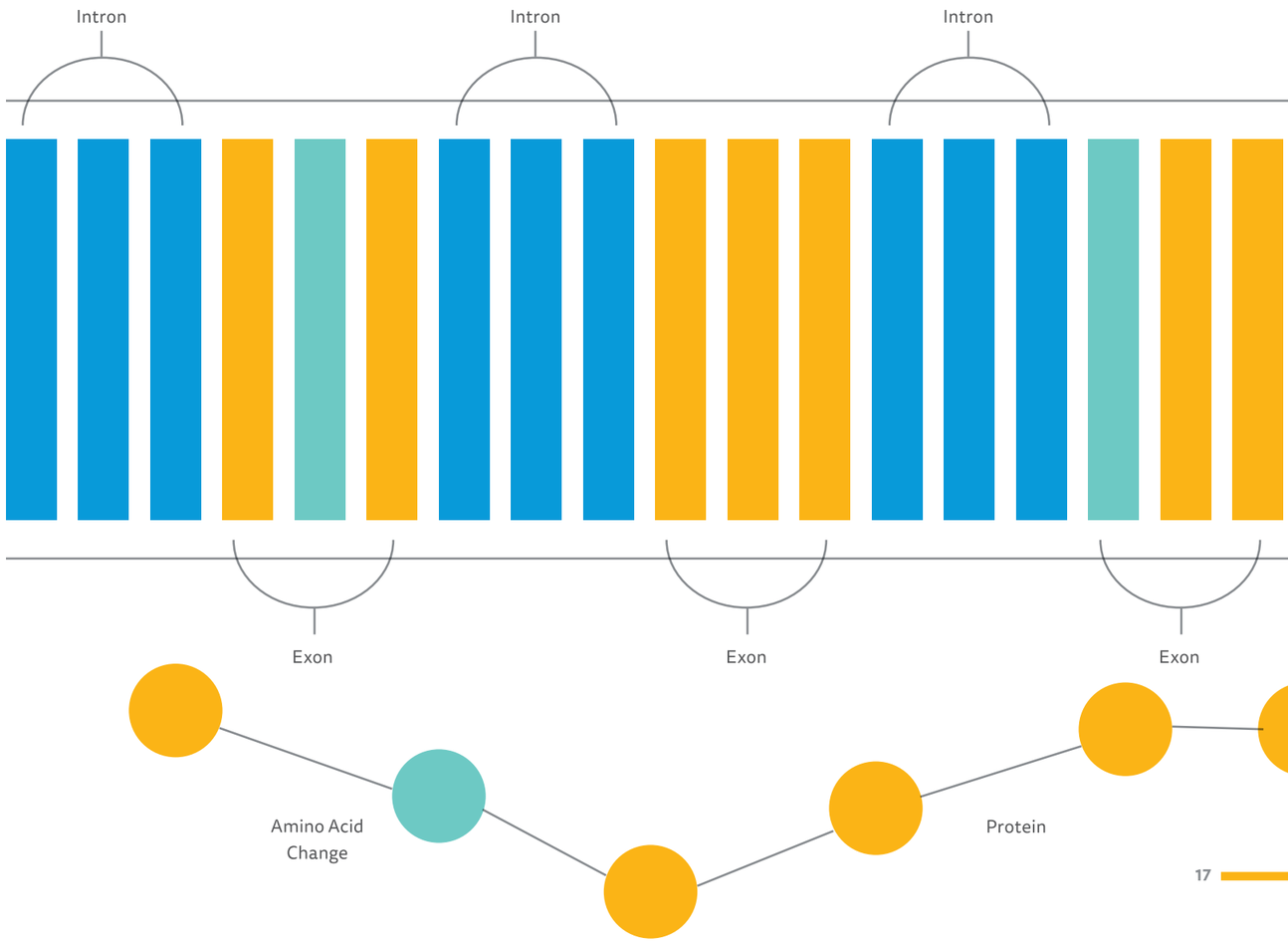


Master Sequence continued

there's no way to go back in time. We're doing it because it's the right thing to do. Sometimes the best outcome is just helping the family prepare and make decisions accordingly."

And although many more rare conditions are not treatable currently, some may be someday — but first they need to be identified.

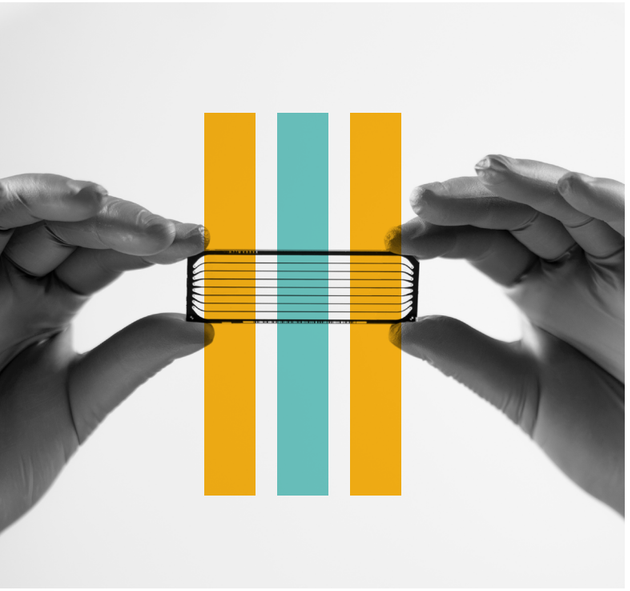
"There's never going to be a treatment," he says, "unless we diagnose and categorize and figure out the mechanisms that cause disease." ●

Pure potential

Q: Could whole exome sequencing lead to viable therapies even for novel variants?

An interesting thing happens when you suspend stem cells in three-dimensional media: They start to build organs.

"We can take primary tissues from a patient and isolate and expand various tissues of interest," says molecular and developmental biologist Sean McGrath, PhD, who manages the Organoid and Tissue Modeling Shared Resource at the University of Colorado School of Medicine. "Or if we can't get at the primary tissue, we can take a patient sample, reprogram the stem cells into pluripotent stem cells, and then differentiate them into various tissues of interest. We do a lot of gene editing as well, where we can make patient mutations or correct them."



Of course, the technology is still in its early stages, says Dr. McGrath. For now, his participation in the Colorado Fetal Care Center's precision medicine board is exploratory: If whole-exome sequencing identifies a new mutation, for example, his lab could potentially build an organoid with it to see how the mutation might affect development or cause disease.

SEAN MCGRATH, PHD

Instructor, Molecular and Developmental Biology
Manager, Organoid and Tissue Modeling Shared Resource, University of Colorado School of Medicine

Other teams might incorporate the same mutation into animal models to understand how the mutation correlates with phenotype. Still other teams might do drug modeling, testing the effect of different therapies on animal models or organoids, like the ones McGrath grows in the lab.

"You could screen the best options while that baby is still developing and have a good idea of how to treat when the baby is born," he says. "The holy grail would eventually be that you could identify a disease-causing mutation in utero, take a sample, grow it in vitro, correct the mutation and have a tissue you could use for regenerative therapeutics once the patient is born."

That's all decades down the road, he says. So far, his team has yet to identify a good candidate case for modeling in the lab.

"It's all a pipe dream at this point," he says. "But the potential is there." ●

Generating answers

Q: Could whole-exome sequencing link a mysterious phenotype to a genetic cause?

The patient was 9 months old when she was transferred to Children's Colorado with a severe respiratory infection and a complete inability to produce antibodies. Whatever it was, it ran in the family: The patient's father, paternal grandfather and aunt all shared faulty antibody production.

Over the coming months, the patient was diagnosed with a rare infection known as Pneumocystis jirovecii pneumonia, most often seen in immunocompromised patients – but not usually in patients solely with antibody production issues. Remarkably, the patient's paternal grandfather and aunt had contracted the same infection.

"Our interest is solving these mystery cases," says immunologist Cullen Dutmer, MD, part of a group of researchers on the Anschutz Medical Campus dedicated to identifying new disorders and describing novel processes of known ones. "We now have funds to look expansively through the genome to generate answers for these families."

In this family's case, Dr. Dutmer's first stabs at a sequencing panel didn't yield an answer. But he had a potential clue. A link between antibody production issues and susceptibility to Pneumocystis jirovecii pneumonia had recently been described in individuals harboring mutations in genes encoding Ikaros zinc finger transcription factors, key regulators of immune cell development.

Dr. Dutmer knew someone with a clinical interest in just that: Sergio Rosenzweig, MD, PhD, chief of Immunology Service at the National Institutes of Health's Clinical Center, who'd described a unique mutation in a gene called *IKZF1* (1).

"That mutation resulted in low production of antibodies and susceptibility to Pneumocystis jirovecii pneumonia, so this family's clinical phenotype looked a lot like what he'd described," Dr. Dutmer says. "I reached out to Sergio to work on whole-exome sequencing together and see if we could identify some candidate genes."

"Turns out that was a good choice," he adds.

Through sequencing, Drs. Dutmer and Rosenzweig identified a mutation in a gene similar to *IKZF1*, in this case the gene *IKZF3*. In fact, Dr. Rosenzweig was already collaborating with a group in Japan, which had developed a murine model to assess the impact of mutations in the *IKZF3* gene.

"So we were able to use that model and cells from this family to prove this mutation disrupts the ability of the T and B cell to function properly," Dr. Dutmer says. "The B cells are there, but they can't produce antibodies."

They published the study in the Journal of Experimental Medicine in December 2021 (2).

For Dr. Dutmer's 9-month-old patient, now 2 years old, the diagnosis means a more informed course of treatment — including prophylactic treatment for Pneumocystis jirovecii pneumonia, which had previously been a life-threatening infection for her. Another possible option: bone marrow transplant, which could potentially be curative.

Of additional interest, for Dr. Dutmer, is the paternal aunt's history of chronic lymphocytic leukemia, or CLL, diagnosed at a relatively young age. Given that history and a known link between somatic *IKZF3* mutations and CLL, there's a good argument for increased vigilance against CLL in family members who have the mutation.

"As we start to find more patients who have this mutation, I think that's going to confirm this association," says Dr. Dutmer. "And I can guarantee you more patients will be found. We'll just have to see where they are." ●

1. Boutboul D, Kuehn HS, Van de Wyngaert Z, Niemela JE, Callebaut I, Stoddard J, Lenoir C, Barlogis V, Farnarier C, Vely F, Yoshida N, Kojima S, Kanegane H, Hoshino A, Hauck F, Lhermitte L, Asnafi V, Roehrs P, Chen S, Verbsky JW, Calvo KR, Husami A, Zhang K, Roberts J, Amrol D, Sleaseman J, Hsu AP, Holland SM, Marsh R, Fischer A, Fleisher TA, Picard C, Latour S, Rosenzweig SD. Dominant-negative IKZF1 mutations cause a T, B, and myeloid cell combined immunodeficiency. J Clin Invest. 2018 Jul 2;128(7):3071-3087.
2. Kuehn HS, Chang J, Yamashita M, Niemela JE, Zou C, Okuyama K, Harada J, Stoddard JL, Nunes-Santos CJ, Boast B, Baxter RM, Hsieh EWY, Garofalo M, Fleisher TA, Morio T, Taniuchi I, Dutmer CM, Rosenzweig SD. T and B cell abnormalities, pneumocystis pneumonia, and chronic lymphocytic leukemia associated with an AIOLOS defect in patients. J Exp Med. 2021 Dec 6;218(12):e20211118. doi: 10.1084/jem.20211118. Epub 2021 Oct 25. PMID: 34694366; PMCID: PMC8548914.

CULLEN DUTMER, MD

Medical Director, Clinical Immunology
Associate Program Director, Allergy & Immunology Fellowship
Co-Director, Severe Combined Immunodeficiency Newborn Screening Program
Children's Hospital Colorado

Assistant professor, Pediatrics-Allergy and Immunology, University of Colorado School of Medicine

Setting a New Standard

STACEY MARTINIANO, MD
Pediatric Pulmonology, Children's Hospital Colorado
Associate professor, Pediatrics-Pulmonary Medicine, University of Colorado School of Medicine

In late 2021, the Colorado Newborn Screening program implemented a new strategy aimed at better identifying infants with cystic fibrosis (CF). This work was undertaken in partnership with Children's Hospital Colorado, the Colorado Department of Public Health and Environment, and primary care physicians.

Since 1982, the Colorado Newborn Screening program has screened every newborn in Colorado and Wyoming for elevated immunoreactive trypsinogen (IRT) using a blood spot test within 24 to 48 hours of birth. Newborns secrete IRT, a pancreatic enzyme, at higher levels when under stress, and CF patients release even more.

A new study, conducted by Children's Colorado pediatric pulmonologist Stacey Martiniano, MD, found that the fixed IRT cutoff (60 ng/mL) the state had used to evaluate whether infants would need a second test and ultimately genetic screening was no longer sensitive enough to catch every baby with CF. As a result, from 2016 to 2020, the screening missed eight cases of CF. Though all these cases were ultimately identified, and these children received the care they needed, Dr. Martiniano says this new approach will ensure early detection for more children.

Changes in the population, season and even daily temperature can affect IRT levels. To accommodate these changes, the newborn screening program would benefit from a floating IRT cutoff, she says.

The study recommends using a floating cutoff, wherein each day, the team determines the IRT value that represents the 96th percentile and uses that as the cutoff. This, the study says, will allow more accurate and robust detection during a critical period. Left untreated even for just a few months, these patients can experience significant nutritional deficits with long-term impacts. Early detection allows doctors to replace critical enzymes, vitamins and salts that help infants stave off malnutrition.

Though Colorado is not the first state to implement this approach, Dr. Martiniano hopes the study's clear data might push others to adjust their own approaches. This is especially true for states that have a decentralized approach to screening. Where other states might have multiple CF care centers, Colorado has just one, allowing Dr. Martiniano and her team access to a wide and complete data set.

"We're lucky that we are able to have this partnership, get this data and make these changes," Dr. Martiniano says. "We are one of the few places that could have pulled these data and put this forward to help advance the field." ●

1. Martiniano, Stacey L et al. "Improving outcomes for Colorado's IRT-IRT-DNA cystic fibrosis newborn screening algorithm by implementing floating cutoffs." Molecular genetics and metabolism vol. 134,1-2 (2021): 65-67.

Building Basics

Q: Can implementation science cure pediatric cancer on a global scale?

Worldwide, 1,000 children are diagnosed with cancer every day, more than 80% of them in low- and middle-income countries. Even so, while children and families in high-income countries can expect a cure rate of better than 80%, for most children around the globe, the rate is more like 15 to 45%. Working with St. Jude Global Medicine and the World Health Organization, pediatric oncologist Sandra Luna-Fineman is part of an international team leading the effort to close that gap.

Say a 4-year-old in the United States is diagnosed with acute lymphoblastic leukemia. From diagnosis on, that child has access to an enormous array of technologies and treatments, from genetic testing to bone marrow transplant to genetically engineered cell products.

The picture looks a lot different in, say, Central America. That same 4-year-old's family may not have easy access to medical care, so the cancer is likely to be advanced by the time it's diagnosed. It may be hard to secure access to genetic testing or chemotherapy, and if the child relapses, there's no bone marrow transplant. The child is also more likely to be malnourished, carrying a higher risk of infection.

"Many childhood cancers are very curable," says Dr. Luna-Fineman. "But you need to build the infrastructure to do it."

And it's easier said than done.

FROM THE GROUND UP

Dr. Luna-Fineman saw the need for infrastructure firsthand as a medical student in Guatemala, where she was raised. She saw it again later, after completing pediatrics and oncology fellowships at New York University and Stanford, when she returned there in collaboration with St. Jude Children's Research Hospital to help establish that country's Pediatric Oncology National Unit, or UNOP, the first of its kind. There was a need for oncology, sure. But to get there you needed buy-in from the ground up.

"You need institutional funding. You need to teach oncologists and nurses how to do this work in their environment. That's implementation science," she says. "We realized then that, without the participation of governments, nothing was going to happen."

In 2018, the World Health Organization kicked off the Global Initiative for Childhood Cancer. Central to that effort was a framework developed in collaboration with St. Jude and the International Society of Pediatric Oncology, Dr. Luna-Fineman and a team of pediatric oncologists, epidemiologists and public health specialists from across the globe. It's known as Cure*ALL*: Centers of excellence, Universal insurance coverage, Regimens of

Continued on the following page

Building Basics continued

treatment and supportive care and Evaluation and monitoring of outcomes, supported by Advocacy, Leveraged financing and Linked governance.

The foundation of that effort is a technical package written by Dr. Luna-Fineman, André Ilbawi, MD, and Roberta Ortiz, MD, MPH, of the WHO's Cancer team (1). The package lays out for policymakers, nongovernmental organizations and anyone else who might contribute every component needed to diagnose, treat, support the child and family and ultimately cure the six most common childhood cancers: acute lymphoblastic leukemia, Burkitt lymphoma, Hodgkin lymphoma, retinoblastoma, Wilms tumor and low-grade glioma (2).

BUILDING THE FRAMEWORK

The technical package offers tools for governments to assess where they are and what they need, as well as tools to estimate how much it will cost.

"Now we're working on policy briefs that tell you what you need for each individual cancer," says Dr. Luna Fineman. "Treatment, instruments, therapies — surgery, chemotherapy, radiation. Also personnel, supplies, outcomes and overall results, and clinical and epidemiological monitoring. I'm in charge of retinoblastoma, Hodgkin lymphoma and acute lymphoblastic leukemia."

The goal is ambitious — a 60% global cure rate in 10 years — but the effort looks promising. So far, 23 governments have committed to strengthening their pediatric cancer programs using the Cure*ALL* framework, and more than 110 partner organizations are involved.

And there's a lot of reason to believe it'll pay off. In Guatemala today, in large part thanks to Dr. Luna-Fineman's work establishing UNOP, the cure rate for low-risk ALL approaches 68%. ●

1. Cure*ALL* Framework: WHO Global Initiative for Childhood Cancer. Increasing access, advancing quality, saving lives. Geneva: World Health Organization; 2021.
2. Atun R, Bhakta N, Denburg AE, Fraizer AL, et al. Sustainable care for Children with cancer: a Lancet Oncology Commission. Lancet Oncol. 2020 21(4):e185-e224.

SANDRA LUNA-FINEMAN, MD

Pediatric hematologist-oncologist, Children's Hospital Colorado

Associate professor, Pediatric Hematology-Oncology, University of Colorado School of Medicine

Member, University of Colorado Anschutz Center for Global Health

Consultant, St Jude Children's Research Hospital

A(:) List

Recent awards and accolades

Endocrinology

JDRF, a nonprofit that funds type 1 diabetes research, recently awarded Children's Hospital Colorado's Kristen Nadeau, MD, MS, its 2021 Mary Tyler Moore and S. Robert Levine, MD, Excellence in Clinical Research award. With this award, JDRF recognizes Dr. Nadeau's innovative research in the field of pediatric endocrinology and insulin resistance in type 1 diabetes, focused on defining the mechanisms behind insulin resistance in youths with diabetes. Dr. Nadeau has received a $416,000, two-year grant for a project conducted alongside pediatric endocrinologist Melanie Cree Green, MD, PhD, to measure insulin sensitivity in adipose, liver and muscle tissue using an oral glucose tolerance test.

JDRF also highlighted the work of Petter Bjornstad, MD, with its 2021 Dr. Robert Goldstein award, which recognizes notable early career type 1 diabetes researchers who show great promise. Dr. Bjornstad specializes in integrating state-of-the-art functional imaging techniques with gold-standard renal physiology methods and kidney biopsies to examine perturbed energetics in early diabetic kidney disease. A $535,000, three-year JDRF grant will help him and his team determine the intrarenal molecular effects of SGLT2 inhibition in young adults with type 1 diabetes.

KRISTEN NADEAU, MD, MS

Pediatric endocrinologist, Children's Hospital Colorado

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

Research Director, CU Anschutz Medical Campus Pediatric Endocrinology and Bariatric Surgery

Co-Chair, NIH Diabetes Research Center Clinical Research Core

PETTER BJORNSTAD, MD

Pediatric endocrinologist, Children's Hospital Colorado

Assistant professor, Pediatrics-Endocrinology and Medicine-Nephrology, University of Colorado School of Medicine

Co-Chair, Renal Working Group of TODAY

No. 1 in physician satisfaction

Children's Hospital Colorado ranked No. 1 and was one of only four medical centers to receive 100% positive reviews in a recent physician satisfaction survey administered by Doximity, a professional medical network that collected more than 11,000 verified physician reviews. According to Doximity, the surveys revealed a few core areas that strongly impact a physician's opinion of a hospital, including support staff, administration, facility quality and work-life balance. One anonymous Children's Colorado reviewer wrote, "I have never seen a place like this in terms of the delivery of consistent and cohesive patient- and family-centered care driven by quality, safety, transparency, advocacy and stewardship. These principles are ingrained in everybody's culture and state of mind." This isn't the only excellent rating Children's Colorado has seen lately. The University of Colorado School of Medicine's pediatric residency program, whose residents serve at Children's Colorado, recently was ranked No. 6 in the nation by reputation, as well.

Pediatric Orthopedic Surgery

The Pediatric Orthopaedic Society of North America, or POSNA, recently appointed Sumeet Garg, MD, to its board as an at-large member. POSNA is the largest professional society of pediatric orthopedic surgeons in the country, and Dr. Garg is excited to serve as a voting member of the board. Through this role he will have the opportunity to shape the organization's direction and help it achieve its mission of advancing pediatric orthopedics through education, research and quality care. "My specific goals are to be a responsible steward for our society, ensuring we remain the best source of education, research and advocacy for our profession and our patients," Dr. Garg says. "One specific goal I have is to make it easier for new members to get involved with the society's work by active participation in committees."

SUMEET GARG, MD

Orthopedic Surgery, Children's Hospital Colorado

Associate professor, Orthopedics, Pediatric Orthopedics, University of Colorado School of Medicine

Excellence in rare disease research

The Anschutz Medical Campus earned a designation as a National Organization for Rare Disorders (NORD) Rare Disease Center of Excellence. It is just one of 31 organizations with this designation in the U.S., and the only one in Colorado.

This new distinction comes thanks to Children's Hospital Colorado's status as one of the few hospitals serving as a true medical "supercenter" providing care for a huge variety of rare (and common) disorders, including treating novel genetic disorders with allele-specific oligonucleotide therapies. Children's Colorado is also rolling out an exome-based DNA sequencing platform, is involved in numerous gene and molecular therapy trials, and houses multidisciplinary clinics designed for children with rare diseases.

Work like this is happening across Anschutz Medical Campus, which, in addition to Children's Colorado, includes UCHealth and the CU School of Medicine. By working together on one cohesive campus, rare disease specialists can care for patients at each life stage.

That is what makes this designation so special. "Recognition as a NORD Rare Disease Center of Excellence is a tribute to the high-quality care we provide across the nation," says Shawn E. McCandless, MD, Chair of Children's Colorado's Department of Genetics and Metabolism. "We are proud for our patients to see this new recognition of the world-class healthcare available here."

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School of Medicine
UNIVERSITY OF COLORADO
ANSCHUTZ MEDICAL CAMPUS

Connected through care

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

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BEST CHILDREN'S HOSPITALS U.S.News & WORLD REPORT HONOR ROLL 2021-22

Ranked among the best of the best

This year, for the second year in a row, we're the #6 pediatric hospital in the nation, and our Gastroenterology & GI Surgery program ranked #1. In fact, we've been ranked among the best of the best for years. That consistency sets us apart, but it's our unwavering commitment to kids that makes the difference. Always.

We rank among the best in all 10 recognized specialties:

Cancer: #9

Cardiology and Heart Surgery: #6

Diabetes and Endocrinology: #4

Gastroenterology and GI Surgery: #1

Neonatology: #24

Nephrology: #16

Neurology and Neurosurgery: #10

Orthopedics: #15

Pulmonology: #5

Urology: #6