2021

RESEARCH DISCOVERIES

Cincinnati Children's™
Research Foundation


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Illustration by Reed DeWinter

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Dear Colleagues, It is with deep gratitude and pride that I present to you our fiscal 2021 Research Annual Report. As these pages show, the distinguished faculty of the Cincinnati Children's Research Foundation found many ways to drive discovery and innovation despite the disruptions of the COVID-19 pandemic. It was truly a remarkable year.

Investigators here attracted nearly $271.3 million in sponsored program awards—a new record! Meanwhile, even though we needed to adjust our work patterns to stay safe during the pandemic, our research mission continued as staff and faculty successfully protected critical materials and maintained vital shared facilities to allow work to resume promptly upon returning to our labs.

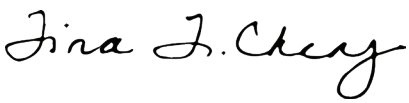
The research achievements detailed here span a wide range of disciplines, technologies and approaches that demonstrate significant impact upon the entire spectrum of discovery: breakthrough basic science, immediately translatable clinical learnings, important population health advances, and new strides toward achieving social justice by reducing inequities in child health.

Thanks to our well-established expertise in vaccine research, Cincinnati Children's played a central role in evaluating the safety and efficacy of the widely distributed Pfizer-BioNTech vaccine and important roles in studying other COVID vaccines. While COVID-19 has claimed far too many lives, many more people have survived the pandemic thanks to those who helped the nation—and the world—rapidly develop, adopt and distribute safe and effective vaccines.

The collaborative spirit of Cincinnati Children's shined above the pandemic discord as our colleagues shared COVID-related learnings at every level. Experts here analyzed the mechanisms of the virus' effect on organ systems, delved into the complexities of protecting children with rare and chronic diseases, advised local schools and state health officials during fast-changing times, and focused on ways to manage immense mental health concerns stemming from the crisis.

Now, as we begin to put the pandemic behind us, we are building a fresh strategic plan for the Research Foundation. A steering committee has been working on details for the past several months. The outcome of that work has begun to be shared and will be further communicated in the weeks and months ahead.

I thank everyone who has devoted so much work to respond to COVID-19, to continue our research mission, and to plan for the future. I look forward to an even more productive year ahead.



Tina L. Cheng, MD, MPH
BK Rachford Professor
Chair, Department of Pediatrics, University of Cincinnati
Director, Cincinnati Children's Research Foundation
Chief Medical Officer, Cincinnati Children's Hospital Medical Center

We will learn many lessons from the COVID-19 pandemic in the months and years to come, but one point has been made crystal clear: children and families thrive when they are supported by the expertise, compassion, and leadership of an outstanding pediatric medical and research center. Few communities anywhere in the world have been as fortunate as ours to have the faculty and staff of Cincinnati Children's at their side.

Highlights of extraordinary discoveries from Fiscal Year 2021 are featured in this report. These breakthroughs represent discoveries from more than 50 research divisions that responded with passion to address COVID-19 concerns while publishing more than 2,000 research articles on the many other diseases and conditions that never stopped affecting children. We are grateful to our staff, families, donors and partners for making these achievements possible.

As we look to the future, we move forward in the light of a growing body of research demonstrating that many adult chronic conditions trace their roots to childhood. Thus, we understand and will build upon the concept that the fundamental basic science and early childhood research conducted here can benefit the entire life course.

Fundamental basic science and early childhood research conducted here can benefit the entire life course.

Our mission includes striving to eliminate the health inequities that were so baldly exposed by the COVID-19 pandemic. Now, our new Michael Fisher Center for Child Health Equity, founded in recognition of our former president and CEO's leadership in this area, will help ensure all of Cincinnati's kids can be the healthiest in the nation.

We each play a role in creating a better system. By eliminating disparities and ensuring that all children can flourish, we can improve outcomes for generations to come. As one of the world's leading pediatric academic care and research centers, we are uniquely positioned to set a bold course for the future of children. We look forward to sharing that journey, together.

Mark Jahnke
Chair, Board of Trustees

Nancy Krieger Eddy, PhD
Research Chair

Steve Davis, MD, MMM
President and CEO

The Year That Transformed

Ruxolitinib in treatment of severe coronavirus disease 2019 (COVID-19): A multicenter, single-blind, randomized controlled trial — *The Journal of Allergy and Clinical Immunology* Air pollution, racial disparities, and COVID-19 mortality — *The Journal of Allergy and Clinical Immunology* Eosinophil responses during COVID-19 infections and coronavirus vaccination — *The Journal of Allergy and Clinical Immunology* Finding ordinary magic in extraordinary times: child and adolescent resilience during the COVID-19 pandemic — *European Child & Adolescent Psychiatry* COVID-19 preparedness in Malawi: a national facility-based critical care assessment — *The Lancet Global Health* Laboratory abnormalities in children with mild and severe coronavirus disease 2019 (COVID-19): A pooled analysis and review — *Clinical Biochemistry* Addressing the Impact of the Coronavirus Disease 2019 (COVID-19) Pandemic on Hematopoietic Cell Transplantation: Learning Networks as a Means for Sharing Best Practices — *Biology of Blood & Marrow Transplantation* Clinical testing for COVID-19 — *The Journal of Allergy and Clinical Immunology* Elevated serum levels of S100A8/A9 and HMGB1 at hospital admission are correlated with inferior clinical outcomes in COVID-19 patients — *Cellular & Molecular Immunology* A mechanistic model and therapeutic interventions for COVID-19 involving a RAS-mediated bradykinin storm — *eLife* Clinical Best Practice Advice for Hepatology and Liver Transplant Providers During the COVID-19 Pandemic: AASLD Expert Panel Consensus Statement — *Hepatology* COVID-19: FAQs—Congenital Heart Surgery Recovery and Defining a "New Normal" — *World Journal for Pediatric and Congenital Heart Surgery* Collateral Damage: How COVID-19 Is Adversely Impacting Women Physicians — *Journal of Hospital Medicine* No body is expendable: Medical rationing and disability justice during the COVID-19 pandemic. — *American Psychologist* False negative RT-PCR or false positive serological testing in SARS-CoV-2 diagnostics- Navigating between Scylla and Charybdis to prevent misclassification bias in COVID-19 clinical investigations — *Diagnosis* Shoring up the safety net for children in the COVID-19 pandemic — *Pediatric Research* Tackling COVID-19 infection through complement-targeted immunotherapy — *British Journal of Pharmacology* GM-CSF blockade with mavrilimumab in severe COVID-19 pneumonia and systemic hyperinflammation: a single-centre, prospective cohort study — *The Lancet Rheumatology* Can tocilizumab calm the cytokine storm of COVID-19? — *The Lancet Rheumatology* Hyperinflammation and derangement of renin-angiotensin-aldosterone system in COVID-19: A novel hypothesis for clinically suspected hypercoagulopathy and microvascular immunothrombosis — *Clinica Chimica Acta* COVID-19: Crisis management in congenital heart surgery — *Journal of Thoracic and Cardiovascular Surgery* COVID-19: Crisis Management in Congenital Heart Surgery — *The Annals of Thoracic Surgery* Virtual Cafes: An Innovative Way for Rapidly Disseminating Educational Best Practices and Building Community During COVID-19 — *Academic Pediatrics* Raising awareness of disabled lives and health care rationing during the COVID-19 pandemic. — Psychological trauma: theory, research, practice, and policy Novel Educational Responses to COVID-19: What is Here to Stay? — *Academic Pediatrics* Ventilator Triage Policies During the COVID-19 Pandemic at U.S. Hospitals Associated With Members of the Association of Bioethics Program Directors — *Annals of Internal Medicine* The need to balance basic and clinical research with the safety of the research environment and personnel in the time of COVID-19 in the United States — *Current Medical Research & Opinion* Commentary: Reflections on the COVID-19 Pandemic and Health Disparities in Pediatric Psychology — *Journal of Pediatric Psychology* Systems biological assessment of immunity to mild versus severe COVID-19 infection in humans — *Science* Phase I/II study of COVID-19 RNA vaccine BNT162b1 in adults — *Nature* Red Blood Cell Distribution Width (RDW) Predicts COVID-19 Severity: A Prospective, Observational Study from the Cincinnati SARS-CoV-2 Emergency Department Cohort — *Diagnostics* Early Impact of the COVID-19 Pandemic on Congenital Heart Surgery Programs Across the World: Assessment by a Global Multi-Societal Consortium — *World Journal for Pediatric and Congenital Heart Surgery* Association Between Statewide School Closure and COVID-19 Incidence and Mortality in the US — *JAMA: Journal of the American Medical Association* The Pandemics of Racism and COVID-19: Danger and Opportunity — *Pediatrics* Letter to the Editor - Circulating plasma levels of angiotensin II and aldosterone in patients with coronavirus disease 2019 (COVID-19): A preliminary report — *Progress in Cardiovascular Diseases* Effect of COVID-19 on Emergent Stroke Care — *Stroke* Lactate dehydrogenase levels predict coronavirus disease 2019 (COVID-19) severity and mortality: A pooled analysis — *American Journal of Emergency Medicine* COVID-19 and the Editorial Process: Reflections from The Journal of Pediatrics — *Journal of Pediatrics* COVID-19, Climate Change, and the American Thoracic Society. A Shared Responsibility — *Annals of the American Thoracic Society* Pediatric emergency department volumes and throughput during the COVID-19 pandemic — *American Journal of Emergency Medicine* Circulating Plasminogen Concentration at Admission in Patients with Coronavirus Disease 2019 (COVID-19) — *Seminars in Thrombosis & Hemostasis* Diagnosis and principles of management of gestational diabetes mellitus in the prevailing COVID-19 pandemic — *International Journal of Diabetes in Developing Countries* Management of children and adolescents having type 1 diabetes during COVID-19 pandemic in India: challenges and solutions — *International Journal of Diabetes in Developing Countries* Effect of the COVID-19 Pandemic on Pediatric Intestinal Failure Healthcare Delivery — *JPEN Journal of Parenteral & Enteral Nutrition* Warp Speed for COVID-19 Vaccines: Why are Children Stuck in Neutral? — Clinical Infectious Diseases The Impact of COVID-19 on Pediatric Adherence and Self-Management — *Journal of Pediatric Psychology* Validity of Data Collected from Randomized Behavioral Clinical Trials During the COVID-19 Pandemic — *Journal of Pediatric Psychology* Pediatric Endoscopy During the COVID-19 Pandemic: Addressing the Implications of Universal Preprocedural Testing for PPE Utilization — *Journal of Pediatric Gastroenterology & Nutrition* Anemia and COVID-19: A prospective perspective — *Journal of Medical Virology* Introductions to the Community: Early-Career Researchers in the Time of COVID-19 — *Cell Stem Cell* Multidisciplinary care of epidermolysis bullosa during the COVID-19 pandemic—Consensus: Recommendations by an international panel of experts — *Journal of the American Academy of Dermatology* American College of Rheumatology Clinical Guidance for Multisystem Inflammatory Syndrome in Children Associated With SARS–CoV-2 and Hyperinflammation in Pediatric COVID-19: Version 1 — *Arthritis & Rheumatology* Comorbidities, Cardiovascular Therapies, and COVID-19 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Care Policy — *Clinical Pediatrics* Longitudinal Multi-omics Analyses Identify Responses of Megakaryocytes, Erythroid Cells, and Plasmablasts as Hallmarks of Severe COVID-19 — *Immunity* COVID-19 pandemic: The African paradox — *Journal of Global Health* Remote Learning During COVID-19: Examining School Practices, Service Continuation, and Difficulties for Adolescents With and Without Attention-Deficit/Hyperactivity Disorder — *Journal of Adolescent Health* Defining the scourge of COVID-19 hyperinflammatory syndrome — *The Lancet Rheumatology* Real-World Issues and Potential Solutions in Hematopoietic Cell Transplantation during the COVID-19 Pandemic: Perspectives from the Worldwide Network for Blood and Marrow Transplantation and Center for International Blood and Marrow Transplant Research Health Services and International Studies Committee — *Biology of Blood & Marrow Transplantation* Airway emergency management in a pediatric hospital before and during the COVID-19 pandemic — *International Journal*

HOW SCIENCE SURVIVED, RESPONDED & THRIVED AT CINCINNATI CHILDREN'S

The first public glimpses of the global COVID-19 pandemic trace back to December 2019, when a cluster of people suffering fever and shortness of breath from an unknown pathogen emerged in Wuhan, China. By January 2020, the World Health Organization and the US Centers for Disease Control and Prevention were cranking up their responses as initial reports revealed that a novel coronavirus was on the loose.

Quickly, cases popped up in other countries. Then on Jan. 17, 2020, the first US case was reported involving a nursing home patient in Washington state. The virus spread like wildfire. By March, a national emergency had been declared. New York City closed its schools. Shutdowns started happening everywhere—including here at Cincinnati Children's.

As of July 1, 2020, the beginning of fiscal 2021, 127,681 Americans were dead from exposure to SARS-CoV-2. The worst pandemic since 1918 grimly steamrolled every rosy prediction that the situation would be akin to a bad flu season. By June 30, 2021, the end of fiscal 2021, the death toll had reached 604,656. By the end of 2021, more than more than 824,000 Americans had died.

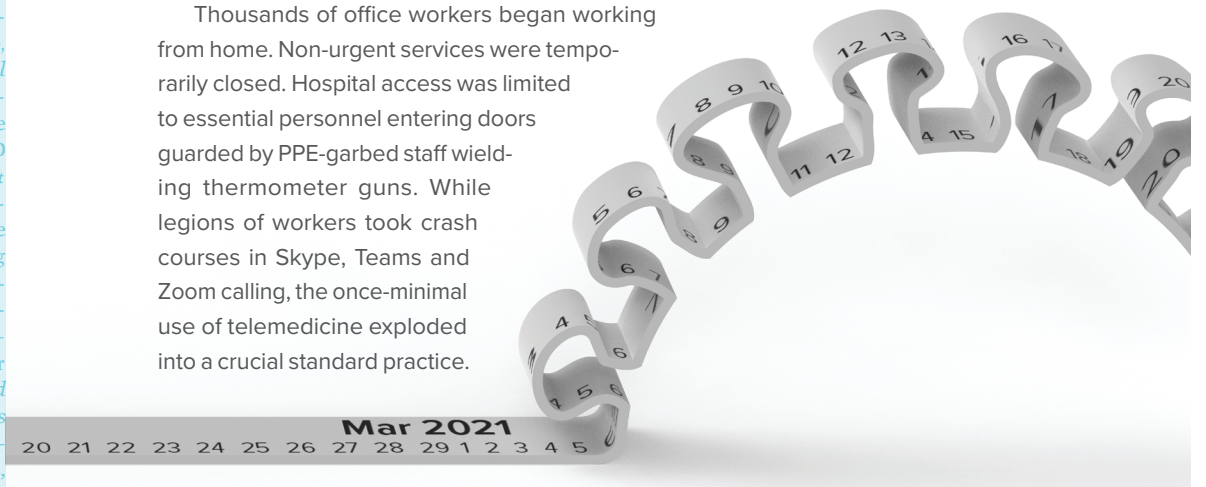
In between, every day was a COVID day and everything about care, research and work for more than 16,000 employees at Cincinnati Children's had been affected.

Thousands of office workers began working from home. Non-urgent services were temporarily closed. Hospital access was limited to essential personnel entering doors guarded by PPE-garbed staff wielding thermometer guns. While legions of workers took crash courses in Skype, Teams and Zoom calling, the once-minimal use of telemedicine exploded into a crucial standard practice.

Amid the swirling events, leadership teams at the Cincinnati Children's Research Foundation bore down on the details of how to safely shutter massive chunks of a research enterprise that includes thousands of active projects funded by more than $271 million in grant awards per year. While some labs could continue some of their tasks from home, many experiments could not be easily or quickly paused. Some work could not be stopped at all without wasting millions of dollars and uncounted hours of work—which required staff to learn new ways to function.

The inside story of how Cincinnati Children's managed to keep its research programs going amid the pandemic appears on page 22. As this 150-page report illustrates, an enormous amount of discovery occurred across many fields, despite the disruptions brought by COVID.

Yet even as scientists scrambled to protect their teams from exposure risks, many also found themselves suddenly switching gears. Their expertise in fields including vaccine research, infectious diseases, immunology, cardiology, mental health, hospital medicine, critical care, human genetics, bioinformatics, and improving systems of care required putting down day-to-day science to join the battle against COVID



Cincinnati Children's Plays Central Role in COVID-19 Vaccine Clinical Trials

Vaccine research has been an important line of discovery at Cincinnati Children's since the days of Dr. Albert Sabin.

Dreading the prospect of their children spending weeks in the iron lung or suffering permanent paralysis, parents lined their kids up with urgency to receive polio vaccines. Yet the dangers posed by polio pale in comparison to the COVID-19 pandemic.

The worst polio outbreak in US history occurred in 1952, when a total of 57,628 cases were reported, including 3,145 deaths and 21,269 people struck by varying levels of paralysis. In January 2021 alone, COVID death tolls in America exceeded 3,000 in a single day more than a dozen times, and on just one day of that month new cases exceeded 300,000.

Once again, as the COVID-19 pandemic surged, scientists at Cincinnati Children's stepped up to the challenge. As a furious global race to develop vaccines produced more than 120 possible candidates, Cincinnati Children's helped study vaccines made by Moderna, Johnson & Johnson and AztraZeneca. It also became one of only four centers to begin evaluating an mRNA vaccine developed by Pfizer and BioNTech, which ultimately became one of the three vaccines approved for use in the United States.

The media blitz that began May 5, 2020—the day the first phase I/II clinical trial of the Pfizer vaccine was announced—continued all the way through 2021. While serving as a leading investigator for one of the most intense clinical trials ever conducted, Robert Frenck, MD, director of the Gamble Vaccine Research Center, also gave hundreds of interviews that were shared worldwide in thousands of news articles translated into numerous languages.

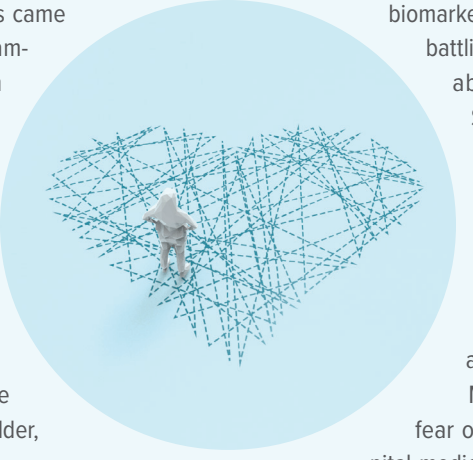
He appeared on CNN, ABC, NBC, CBS, "Good Morning America", and "The Today Show." He spoke with reporters from the *New York Times*, the *Wall Street Journal*,

Studying the Heart in the Storm

EARLY IN THE PANDEMIC, CLINICIANS TREATING THE MOST SERIOUSLY AFFECTED CHILDREN BEGAN NOTICING HEART INFLAMMATION THAT RESEMBLED THE CYTOKINE "STORMS" ASSOCIATED WITH OTHER CONDITIONS LIKE KAWASAKI DISEASE AND MACROPHAGE ACTIVATION SYNDROME (MAS).

Kawasaki disease is the leading cause of acquired heart disease in children. If not treated promptly, it can cause coronary artery aneurysms, mitral valve leakage and pericardial effusion. MAS is a rare and more systemic complication of Kawasaki disease that's more commonly seen among children with systemic juvenile idiopathic arthritis (sJIA).

COVID-19-associated cases came to be labeled multisystem inflammatory syndrome in children (MIS-C). These children presented with persistent fever, abdominal pain, vomiting, diarrhea, skin rashes and lesions, and in severe cases, with hypotension and shock. In addition to heart complications, MIS-C can cause inflammation in the liver, spleen, kidneys, gallbladder, pancreas and intestine.



Enter Grant Schulert, MD, PhD, an expert in sJIA and MAS at Cincinnati Children's. He and colleagues shifted gears rapidly to respond to the emerging threat. Ultimately, they discovered that tracking the cytokine CXCL9 serves as a useful biomarker to distinguish MIS-C from Kawasaki disease (see page 136 Rheumatology).

"This study was incredibly difficult to do under the conditions of the early pandemic when clinical research was largely shut down," Schulert says. "We were very lucky that we had launched this study for patients with Kawasaki disease prior to 2020, so were able to adapt our already approved protocol to study these MIS-C patients. Even so, completing the work wouldn't have been possible without the efforts of our Rheumatology clinical fellows who diagnosed the first MIS-C patients at Cincinnati Children's and ensured we collected information needed to do this study."

Even as the team pursued this important biomarker, experts found themselves battling waves of misinformation about MIS-C. Repeatedly, Schulert, Hector Wong, MD, Patty Manning, MD, and others were called upon to clarify that the MIS-C risks from COVID-19 itself far outweighed the risk of developing MIS-C as a reaction to the vaccine.

Meanwhile, the widespread fear of MIS-C left experts in hospital medicine wrestling with the risks of over-testing children to avoid missing the hard-to-diagnose condition. Matthew Molloy, MD, MPH, Karen Jerardi, MD, MEd, and Trisha Marshall, MD, MSc later described in *Hospital Pediatrics* how Cincinnati Children's shifted to a tiered diagnostic approach to reduce over-testing.

Still to be determined: the long-term impact of inflammatory damage caused to infected children. "With increasing numbers of positive children associated with the arrival of the Omicron variant, comes the risk of more children developing complications from COVID, MIS-C and long COVID issues," Manning says.

Atlantic, *Time*, *Newsweek*, *STAT*, Medscape, Kaiser Health News, and many more. He appeared numerous times on every local news outlet, answering detailed questions about the science behind the vaccines, debunking myths, discussing which activities were safer than others, and constantly repeating the message that no corners were cut despite the speed of the work.

"If you look at a more typical vaccine trial, you'd be sending things in batches," Frenck told CNN. "For this study, they are saying they need information back in 24 hours. We are cutting out the lag time. Because this is an emergency, we are getting people to work as hard as we can."

In addition to directing the Gamble Center, Frenck is the principal investigator of the NIH-funded Vaccine and Treatment Evaluation Unit (VTEU) at Cincinnati Children's, one of 10 such units nationwide. For years, the VTEU has evaluated annual flu vaccines and has conducted research on a wide range of vaccine candidates for Ebola, MERS, rotavirus, and many other viruses.

As the leader of the pediatric arm, he co-authored Pfizer's key clinical trial findings, which were published Dec. 10, 2020, in *The New England Journal of Medicine*. That study became the fourth most-shared paper of more than 2 million studies published in 2020, according to Altmetric. The paper was directly cited in more than 2,200 news stories from more than 750 news outlets. It was shared by more than 27,000 Twitter users with a combined 13.6 million followers. It attracted more than 6,200 readers on Mendeley and has more than 3,400 citations on Dimensions.

The overall Altmetric score for the paper—25223 as of Oct. 11—set an all-time record for the most-shared paper co-authored by a Cincinnati Children's faculty member. Its score will continue to climb as more people share or cite the paper in years to come.

VACCINE WORK EXTENDED WELL BEYOND PFIZER'S VACCINE

Paul Spearman, MD, director, Division of Infectious Diseases at Cincinnati Children's, also played a significant national role in COVID-19 vaccine work. He recently completed a four-year term as a member of the Vaccines and Related Biological Products Advisory Committee (VRBPAC), which reviews and evaluates vaccine research and makes recommendations to the FDA.

In October 2020, this committee refused to rush its recommendations despite pressure from the Trump administration to approve emergency use of Pfizer's vaccine before the November elections. The FDA action occurred in December.

Above: Robert Frenck, MD, chats with Ian Hummel. Right: Lab team manages COVID-19 clinical trial documentation.

Because of Cincinnati Children's role as a vaccine trial site, Spearman had to recuse himself from some proceedings. Nevertheless, he served as an important media source for explaining how the process works. Meanwhile, Spearman served as principal investigator for a portion of the clinical trials organized to evaluate Moderna's COVID vaccine. Other testing for that vaccine had been overseen locally at the University of Cincinnati.

And now Spearman leads a study of Georgia-based CyanVac's CVXGA1 vaccine, a nasal spray vaccine candidate for preventing COVID.

FAMILIES STEP UP AMID CONTROVERSY

In August 2020, as political disagreements swirled around vaccination and masking issues, Cincinnati Children's began a phase III trial of the Pfizer-BioNTech vaccine, including hundreds of adolescents. Oak Hills High School student Katelyn Evans became the first adolescent enrolled in the clinical trial.

"It's just really cool knowing that I got to be part of something," Katelyn told "Good Morning America." Meanwhile Melanie Mitchell, 16, a Walnut Hills High School student and daughter of Cincinnati Children's Monica Mitchell, PhD, told her story to U.S. Sens. Rob Portman and Sherrod Brown in a virtual congressional briefing. By participating, Melanie said she was helping move the vaccine forward for all kids and for women of color, but she was also helping her own school friends understand that the COVID-19 vaccine is safe.

> "Someone has to go first,"
> — Eli Dropic

"Most of my friends were pretty supportive. I did have a few comments ... of people that didn't trust the vaccine," Melanie told the *Cincinnati Enquirer*. In Florence, Ky., pediatrician Amanda Dropic, MD, enrolled four children in COVID trials as they opened to younger age groups, including 16-year-old Ben, 14-year-old Ty, 10-year-old Eli, and 8-year-old Lila.

"Someone has to go first," Eli Dropic told WLWT in April 2021. "I was very nervous. I thought there are so many things that could go wrong, but there are a ton more that can go right."

Some of the families participating in the trial found themselves targeted by anti-vaccine critics on social media. But they stood up for science. Ultimately, more than 400 children, ages 6 months to 17 years old took part.

Dr. Frenck works with children during the COVID-19 vaccine trials.

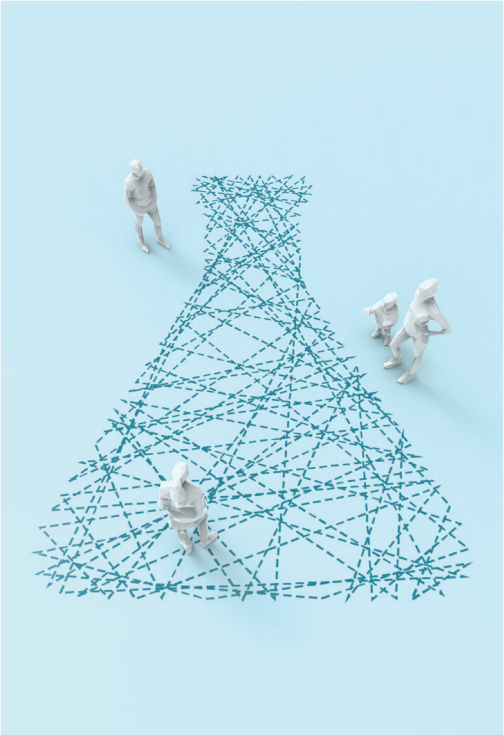
ANALYSIS

Seeking Trust Through Science

ALMOST AS SOON AS PEOPLE STARTED GETTING SICK, SCIENTISTS TRACKING THE COVID-19 EPIDEMIC COULD SEE THAT LESS-ADVANTAGED POPULATIONS WERE SUFFERING THE HARSHEST CONSEQUENCES.

When widescale shutdowns occurred early on, lower-income workers were among the first to lose jobs, which disproportionately affected people of color. Then, when "essential workers" were called upon to work in risky conditions, disadvantaged families paid the highest price as employees brought infections home. Later, as vaccines arrived, reaching out to disadvantaged communities became a live-action lesson in how to address widespread distrust, language barriers and more.

From the beginning, Cincinnati Children's leaders, clinicians and scientists strived to bridge trust and communication gaps that limited participation in clinical trials, complicated access to care and slowed distribution of vaccine. And many experts resolved to study the situation as it unfolded.



In July 2020, challenge grant funds from the Center for Clinical and Translational Science and Training (CCTST) launched several projects:

- Katherine Bowers, PhD, and colleagues dove into COVID transmission data affecting Hispanic and Black families.
- Lori Crosby, PsyD, led efforts to craft specific messaging to reflect learnings from surveying Black families. Keith Martin, DO, and Amy Rule, MD, MPH, explored similar barriers affecting Latinx families.
- Clinical researcher Aimee Miley and Claire Seid delved into concerns related to homeless persons and those recently released from jails and prisons.

A flurry of local partnerships and programs followed, including co-launching a successful bi-lingual digital campaign with the Health Collaborative called "Test and Protect."

Several of the investigators presented preliminary findings in November 2020, but much of the work will continue until the pandemic ends—and beyond.

"Look, I know there's a long and painful history of research abuses on Black and Latino populations in this nation's history," says Calvin Williams, president of a Cincinnati-based Black-owned business, in a recruiting video for an ongoing study. "I also know Dr. Lori Crosby, who is leading the A.T.T.A.C.H. study. And I know that she and Cincinnati Children's Hospital Medical Center can be trusted to maintain your anonymity, confidentiality, dignity and safety."

Mitigating the Mental Health Burden of COVID-19

Cincinnati Children's applies expertise to a vital, yet long-underfunded health need

With 1 million deaths nationwide and counting, millions of Americans are grieving the loss of loved ones to the pandemic. In too many cases, dying caregivers have left children behind to cope, including more than 200,000 kids robbed of at least one parent or custodial grandparent.

Many more young lives have been disrupted in other ways, including enduring the fear of having loved ones in intensive care and adjusting to life after adult caregivers lost jobs. Students personally coped with weeks and months of remote education, all-day masking rules, and other limitations on their activities.

Many missed out on milestone events, from birthday parties to graduations. Restrictions came down on gathering with friends, playing sports, or going to crowded places. Meanwhile, children were last in line for vaccines as the Delta variant gave way to the Omicron variant that affected many more children.

All of these disruptions occurred unevenly and unfairly from family to family across populations as endless political arguments and waves of misinformation crashed around.

"We know that the negative impacts of trauma on health are significant, and trauma comes in many forms. The impacts of the pandemic have exposed children to trauma over the past almost two years, and the chronic nature of the stressors have exacerbated existing mental health symptoms and led to the development of symptoms in others," says Lori Stark, PhD, director, Division of Behavioral Medicine and Clinical Psychology. "Youth have been presenting at a higher frequency and with more intensive symptoms of anxiety and depression even as coping strategies and resources that had been available became more limited during the pandemic."

It will likely take years to unpack all the ways the COVID-19 pandemic affected this rising generation. But here at Cincinnati Children's—a national leader in providing and improving child mental health care—responses and research began immediately and have carried on since.

STUDYING TELEHEALTH WHILE USING IT

Even as the hospital began shifting 80% or more of its vast outpatient services to telehealth, investigators understood that such dramatic change could affect outcomes and would require tracking and analysis. By May 2020, Cincinnati Children's teams had begun studying the implications of remote medicine, especially on counseling services, and especially for children in low-resource families. Some preliminary data have emerged, but as the pandemic continues, so does the analysis.

Among the projects, Stephen Becker, PhD, has expanded an ongoing study of how ADHD affects emotions, sleep, academics, media use, family relations to also compare how this population fared during the pandemic. How will the surge of remote care affect outcomes?

Exploring Intersections Between COVID-19 and Co-Morbidities

MUCH POLITICAL DISCUSSION ABOUT THE PANDEMIC REVOLVED AROUND WHETHER OTHERWISE HEALTHY PEOPLE WERE DYING FROM SARS-COV-2 INFECTIONS OR WHETHER THE VIRUS WAS A FINAL STRAW OF SORTS FOR PEOPLE WITH PRE-EXISTING CONDITIONS. FOR CHILDREN WITH CHRONIC DISEASE, THIS WAS MUCH MORE SERIOUS THAN A POLITICAL DEBATE.

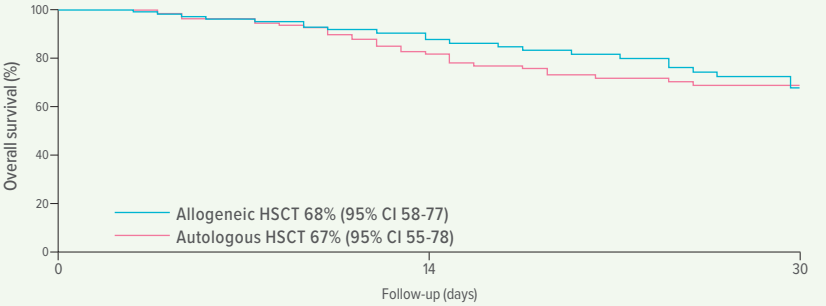
This issue cut across many conditions, including diabetes, lung diseases, blood disorders and many rare chronic conditions. At Cincinnati Children's, experts quickly dove into questions about how to manage infected children already immunosuppressed as organ or bone marrow transplant recipients.

Christopher Dandoy, MD, MSc, was a co-author in a large observational study, published in March 2021 in *The Lancet Haematology*, that analyzed outcomes for 318 stem-cell transplant patients who were affected by COVID-19.

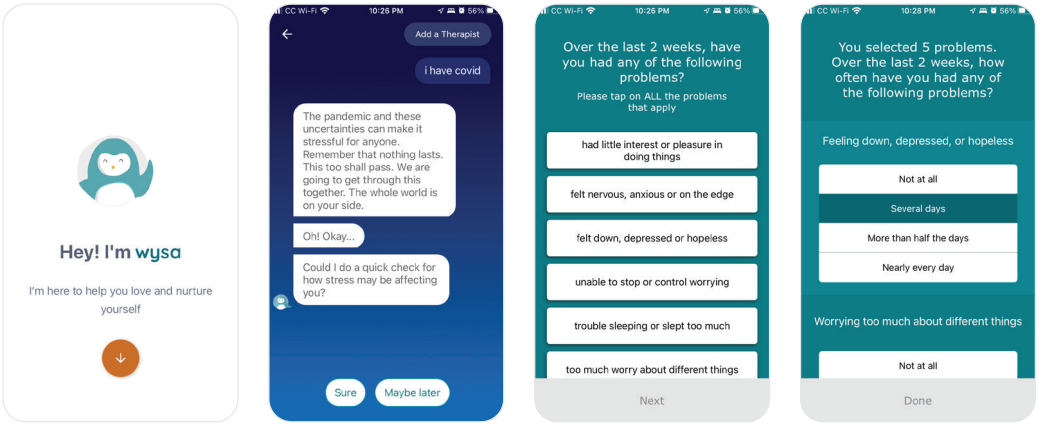
Of those who caught the virus, 45 needed mechanical ventilation. More than 30% of transplant recipients died within a month of infection with COVID. Older age and male sex increased mortality risk. Those with lymphomas also fared worse compared to those with myelomas.

Lara Danziger-Isakov, MD, MPH, was the senior author for an outspoken group of experts who urged placing higher priority on vaccination for transplant patients in an article published online in January 2021 in the *Journal of Heart and Lung Transplantation*.

"Our transplant recipients are far more likely to suffer a severe outcome from COVID-19 than from the vaccine," the co-authors stated. "Transplant recipients with COVID-19 had a 30% increased risk of death or mechanical ventilation compared with matched controls." Protecting these children "now hinges on widespread acceptance of the vaccines. In a pandemic marked by political divisions, misinformation exponentially amplified by social media, and an undercurrent of distrust of science, we believe it is critical that we engage our patients to encourage vaccination as soon as it is available."



Number at risk (number censored)			
Allogeneic HSCT	153 (0)	71 (62)	39 (83)
Autologous HSCT	109 (0)	65 (34)	28 (58)



Screenshots of the Wysa app in use.

"The experience of the COVID-19 pandemic and its consequences are likely to be particularly magnified and salient in youth with pre-existing mental health and neurodevelopmental risk, such as ADHD," Becker says.

CAN 'CHATBOTS' FILL A VOID?

With necessity driving invention, years of gradual improvements in "chatbot" services based on machine learning technologies took sudden leaps in sophistication and usage.

At Cincinnati Children's, the crisis prompted John Pestian, PhD, an expert in natural language processing and machine learning tools to team up with Michael Sorter, MD, director, Division of Child and Adolescent Psychiatry and Jeffrey Strawn, MD, an anxiety expert in the Department of Psychiatry and Behavorial Neuroscience at the University of Cincinnati.

By August, 2020, they had built a working relationship with Wysa, a company that had introduced a digital behavioral health platform a few years prior in the United Kingdom and several other nations. Together, they launched an upgraded Covid Anxiety module, distributed through the Wysa app, that allowed young adults and teens to use their smartphones to chat with a "4 a.m. friend." While not a direct counseling service, the tool invited users to explore nine exercises vetted by mental health experts.

"These self-help techniques are important because anxiety is common among the population," says Sorter. "Unfortunately, anxiety often goes undiagnosed, and then untreated for long periods of time."

The anxiety app creators fed their learnings to a team at Cambridge University that described an explosion of digital mental health solutions in a study published Feb. 10, 2021, in *Frontiers in Digital Health*. The report, based on data from 20 nations, documented a 7,500% increase in searches for health-apps related to the prevention of self-harm, a 176% increase for apps dedicated to the management of depression, an 86% increase in searches for mental health apps for the treatment of anxiety, and a 328% increase in searches for apps related to sleep.

"We've shown that it's possible for a large number of providers to work together across borders to rapidly gather valuable insights," said Cambridge neuroscientist Becky Inkster, DPhil, principal investigator for the study. "This could be used to set up an integrated digital system to better understand and respond to people's mental health needs on a global scale in real-time"

SHIFTING RESEARCH FOCUS ON THE FLY

As COVID arrived, Drew Barzman, MD, director of the Child and Adolescent Forensic Research Program at Cincinnati Children's, had been pursuing a $7.5 million grant from the Patient-Centered Outcomes Research Institute (PCORI) to compare

existing and emerging treatment options for adolescents with suicidal thoughts.

By July 2021, the pandemic's impact on mental health prompted the team to re-work the multi-center grant's aims to build in a more extensive analysis of telehealth services.

"What we're really wanting to take a look at is how patients are doing three months and six months out after they receive these initial services and see if there's a clinically significant difference among the different treatment options that are available to the teens who are experiencing suicidal thoughts," says Jennifer Combs, senior research clinical coordinator and study project manager.

To the surprise of some, the actual overall number of suicides in 2020 was 3% lower than in 2019, according to the Centers for Disease Control and Prevention's National Center for Health Statistics. However, the numbers varied by age groups. Despite the overall decline, suicide rates increased 13% among young men ages 10 to 14 and 5% among those 25 to 34. Data from 2021 is not yet available. Researchers are watching closely to determine how suicide and suicide ideation trends may shift as the pandemic drags on.

JUST THE BEGINNING

The full extent of the pandemic's impact on child mental health cannot be known until the pandemic actually ends. For now, the main objectives have been to use technology to extend otherwise limited resources, to raise awareness of the soaring demand for mental health support, and to capture the data needed to assure that lessons can be learned.

"Children and adolescents were experiencing increasing mental health challenges before COVID-19, particularly depressive symptoms and suicidal ideation, and the pandemic has greatly exacerbated children's mental health difficulties," Stark says. "Further, the pandemic has proceeded in parallel with national attention to and reckoning with structural racism, and the mental health crisis has disproportionately impacted children from communities of color."

The concern is so pressing that on Dec. 7, 2021, the U.S. Surgeon General released an advisory to highlight the urgent need to address the nation's youth mental health crisis.

> "The mental health crisis has disproportionately impacted children from communities of color."
>
> — Lori Stark, PhD
> Director, Behavioral Medicine and Clinical Psychology

Looking ahead, Stark says research priorities coming out of the pandemic include identifying subpopulations at highest risk, identifying resilience factors that may be useful to promote, building and evaluating school and community based interventions to connect more youth in need to evidence-based care, and establishing expectations for telehealth and other new models of care.,

On the research side, many behind-the-scenes improvements are needed to achieve these tasks, Stark says. Currently, many systems collect data separately and communicate with each other poorly. Regulatory challenges pose challenges for effective use of telemedicine. And the entire system needs more mental and behavioral health providers, especially from underrepresented populations.

"We are fortunate to have a broad continuum of services and providers that is likely unmatched in the United States," Stark says. "Unfortunately, we also recognize that it often is not enough. We continue to see unmet needs in the community for children and their families seeking out additional services."

Anderson Center Team RACEs to Respond to COVID

When COVID-19 emerged, the need for rapid learning and rapid dissemination of emerging data became critical to many stakeholders working to minimize damage from the pandemic. It was the exactly the kind of co-creation and shared learning challenge that the Anderson Center for Health Systems Excellence was created to address.

From the governor's office to school board meetings, the members of the Rapid, Adaptive Control of Epidemics (RACE) team shared their expertise in both the scientific aspects of the pandemic and their experience at bringing together highly disparate groups to work together to reach common goals.

As a result, four team members were honored as local leaders in the 2021 Inspire Healthcare Awards sponsored by the Health Collaborative. Recipients were: Peter Margolis, MD, PhD, Robert Kahn, MD, MPH, Andrew Beck, MD, MPH, and David Hartley PhD, MPH.

Within 10 days of the region's first diagnosed case, the situational awareness and strategy team was working with regional leaders to develop shared goals, define key populations, and align resources to bend the curve. Partners included public health departments, hospitals, adult living facilities, group homes, schools, and business groups.

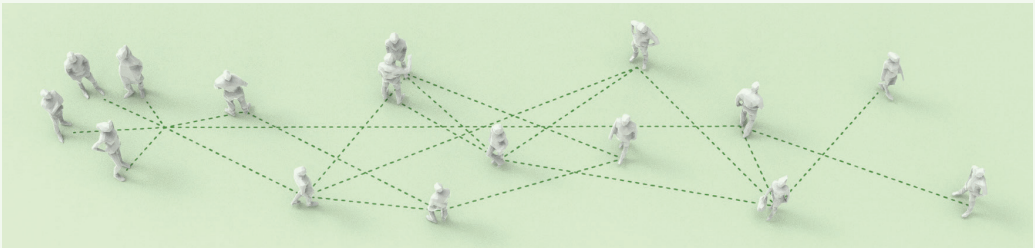
By early May 2020, a dashboard of COVID data was being shared publicly to inform the community. Among the decisions and activities supported by the RACE team:

- Not opening Cincinnati's Convention Center as a field hospital because data showed stable hospital capacity at that time, saving tens of millions of dollars.
- Using changes in case incidence to win business community support for a community-wide "Mask On" communication campaign.
- Selecting testing and vaccination sites to respond to data showing how underserved and disadvantaged populations were bearing a disproportionate burden of impact.
- Working frequently with the Cincinnati Public Schools and many other regional school districts to make closing and re-opening decisions amid the fast-changing dynamics of the pandemic.

Beyond the city, much of the data-gathering infrastructure that helped experts rapidly assess the pandemic was established long before COVID struck thanks to the PEDSnet organization, which Cincinnati Children's has supported for years.

Nathan Pajor, MD, was among the co-authors of a PEDSnet study that documented the disproportional impacts COVID-19 had upon children from disadvantaged populations. Their findings, based on electronic medical records data from over 135,000 children, were published Nov. 23, 2020, in *JAMA Pediatrics*.

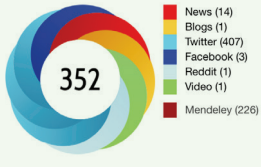
"PEDSnet provides a national digital architecture that can harness the power of the electronic health record to advance knowledge," Margolis says. "Without PEDSnet, gathering the information we needed right away during the pandemic would have taken years."



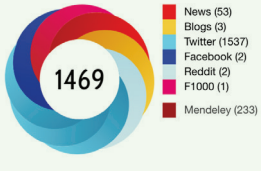
Contributing to COVID Knowledge

THE COVID-19 PANDEMIC TOUCHED SO MANY ASPECTS OF SCIENCE AND MEDICINE, IT'S NOT POSSIBLE TO SHARE DETAILS ABOUT EVERY CONTRIBUTION MADE BY INVESTIGATORS AT CINCINNATI CHILDREN'S. IN FISCAL 2021 ALONE (ENDED JUNE 30), OUR FACULTY AUTHORED OR CO-AUTHORED MORE THAN 225 PEER-REVIEWED PUBLICATIONS EXPLORING THE MANY IMPACTS OF SARS-COV-2 ON OUR LIVES. HERE ARE SOME OF THE MOST-SHARED CONTRIBUTIONS:

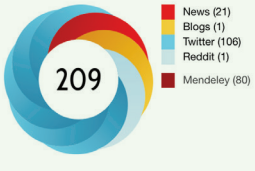
Jeffrey Whitsett, MD, and **Minzhe Guo, PhD**, were among a group of investigators with the NHLBI LungMap Consortium and The Human Cell Atlas Lung Biological Network that combined data from more than 30 studies to publish an extensive single-cell analysis of COVID-related "entry genes." The study, published March 2, 2021, in *Nature Medicine*, reported that the gene *ACE2* and accessory proteases TMPRSS2 and CTSL are needed to produce severe respiratory distress from infection.



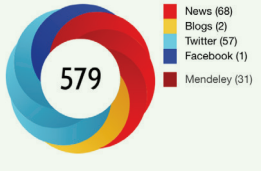
Mary Staat, MD, MPH, Division of Infectious Diseases, joined fellow members of the Overcoming COVID-19 Investigators group to publish key findings gathered from 52 medical centers about neurologic involvement among nearly 1,700 children hospitalized with COVID-19 or MIS-C. Their findings appeared March 5, 2021, in *JAMA Neurology*.



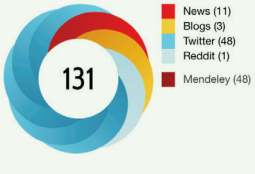
Sreeja Parameswaran, PhD, **Joseph Wayman, PhD**, **Emily Miraldi, PhD**, and **Matthew Weirauch, PhD**, were among co-authors reporting that topotecan (a TOP1 inhibitor used as a chemotherapy) showed the ability to reduce inflammatory gene expression in mice infected with SARS-CoV-2. Their work was published March 30, 2021, in *Cell*. The findings prompted an ongoing clinical trial involving patients with cancer and COVID-19.



Samir Shah, MD, was a co-author on a 44-center study in the *Journal of Hospital Medicine* documenting the impact of COVID-19 public health interventions on pediatric illnesses nationwide.



Abdelkader Mahammedi, MD, was first author for a multinational study that analyzed chest and brain CT scans from 135 people with COVID-19. They found that the CT lung disease severity score may be predictive of acute neurological abnormalities. The study in the *American Journal of Neuroradiology* also involved nine other imaging experts from UC and Cincinnati Children's.



225+ Papers

of Pediatric Otorhinolaryngology ADAMTS13 activity to von Willebrand factor antigen ratio predicts acute kidney injury in patients with COVID-19: Evidence of SARS-CoV-2 induced secondary thrombotic microangiopathy — *International Journal of Laboratory Hematology* Impact of COVID-19 Pandemic on Pediatrics and Pediatric Transplantation Programs — *Frontiers in Pediatrics* Are e-learning Webinars the future of medical education? An exploratory study of a disruptive innovation in the COVID-19 era — *Cardiology in the Young* Safety and Immunogenicity of Two RNA-Based Covid-19 Vaccine Candidates — *New England Journal of Medicine* Physical Health, Media Use, and Mental Health in Children and Adolescents With ADHD During the COVID-19 Pandemic in Australia — *Journal of Attention Disorders* Inequities in Diabetic Ketoacidosis Among Patients With Type 1 Diabetes and COVID-19: Data From 52 US Clinical Centers — *The Journal of Clinical Endocrinology & Metabolism* Use of Telehealth in Fellowship-Affiliated Developmental Behavioral Pediatric Practices During the COVID-19 Pandemic — *Journal of Developmental & Behavioral Pediatrics* Fabry disease and COVID-19: international expert recommendations for management based on real-world experience — *Clinical Kidney Journal* Safety and Efficacy of the BNT162b2 mRNA Covid-19 Vaccine — *New England Journal of Medicine* The Impact of COVID-19 on Job Prospects and Educational 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One Does Not Simply… Shut Down Science

When the COVID-19 pandemic prompted Ohio Gov. Mike DeWine to issue "Stay at Home" orders on March 22, 2020, leaders at Cincinnati Children's faced an enormous challenge: What does it mean to shut down research?

On a normal day, the Research Operations team under Kristine Justus, PhD, Vice President, spends its time ensuring researchers have what they need for each of their scientific programs.

Danny Burdine, MBA, Laura Runck, MSc, and Ryan Varney, MA, (aka the "Justus League") partner with nearly every department at Cincinnati Children's—Supply Chain, Plant Engineering, Marketing & Communications, ORCRA, OSEH, Environmental Services, Protective Services, Information Services, and others. They often work with third-party vendors to solve issues. They remove roadblocks, streamline processes, lead efforts in safety, assist with garnering and negotiating the best price for resources, and provide general communications across the research enterprise.

But this was not a normal day. A shutdown is the antithesis of what the operations team does. When the governor's order was given, Justus' first action was to get with her team and come up with a plan. "We had two, and only two, goals. The first was to keep everyone safe," she says. "The second was to minimize damages so that as soon as the governor lifted the order, we would be poised for a rapid recovery."

SHUTTING DOWN A COMPLEX ORGANIZATION WITH CARE

It's not easy to shut down research. With clinical trials, and in particular interventional trials, it can be detrimental to just stop. It's not reasonable to suddenly withhold a study drug from a study participant, for example.

Likewise, there are major challenges in a wet lab scenario: cell cultures need proper care and feeding; haz-

Pandemic Prompts Dash to Build Dashboards

AMONG THE MOST PRESSING EARLY CHALLENGES POSED BY THE RAPIDLY SPREADING SARS-COV-2 VIRUS WAS GATHERING ACCURATE DATA QUICKLY ENOUGH TO MAKE A DIFFERENCE.

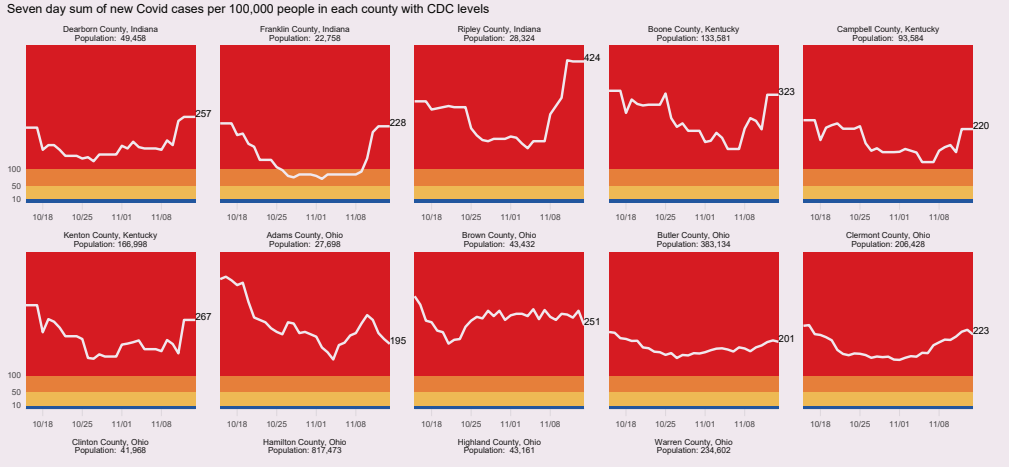
Within three months of the pandemic reaching the United States, Ben Wissel and PJ Van Camp, graduate students at Cincinnati Children's and the University of Cincinnati, had launched "The COVID-19 Watcher," which rapidly compiled city and county-level data on cases, deaths, and testing volumes. Judith Dexheimer was senior author of a paper about the tool that was published in the *Journal of the American Medical Informatics Association (JAMIA)*.

Soon, Cincinnati regional health leaders realized they needed even more granular local data about how infections were moving through the population.

Several Cincinnati Children's experts worked in conjunction with UC's Center for Clinical and Translational Science and Training (CCTST) to build the Health Collaborative Situational Dashboard. This dashboard, updated daily, became the definitive COVID data resource for the community. Key creators included: Stuart Taylor, MA, the data scientist who corrals the data, and project leaders Andrew Beck, MD, MPH, David Hartley, PhD, MPH, Robert Kahn, MD, MPH, and Peter Margolis, MD, PhD. (See page 28)

Meanwhile, scientists led by Jeffery Molkentin, PhD, a co-director of the Heart Institute at Cincinnati Children's, quickly gleaned insights from more than 9,500 area residents who had donated blood to Hoxworth Blood Center during a time when interest was high in collecting convalescent plasma. The project explored who had developed antibodies against COVID-19 before vaccines were available. Findings were later published in *PLOS One*.

This team reported COVID prevalence nearly doubling from 7.56% in August 2020 to 13% by December 2020. The data also showed that early infection rates ran higher on the west side of the city vs. the east side and north of the Ohio River vs. south. Meanwhile, the blood tests detected a high rate of infections occurring among donors under 30 years of age that often did not result in severe illness.



Danny Burdine, MBA, Ryan Varney, MA, Laura Runck, MSc , and Kris Justus, PhD, (aka the "Justus League")

ardous chemicals have to be handled, stored or disposed of appropriately; some instruments rely on static gas pressures or uninterrupted power; cold storage may need attention to protect precious contents. The list is long.

Some studies and experiments can be months or years in the making. Halting a research project could mean losing large amounts of valuable data or millions of dollars in reagents. Some experiments would be impossible to reproduce because they involved, for example, unique biological samples that are no longer available.

"Put that in terms of people and careers," explains Justus. "A postdoc, for example, who has spent the past two years of his or her life working on what might be ground-breaking research and who is now interviewing for an academic position somewhere, suddenly has to start over and the position has vaporized. We had several cases like that, with junior faculty, postdocs and students—all of whom lost some ground in their careers."

Research leadership discussed whether it was reasonable to continue critical research and how to define it. Hector Wong, MD, then interim director of the Research Foundation agreed that some research was critical: those studies that could adversely affect study participants and those studies that could not be reasonably reproduced, along with new investigations specific to the pandemic.

RULE ONE: KEEP EVERYONE SAFE. RULE TWO: STAY READY TO RE-START QUICKLY.

In just four hours, Research Operations had created a detailed plan that protected our researchers and our research, and catalogued "what if" scenarios for a shutdown of an unspecified length of time.

Then the team set about inventorying, prioritizing, and tagging more than 100 liquid nitrogen units; updating contacts for hundreds of alarms; working with Praxair, FedEx and other vendors to understand delivery options; securing hazardous chemicals in labs; coordinating chemical waste disposal and biohazardous waste pickups; planning extra monitoring for "special needs" areas, including sensitive cell cultures, crucial deliveries, and small labs lacking sufficient personnel.

Importantly, we requested (per Rule Two) labs not destroy biological lines that they would need on start up. We created a list of employees with experience in PCR, cell and tissue culture, animal husbandry, etc., to be able to mobilize resources if needs arose.

By far, our most significant contribution was the creation of effective communication channels. We compiled contact information for 520 essential staff members (ESMs) to serve as a "first line of defense" team. The Research Ops team is small; the ESM list was our multiplier and would become our eyes and ears.

ESMs were to come in for a couple of hours a week to maintain their area in a "ready state." Ryan and Laura repurposed what had been the "Lab Managers Communications Website" (LMCW) as the primary two-way communication with ESMs, effectively providing real time information across all labs. We used our Research Ops email list for lesser issues. We gave out our personal cell phone numbers to all, for any urgent issues that arose.

Ryan—well connected to the internal communications group—created the CenterLink structure for general broadcasts of COVID-related posts for research. To that, he posted templates and

checklists provided by users for users, along with SOPs and guidelines developed by Research Ops, Shared Facility directors and others.

"We understood what was at risk. We felt every investigator's anxiety," Varney says "Everything had to be checked and re-checked to ensure messages were correct, clear, and consistent."

On March 30th, we did final checks and lab walk-throughs and closed every lab door.

THE SHUTDOWN LASTED SIX WEEKS

Justus is a member of the medical center's Emergency Operations group, led by Nathan Timm, MD, and Amber Antoni, MSN, RN. Daily Emergency Ops meetings enabled bi-directional flow of information between the research enterprise and the hospital, kept our messages congruent across the institution, and allowed Research Ops to pivot instantaneously. After every 90-minute meetings, Justus relayed information to Ryan, Danny and Laura (and others as needed). The Research Ops team then engaged accordingly.

Throughout the shutdown, hospital care teams continued to look after patients. The Research Ops team assisted when they could. For example, using new communication channels, we solicited for and collected PPE, reagents for developing PCR tests, swabs, and other items.

"Our research colleagues were just as eager to help and their responses to solicitations were impressive," Justus says. "We provided equipment, expertise and space for decontaminating an initially limited supply of N95 respirators. Thanks to our freezer update program, we had new freezers on-site and were able to provide ample cold storage for COVID-19 vaccines when freezers were backordered by every vendor in the wider marketplace."

The Office for Clinical and Translational Research (OCTR) and the Schubert Research Clinic developed methods to facilitate—as much as possible—remote clinical research studies. For those studies not amenable to remote work but critical to continue, they worked to ensure protocols aligned with hospital practices.

Although only a fraction of research employees was on campus, Laura set up a volunteer sign-up system and screening stations for research. This mirrored procedures at other clinical locations but every shift was run entirely by volunteers.

About half our Shared Facilities (primarily those that provided clinical services or were necessary to maintain critical research) remained open throughout the shutdown. Shared Facility

Above: Kris Justus analyzing ramp-up plans. Right: Laura Runck with handwritten visitor and staff logs

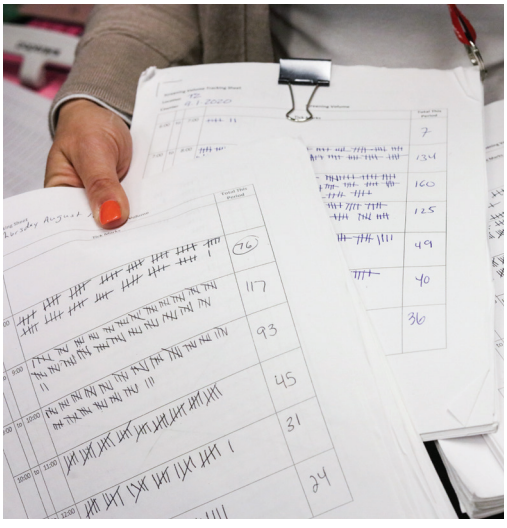
directors adapted on the fly, writing new sanitizing procedures, maintaining glass-wash services needed by labs doing critical COVID-related experiments, relocating large instruments to isolated areas, and innovating ways to train or troubleshoot. Our vivarium staff reduced services to only core animal husbandry, but we never needed to resort to large-scale reductions in biomass.

More than once, Research Ops activated its "what if" plans. Freezer monitoring systems went down on several occasions: Danny hosted vendor technicians to repair them. Freezers failed: essential personnel were called in and Danny supplied a backup to transfer samples. Laura worked with Supply Chain to re-route deliveries containing dry ice until lab personnel could tend to them.

The team remedied vendor issues, access issues, purchasing issues, delivery issues, connectivity issues, and more. From March 2020 through January 2021, the three-person team received as many as a dozen texts per week about urgent issues.

"I feel like we were juggling so many things at once that we didn't even realize how much we were actually doing," recalls Runck. "We all felt like there was a lot at stake and we couldn't let anyone down."

One of the most difficult issues was an HVAC repair requiring the entirety of Location S be taken off-line for an extended period of time, presenting a dangerous scenario. The lack of air movement for 48 hours meant that hundreds of freezers were at risk for overheating and massive losses of unique biological materials. It also provided a real possibility of toxic or flammable fumes building up in small lab spaces. In preparation, we re-checked every lab and worked with Protective Services to maintain security and a state of readiness with the Cincinnati Fire Department.



Impressively, Plant Engineering completed the fix in just over 36 hours, without event.

A FRENZIED RESTART

The governor lifted the stay-at-home order on May 1. However, firing up the research engine was difficult because the pandemic was still raging. Had the virus cleared entirely, we would not have been concerned about PPE and social distancing, and operations could have returned immediately to business as usual. But it was not business as usual.

Keeping everyone safe (Rule One) meant limiting the number of people on campus long after the restart. That had major effects on every partner to Research Ops: Food Services, Environmental Services, Parking & Transportation, Plant Engineering, Supply Chain, Protective Services, etc.

"We believed that the only real way to restart was to get input from each of our investigators about what they needed so that we could give our partners good information about required resources," Justus says. "We collected investigators' ramp-up plans, analyzed them within days, and the research engines started to rev on May 11."

The resulting activity was substantial and frenetic. We contacted users and remedied out-of-date service records on fume hoods and biosafety cabinets. We sourced items pertinent to safety and a means to distribute them: alcohol, spray bottles and wipes for decontaminating equipment and surfaces, along with hand sanitizers in high traffic areas (at a time when hand sanitizer was hard to obtain!). Signage—both paper and digital—was posted with information about entrances, masking, distancing, and other particulars. We monitored the numbers of employees coming through screening stations. With Jason Luthy, of Design, Con-

Balancing COVID Safety and Learning Needs

WHEN THE FIRST WAVE OF INFECTIONS HIT AND NO ONE COULD SAY WITH CERTAINTY HOW WIDESPREAD COVID-19 WOULD BECOME, THE INITIAL REACTION IN MOST PARTS OF THE UNITED STATES WAS TO SHUT NEARLY EVERYTHING DOWN.

Early on, an unprecedented number of school shut-downs profoundly disrupted family and work life—and likely saved many lives.

In one of the most-shared early studies on the rapidly evolving topic (*JAMA*, July 29, 2020), co-authors Katherine Auger, MD, Samir Shah, MD, and colleagues estimated that school closures were associated with a 62% decline in COVID-19 incidence, based on adjusted relative changes per week, and a 58% decline in mortality. These findings were shared by more than 127 news outlets and more than 8,800 tweets that reached 27 million people.

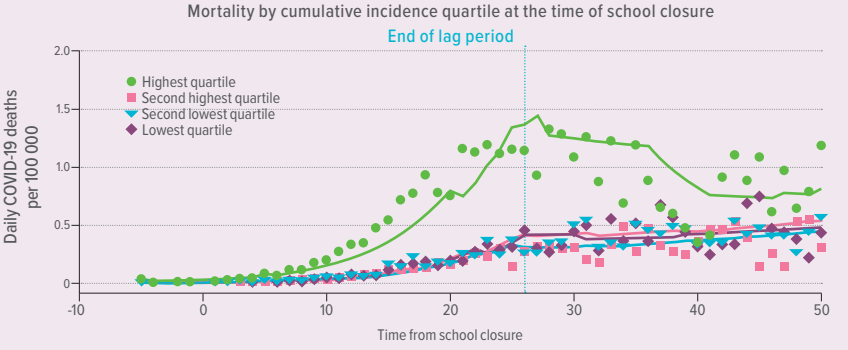
But as the pandemic dragged on, and COVID's direct impact on child health appeared lower than for adults, many parents, public officials and child development experts agreed that schools could not stay closed for the duration. Soon, school leaders called out for expert advice on how to re-open.

Cincinnati Children's responded. Leaders here, including Patty Manning, MD, Hector Wong, MD, Robert Frenck, MD, Robert Kahn, MD, MPH, Andrew Beck, MD, MPH, and others took on advisory roles. Some participated in press conferences with Ohio Gov. Mike DeWine. Others fielded what-would-you-do-with-YOUR-child questions from the media. And an entire team met repeatedly with school boards and superintendents to bring the latest science about the pandemic to the table.

How long should quarantines last? How far apart to set the desks? How long to require masking? When should schools close? When should they re-open? Are sports and music activities safe? Will remote learning leave students behind?

Often, it was less about conducting research and more about how to talk about the findings in ways that fearful people would trust.

"The mission became how to help kids safely get back to in-person learning because the data became clear that extended at-home schooling was making existing learning gaps wider among underserved population groups," Manning says. "Overall, most schools have managed the challenge extremely well even though the pandemic lasted longer than anyone expected."



struction & Space Planning, we reviewed seating areas, and looked at alternatives to maintain social distancing as more people came back to campus.

The first research areas to fully come back online were the Shared Facilities, and each director was thorough in assessing needs and creating new SOPs. The team also worked with many others to get appropriate SOPs in place. For example, with Steve Waggoner, PhD, chair of the Institutional Biosafety Committee, we created new protocols for working with human samples that could harbor SARS-CoV-2. Michelle Adams, PhD, Rebecca Harper, DNP, and Jareen Meinzen-Derr, PhD, MPH, developed models for clinical research (e.g., remote, on-site, group sessions, home studies) and what precautions or restrictions were necessary. Again and again, our communication channels functioned as a significant conduit during the progression of the pandemic. With every new piece of information about the virus and testing and (ultimately) vaccines, came multiple adjustments in logistics and operations for the various types of research performed here. As weeks and months progressed, we adjusted. Screening stations ceased; new practices were deployed. We continued to work with Purchasing to obtain essential materials. Researchers adopted the LMCW to request/donate/share reagents that were unavailable from commercial suppliers. We worked with Plant Engineering and Materials Management to install masking stations and hand sanitizers. We worked with Bob Baer to stay abreast of parking and shuttle services. Through it all, we learned a great deal.

"We believe we were one of the first research organizations in the country to reopen, and to that end we were successful with Rule Two. Not a single case of COVID-19 was traced back to infection within the research complex—success with Rule One," Justus says. "I am proud of what our team accomplished. In addition to the Ops team, many people contributed to Cincinnati Children's successes over the past year and a half. We are grateful to each and every one of our partners across this wonderful organization."

Respect. Truth. Team. Impact.

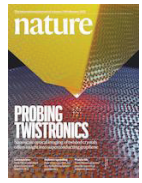
Despite COVID Pandemic, Discovery Marched On

While many aspects of research were affected by the COVID-19 pandemic, investigators at Cincinnati Children's found ways to carry on their mission of discovery. Here are some of the particularly strong basic science advances made in FY21:

Global discovery of lupus genetic risk variant allelic enhancer activity.
Mar 2021. page 58

Pairing of segmentation clock genes drives robust pattern formation.
Jan 2021. page 68

In situ mapping identifies distinct vascular niches for myelopoiesis.
Feb 2021. page 52



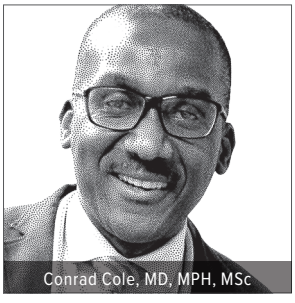
Violet-light suppression of thermogenesis by opsin 5 hypothalamic neurons.
Sept 2020. page 104

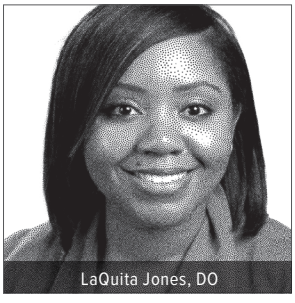
Disease-associated KIF3A variants alter gene methylation and expression impacting skin barrier and atopic dermatitis risk. Aug 2020. page 42

Microbiota-derived metabolite promotes HDAC3 activity in the gut.
Oct 2020. page 90


Jamilah Hackworth, EdD


Jessica Kahn, MD, MPH


Conrad Cole, MD, MPH, MSc


LaQuita Jones, DO


Patricia Vega-Fernandez, MD, MSc

Enhancing Diversity, Equity and Inclusion in Research

Achieving our institutional research goals at Cincinnati Children's depends upon increasing representation and advancing the career development of individuals who are historically underrepresented or marginalized in biomedical research. These are some of the initiatives we accelerated in the past year to build a more diverse research community and a more inclusive, collaborative culture in which all researchers feel safe, valued, connected, and respected.

OPTIMIZING RECRUITMENT, DEVELOPMENT, ADVANCEMENT, AND RETENTION

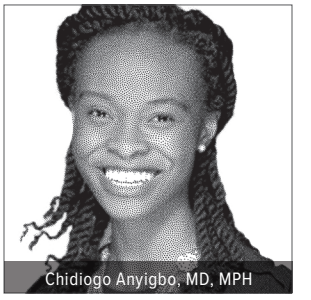
We have developed a comprehensive plan to hire and train diverse, multidisciplinary pediatric faculty researchers. This plan includes enhancing and sustaining an inclusive culture and building a self-reinforcing community of pediatric researchers committed to diversity and inclusive excellence. To achieve this goal, we have responded to a National Institutes of Health funding opportunity announcement with a grant application entitled, "Pediatric origins of disease and health: the Cincinnati Children's Hospital Medical Center FIRST cohort." Several actions outlined in the application are already being implemented.

The Office of Academic Affairs and Career Development (OAACD), directed by Jamilah Hackworth, EdD, and Jessica Kahn, MD, MPH, facilitates multiple pathway programs to promote careers in pediatric research including middle and high school science symposia, the Biomedical Research Internship for Minority Students, the Schmidlapp Young Women's Scholars program (a part of the Summer Undergraduate Research Fellowship Program), and the Schmidlapp STEM Scholars program. More than 250 students participate each year in these programs.

We are convening two Coalition for Pediatric Medical Research events funded by the Burroughs-Wellcome Fund, one held virtually in February 2022 and the second to be held in Washington, DC, in May 2022. The goals include identifying and implementing at scale best practice programs and policies to develop early-career researchers who are underrepresented in pediatric research. Conrad Cole, MD, MPH, MSc, Division of Gastroenterology, Hepatology, and Nutrition, has led the planning efforts, and LaQuita Jones, DO, Division of Oncology, served on a panel of junior investigators during the virtual session. Her research focuses on acute myelocytic leukemia.

We have established a recruitment pathway for diverse junior research faculty. Recent hires include Patricia Vega-Fernandez, MD, MSc, RhMSUS, Division of Rheumatology, who studies the use of ultrasound to diagnose pediatric rheumatologic conditions; Alexandra Sims, MD, MPH, Division of General and Community Pediatrics, a KL2 Scholar whose research focuses on sickle cell disease; and Chidiogo

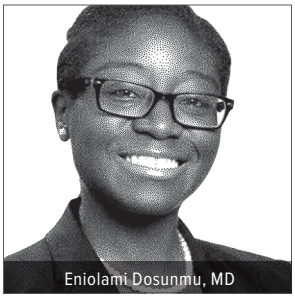

Alexandra Sims, MD, MPH


Chidiogo Anyigbo, MD, MPH

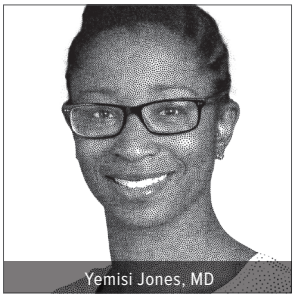

Jareen Meinzen-Derr, PhD, MPH

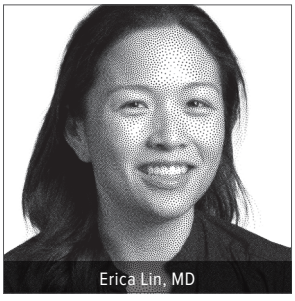

Lori Crosby, PsyD


Rama Ayyala, MD


Eniolami Dosunmu, MD


Christine Heubi, MD


Yemisi Jones, MD


Erica Lin, MD


Sarah Orkin, MD

Anyigbo, MD, MPH, Division of General and Community Pediatrics, whose research focuses on mitigating adverse childhood experiences.

To facilitate promotion of faculty whose efforts focus on DEI, the Department of Pediatrics also has developed a set of promotion metrics that support faculty demonstrating achievements in these areas.

DEVELOPING INFRASTRUCTURE & RESOURCES

To implement the faculty DEI strategic plan, we have named two directors: Jareen Meinzen-Derr, PhD, MPH, Division of Biostatistics and Epidemiology, and Lori Crosby, PsyD, Division of Behavioral Medicine and Clinical Psychology. We also named eight liaisons, including Cole, Sims, Rama Ayyala, MD, Eniolami Dosunmu, MD, Christine Heubi, MD, Yemisi Jones, MD, and Erica Lin, MD. They are working to implement a set of strategies to promote an inclusive research environment where faculty thrive.

Our Diversity and Health Disparities Award provides a $150,000, two-year grant to support researchers who are underrepresented or are conducting health disparities research. Recent awardees include Vega-Fernandez, Sarah Orkin, MD, Nana-Hawa Yayah Jones, MD, Carley Riley, MD, MPP, MHS, and Tesfaye Mersha, PhD.

The OAACD has launched the Faculty Leaders Who Inspire Program (FLIP), a longitudinal leadership development program based on research findings from a previous Core Leadership Program (Hackworth et al., J Pediatr 2018;199-4-6; DePalma et al., J Faculty Development 2020; 34:1-6). The program has been redesigned to better address the specific needs of women and underrepresented faculty.

BUILDING AN EQUITABLE & INCLUSIVE CULTURE

The OAACD sponsors networking groups for underrepresented individuals, including the Black Faculty and Staff Alliance, which provides faculty and staff physicians and psychologists with opportunities to network, share resources, and participate in professional development activities.

We are increasing the number of underrepresented and women speakers in research venues. For example, we have increased the proportion of female speakers from 33% to 72%

and underrepresented minority speakers from 27% to 33% in the Center for Clinical and Translational Research and Training (CCTST) Grand Rounds. In addition, the proportion of topics focused on health equity or racism increased from 40% to 50%.

The Biostatistics, Epidemiology and Research Design core of the CCTST, in collaboration with the Division of Biostatistics and Epidemiology, launched a research seminar speaker series focused on the use of race and ethnicity in research studies in December 2021. To date, 70% of scheduled speakers are women and 80% are people of color.

The theme of the 4th Annual Health Equity Day on April 5, 2022, was "Moving Upstream to Achieve Health Equity." This program was led by Community and Population Health and the OAACD. Sessions focused on equity-oriented initiatives occurring in partnership with our local community.

FOCUSING ON ACHIEVING MORE EQUITABLE HEALTH OUTCOMES FOR CHILDREN

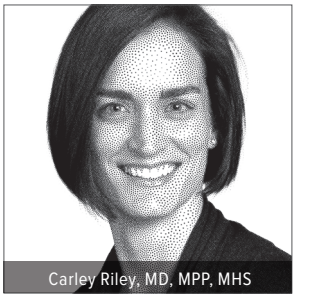
Health equity goals and initiatives are embedded throughout our Pursuing our Potential Together strategic plan.

We have launched the Health Equity Network, which extends a well-established partnership with the Legal Aid Society of Greater Cincinnati beyond our general pediatric clinics into more of our subspecialty services. Clinical teams work to improve equity in health care delivery and to connect with community partners that address hardships, such as toxic housing and food insecurity.

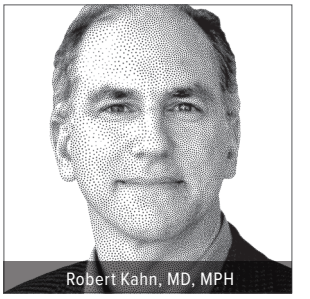
We also announced the new Michael Fisher Center for Child Health Equity to align and accelerate health equity initiatives and research at Cincinnati Children's and create a more welcoming space for community partners to join us in these efforts.

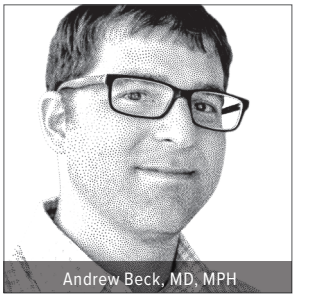
Experts in health equity research including Riley, Robert Kahn, MD, MPH, and Andrew Beck, MD, MPH, are mentoring diverse junior faculty researchers as they pursue equity-oriented health research, including support for grant applications.

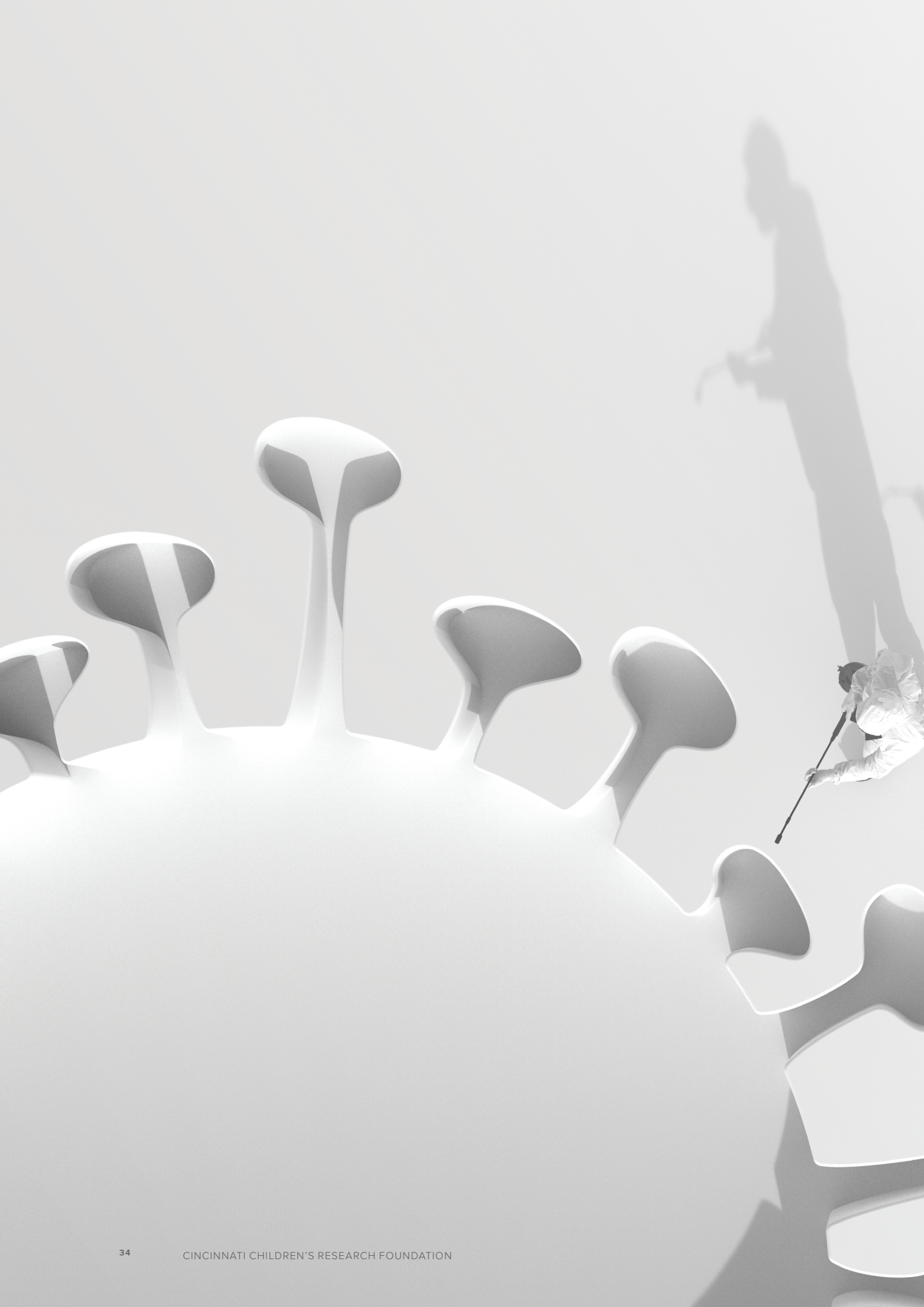

Nana-Hawa Yayah Jones, MD


Carley Riley, MD, MPP, MHS


Tesfaye Mersha, PhD


Robert Kahn, MD, MPH


Andrew Beck, MD, MPH



2021 Scientific Achievements

Investigators here produced more than 2,400 peer-reviewed journal articles, book chapters, and other publications in FY2021. The following pages feature the most significant publication from each of our research divisions.

Gender-Affirming Hormone Therapy May Not Raise Thrombosis Risk in Transgender Youth

Eric Mullins, MD

Tanya Kowalczyk Mullins, MD, MS

PUBLISHED APRIL 2021
Pediatrics

For transgender adults, studies suggest that receiving gender-affirming hormone therapy (GAHT) may be associated with an increased risk of thrombosis, the formation of a blood clot within a blood vessel. However, adolescent and young adult transgender youth do not appear to face a similar increased risk.

In a first-of-its-kind study, senior author Tanya Kowalczyk Mullins, MD, MS, and colleagues examined risk factors and occurrence of thrombosis in a strictly adolescent and young adult transgender population receiving GAHT. Their findings can help patients, families, and clinicians make informed decisions around GAHT for young transgender patients.

Researchers began by conducting a retrospective chart review of 611 patients at a pediatric hospital-associated transgender health clinic. Of these participants, 28.8% were transgender women and 68.1% were transgender men, with a median age of 17 years at GAHT initiation.

Among the cohort, researchers noted multiple thrombotic risk factors, including obesity, tobacco use, and personal and family history of thrombosis. Despite the presence of pre-existing risk factors, they found that no youth in their cohort developed thrombosis, suggesting that GAHT in youth does not carry a significant risk of thrombosis in the short-term.

"Our results provide important initial information about the safety of GAHT use in youth that can be incorporated by clinicians into their counseling of these patients and families," Kowalczyk Mullins says.

Next, researchers will use these results to develop a larger, longer-term study of thrombosis risk associated with GAHT in youth.

RESEARCH & TRAINING DETAILS

Faculty	12
Joint Appointment Faculty	2
Total Annual Grant Awards	$1.7M

Mullins ES, Geer R, Metcalf M, Piccola J, Lane A, Conard LAE, Mullins TLK. Thrombosis Risk in Transgender Adolescents Receiving Gender-Affirming Hormone Therapy. Pediatrics. Apr 2021;147(4).

Hematologic Evaluation and Incidence of Thrombosis

	No. (%)[a]	No. Patients With Testing Performed
Referred to hematology	17 (2.8)	—
Thrombophilia evaluation		—
Elevated factor VIII (>150%)	4 (23.5)	17
Erythrocytosis (>17.7 g/dL)	10 (2.0)	504
Activated protein C resistance ratio (<0.78)	1 (6.3)	16
PAI-1 (<16.3 IU/mL)	5 (31.3)	16
Factor V Leiden heterozygous	2 (11.8)	17
Prothrombin G20210A heterozygous	2 (12.5)	16
MTHFR 677 homozygous	3 (21.4)	14
PAI-1 4G homozygous	5 (35.7)	14
Elevated homocysteine (>10.7 µmol/L)	2 (20.0)	10
Thromboprophylaxis before GAHT		
Overall cohort	5 (0.8)	—
History of thrombosis before GAHT	2 (0.3)	—
No history of thrombosis before GAHT	3 (0.5)	—
Thrombosis on GAHT	0	—

MTHFR, methylenetetrahydrofolate reductase. —, not applicable.
[a] For hematologic testing, results are reported as number of abnormal tests and percentage of patients who had testing performed for which results were abnormal.

Contributing co-authors from Cincinnati Children's also included: Eric Mullins, Rebecca Geer, Megan Metcalf, Jeanne Piccola, Adam Lane, and Lee Ann Conard.

Custom SNP Chip Helps Boost Suspected Gene Associations in EoE from 3 to 13

Leah Kottyan, PhD

Marc Rothenberg, MD, PhD

RESEARCH & TRAINING DETAILS

Faculty	13
Joint Appointment Faculty	8
Research Fellows & Post Docs	2
Research Graduate Students	2
Total Annual Grant Awards	$5.1M
Total Annual Industry Awards	$3.1M

Kottyan LC, Trimarchi MP, Lu X, Caldwell JM, Maddox A, Parameswaran S, Lape M, D'Mello RJ, Bonfield M, Ballaban A, Mukkada V, Putnam PE, Abonia P, Ben-Baruch Morgenstern N, Eapen AA, Wen T, Weirauch MT, Rothenberg ME. Replication and meta-analyses nominate numerous eosinophilic esophagitis risk genes. J Allergy Clin Immunol. Jan 2021;147(1):255-266.

PUBLISHED OCT. 28, 2020
Journal of Allergy and Clinical Immunology

A team of 18 co-authors spread across five research divisions at Cincinnati Children's conducted a complex set of analyses that sharply expands the number of risk genes associated with eosinophilic esophagitis (EoE).

First author Leah Kottyan, PhD, Center for Autoimmune Genomics and Etiology, and senior author Marc Rothenberg, MD, PhD, director, Division of Allergy and Immunology, and colleagues conducted a meta-analysis of previous EoE gene studies to develop a custom single-nucleotide polymorphism (SNP) chip containing 956 possible risk SNPs.

The team used the chip to probe data from 627 people with EoE and 365 controls. Ultimately, the team sifted through more than 8,000 gene variants of potential influence to identify 13 genes that play significant roles, including six risk genes with effects at genome-wide significance and seven EoE risk loci with "strong suggestive significance."

As expected, important risk genes were found to be active in esophageal tissues, but single-cell RNA sequencing also traced risk to genes active in seven other cell and tissue types: the skin, lungs, fibroblasts, whole blood, the spleen, stomach and intestine.

As a group, all 13 of the highlighted risk genes appeared active in samples from people with EoE, while appearing minimally active in control samples. However, the genetic risk burden varied widely.

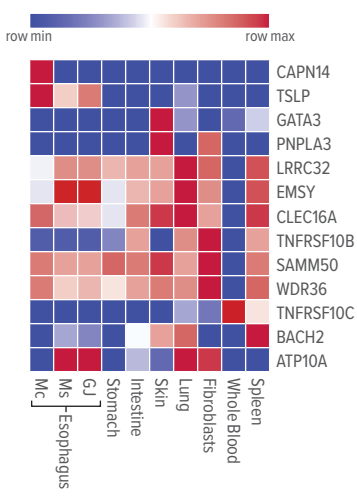
"Those with the highest decile of genetic burden had a greater than 12-fold increased risk of EoE compared with those in the lowest decile," Kottyan says.

The results suggest that some or many of these genes might be used to calculate polygenic risk scores that could assist clinicians with earlier diagnosis and better-targeted treatments. But more study is needed.

"Polygenic risk scores will likely become more clinically useful as more genetic risk loci are identified and additional demographic, environmental, and clinical factors are included," Rothenberg says.

EoE Risk Genes by Tissue Type

A

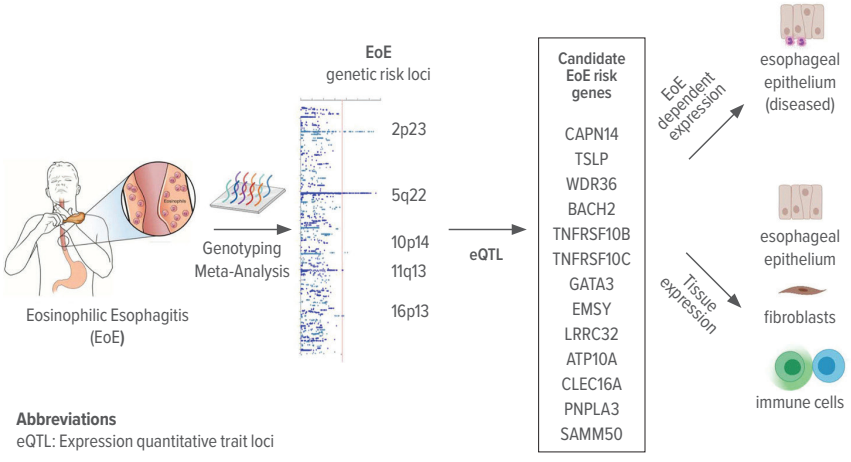


Left: figure A shows the tissue types where EoE risk genes are located. Red indicates highest area of activity while blue suggests minimal presence.

Below: This graphical abstract details 13 genes that carry increased risk of developing eosinophilic esophagitis (EoE) and indicates the variety of tissue types where these genes are expressed.

Replication and Meta-Analyses Nominate Numerous Eosinophilic Esophagitis Risk Genes

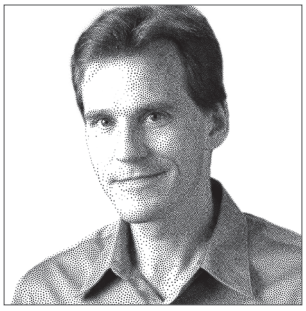
B



Abbreviations
eQTL: Expression quantitative trait loci

Learning How Gene Mutations Contribute to Epilepsy

Candi LaSarge, PhD



Steve Danzer, PhD

PUBLISHED DEC. 9, 2020
Progress in Neurobiology

Scientists still do not fully understand how epilepsy develops. "This lack of knowledge has limited the development of epilepsy prevention therapies in patients at risk for developing the disease, such as following genetic mutations, brain tumor, stroke, head injury or brain infection," says Steve Danzer, PhD, Department of Anesthesia.

Yet over the past decade, it has become clearer that mutations in genes regulating the mTOR pathway (a central regulator of metabolism and physiology) are one significant cause of epilepsy. Epilepsy-causing mutations in these genes may affect small regions of the brain or an entire brain hemisphere. Focusing upon mTORopathies, a class of genetic epilepsies that develop in children, a research team led by Danzer and first author Candi LaSarge, PhD, developed a novel transgenic mouse model of epilepsy and used cutting-edge technology such as optogenetic silencing of abnormal neurons to better understand how gene deletions impact brain excitability and inhibitory cells.

"Children have gene mutations in variable numbers of brain cells, and we modeled this in mice," Danzer explains.

The researchers deleted the gene *Pten*, a negative regulator of mTOR, from 0 to 40% of hippocampal granule cells. Low numbers of knockout cells led to subtle increases in brain excitability and occasional focal seizures, while more deletions reduced the number of protective (inhibitory) brain cells and caused epilepsy characterized by generalized seizures. These results suggest that "pro-epileptogenic changes begin in the brains of children with mTOR mutations before clinical disease is evident," Danzer says. "It may be possible to target these preclinical changes to prevent epilepsy."

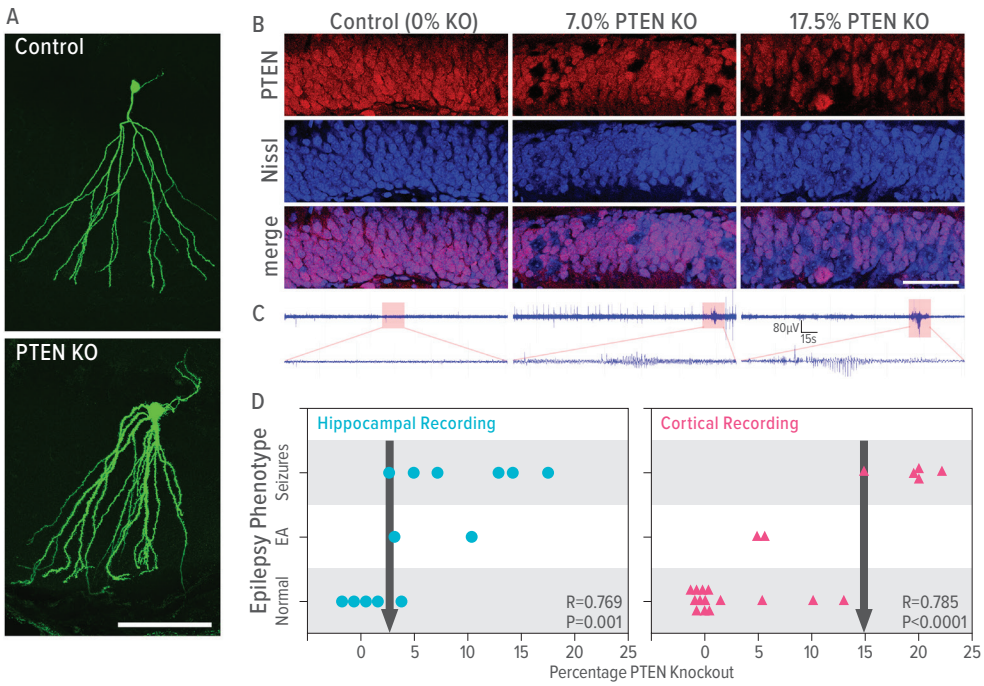
Co-authors presented their findings at a conference in Nice, France, in October 2021. Meanwhile, NIH-supported follow-up studies are ongoing to identify secondary changes that convert sub-clinical epilepsy to clinical epilepsy, with a particular focus on ways to protect the inhibitory system from secondary damage caused by mTOR mutant neurons.

RESEARCH & TRAINING DETAILS

Faculty	63
Research Fellows & Post Docs	2
Research Graduate Students	6
Total Annual Grant Awards	$3M
Total Annual Industry Awards	$253,994

LaSarge CL, Pun RYK, Gu Z, Riccetti MR, Namboodiri DV, Tiwari D, Gross C, Danzer SC. mTOR-driven neural circuit changes initiate an epileptogenic cascade. Prog Neurobiol. May 2021;200:101974.

Epilepsy Risk Grows When More Cells Lack PTEN



A: Examples of biocytin-filled control and Pten knockout (KO) cells. Scale bar = 100 µm. B: Micrographs show Pten immunoreactivity (red) and Nissl staining (blue) in the dentate granule cell body layer of a control mouse and two Pten KO mice. KO cells appear as dark holes in the Pten staining, and blue cells in the merged image. Scale bar = 50 µm. C: Hippocampal depth electrode recordings from each of the corresponding mice in panel B. The control animal shows a normal recording, the 7% KO shows epileptiform spikes and events, while the 17.5% KO has a seizure. D: Graphs show the correlation between the percentage of Pten KO granule cells and the animal's phenotype (hippocampal: n=13; cortical n=21). Control animals (0% KO) are plotted in black, and KOs in red. Animals carrying the DREADD receptor, which was not activated in the present study, are denoted by "#". Animals were categorized as normal, as having epileptiform activity (EA) only or seizures, as determined from hippocampal or cortical recordings.

Gene Variants Increase Risk for Dysfunctional Skin Barrier, Asthma, and Food Allergies

Mariana Stevens

Gurjit Khurana Hershey, MD, PhD

RESEARCH & TRAINING DETAILS

Faculty	5
Joint Appointment Faculty	1
Research Fellows & Post Docs	6
Research Graduate Students	8
Total Annual Grant Awards	$5.2M

Stevens ML, Zhang Z, Johansson E, Ray S, Jagpal A, Ruff BP, Kothari A, He H, Martin LJ, Ji H, Wikenheiser-Brokamp K, Weirauch MT, Supp DM, Biagini Myers JM, Khurana Hershey GK. Disease-associated KIF3A variants alter gene methylation and expression impacting skin barrier and atopic dermatitis risk. Nat Commun. Aug 14 2020;11(1):4092.

PUBLISHED AUG. 14, 2020
Nature Communications

In the fight against allergens, skin is the first barrier. When this barrier is dysfunctional, environmental exposures can more easily reach other tissues, raising the risk of developing asthma and food allergies.

What controls skin barrier function? By integrating data from human and mouse studies, a research team led by first author Mariana Stevens and senior corresponding author Gurjit Khurana Hershey, MD, PhD, found that two common variants in the *KIF3A* gene play a major role. In young children, these variants increase the risk of having a dysfunctional skin barrier and developing atopic dermatitis, also known as eczema, which affects up to 20 percent of all children.

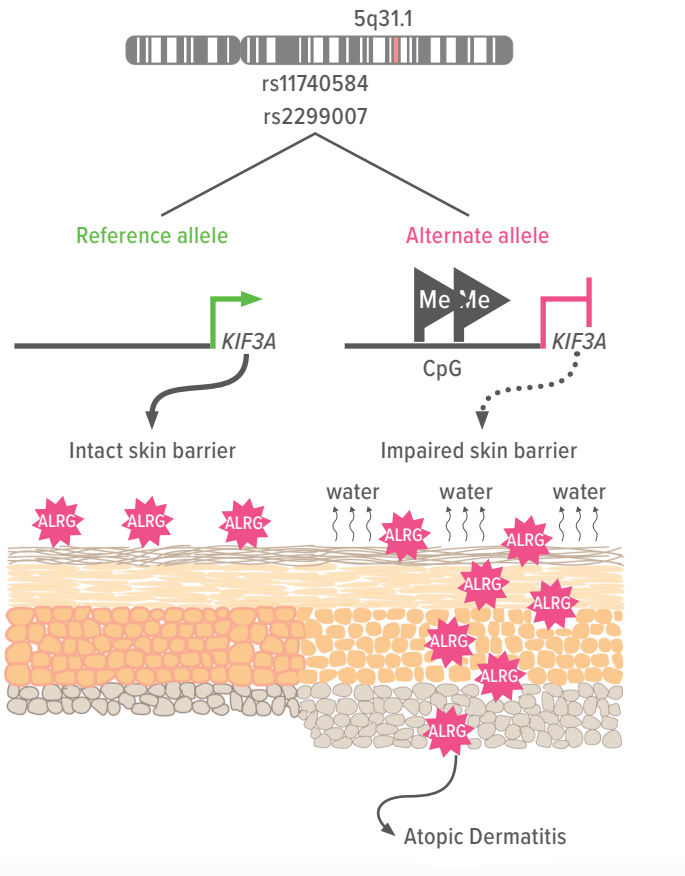
Although eczema usually resolves as children age, many go on to develop more severe conditions including asthma and food allergies. Understanding the genetic mechanisms of eczema could make it easier to identify which of these children are most likely to develop other allergic conditions.

While previous studies have shown that malfunctioning *KIF3A* in lung and gut tissues leads to asthma and food allergies, this study is the first to connect these allergy risks to a damaged skin barrier.

"This study adds evidence to a rising theory that skin health is more closely connected to lung and gut health than many have suspected," Hershey says. "*KIF3A* is a new target for therapies to prevent and treat eczema and allergic diseases."

Next, the research team aims to develop a rapid screening test and search for drug compounds that might someday be useful in restoring the disrupted functions of the *KIF3A* gene.

A Tale of Two SNPs



Allergic disease-associated *KIF3A* SNPs create new CpG sites, which are highly methylated in individuals carrying the alternate allele leading to decreased *KIF3A* expression. Decreased *KIF3A* results in increased TEWL due to defective cell-cell adhesion, and increased susceptibility to the development of atopic dermatitis. ALRG = allergen.

Markers Predict Response to Cognitive Behavioral Therapy in Adolescents with Migraine

Hadas Nahman-Averbuch, PhD

Christopher King, PhD

PUBLISHED FEB. 1, 2021
Pain

Migraine is one of the most common chronic pain conditions in children and adolescents, leading to challenges in academics, psychosocial functioning, and quality of life. While cognitive behavioral therapy (CBT) can help reduce pain, not all patients will show clinically meaningful benefits. Is there a way to predict which patients will respond to CBT?

Leveraging expertise in pain mechanisms and clinical management of migraine, researchers from the divisions of Behavioral Medicine and Clinical Psychology and Neurology assessed the role of two potential mechanisms associated with improvements in pain following CBT in patients with migraine. They found that amygdalar connectivity and pain modulation capacity at baseline predict headache reduction in these patients.

For eight weeks, 20 study participants aged 10 to 17 years completed weekly CBT sessions. Researchers used functional magnetic resonance imaging to assess baseline brain function and amygdalar connectivity. Pain modulation capacity was assessed by conditioned pain modulation (CPM).

The team found a reduction in headache days after CBT, which was larger in patients with greater amygdalar connectivity and a less efficient pain modulatory response. These findings suggest that individual differences in brain function and pain modulation can be associated with clinical improvements, leading to personalized treatments for children and adolescents with migraine.

"This research supports the biological nature of CBT and the ability of a child or adolescent with migraine to change their biological propensity for having a headache," says senior author Christopher King, PhD. "This could also direct more personalized approaches to increase the overall success of CBT."

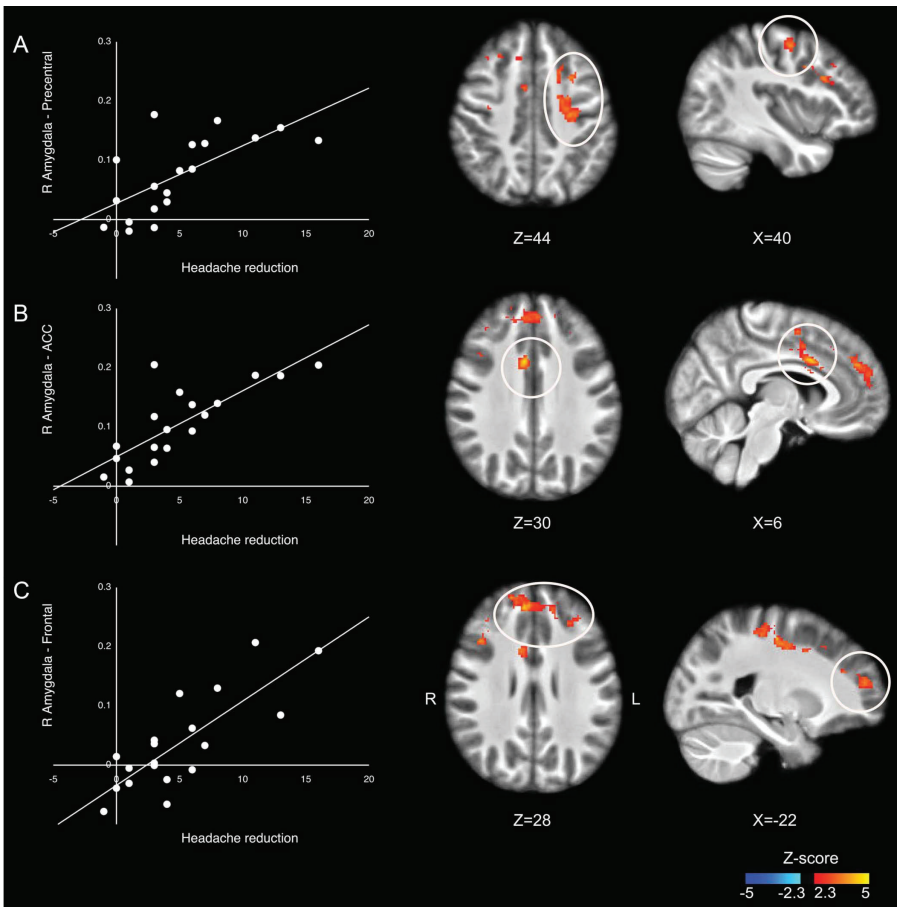
The team is currently building on this preliminary research to explore the neural and psychophysical mechanisms of CBT in two federally funded grants.

RESEARCH & TRAINING DETAILS

Faculty	63
Joint Appointment Faculty	1
Research Fellows & Post Docs	13
Research Graduate Students	8
Total Annual Grant Awards	$17.2M

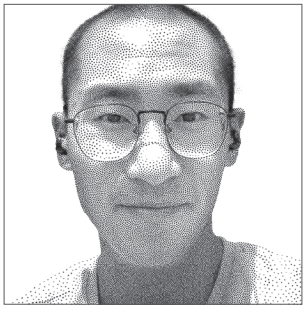
Nahman-Averbuch H, Schneider VJ, 2nd, Chamberlin LA, Kroon Van Diest AM, Peugh JL, Lee GR, Radhakrishnan R, Hershey AD, Powers SW, Coghill RC, King CD. Identification of neural and psychophysical predictors of headache reduction after cognitive behavioral therapy in adolescents with migraine. Pain. Feb 1 2021;162(2):372-381.

Amygdalar Connectivity Relates to Reduced Headache Frequency After Cognitive Behavioral Therapy



Positive correlations between headache frequency reduction after CBT and connectivity between the right amygdala and the following clusters: (A) Precentral cluster, which included the left precentral and the left postcentral gyrus; (B) ACC cluster, which included the right ACC, bilateral supplementary motor area, and the right precentral gyrus; and (C) frontal cluster, which includes bilateral frontal pole, bilateral paracingulate gyrus, bilateral superior frontal gyrus, and the right middle frontal gyrus.

Deep Learning Tool Helps Create Custom T-Cell Vaccines



Guangyuan (Frank) Li, BS

Nathan Salomonis, PhD

PUBLISHED MAY 3, 2021
Briefings in Bioinformatics

Immunotherapies offer promising avenues for treating cancer and other diseases, including infection by deadly viruses such as SARS-CoV-2 (COVID-19). These strategies include vaccines that work by harnessing and reprogramming an individual's own immune system to find and target specific peptides (protein fragments exposed on the surface of a cell).

A significant challenge in the creation of new vaccines is predicting which peptides—among potentially hundreds of thousands—will elicit an immune response. To address this challenge, investigators from three laboratories (Ni, Prasath, and Salomonis) in the Division of Biomedical Informatics designed a new artificial intelligence approach called DeepImmuno to dramatically improve such predictions.

Researchers used real-world datasets to test and evaluate DeepImmuno. They found that the tool's convolutional neural networks (CNN)—deep learning algorithms—outperformed existing methods to improve the prediction of which prior validated cancer or COVID-19 peptides will mount an immune response.

Extending this approach, lead author Guangyuan (Frank) Li created a new way to simulate novel peptides that do not exist in nature, but are likely to induce an immune response, using a method called generative adversarial networks (GANs).

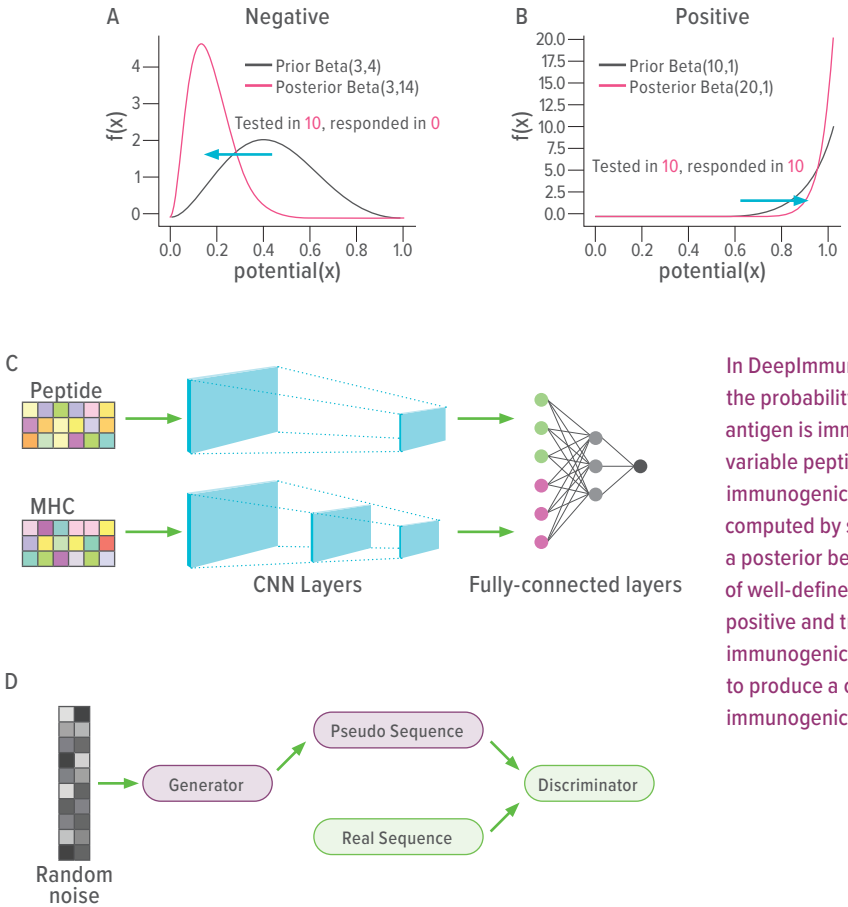
The applications of these approaches are potentially far-reaching, as they could be used to help drive synthetic biological approaches to design new treatments for diseases without existing therapies. To aid in these discoveries, DeepImmuno is available as a free, easy-to-use web interface for the genomics community.

RESEARCH & TRAINING DETAILS

Faculty	13
Joint Appointment Faculty	15
Research Fellows & Post Docs	3
Research Graduate Students	21
Total Annual Grant Awards	$5.5M

Li G, Iyer B, Prasath VBS, Ni Y, Salomonis N. DeepImmuno: deep learning-empowered prediction and generation of immunogenic peptides for T-cell immunity. Brief Bioinform. May 3 2021.

DeepImmuno



In DeepImmuno, to assess the probability that a given antigen is immunogenic, variable peptide immunogenic potential is computed by sampling from a posterior beta distribution of well-defined true-positive and true-negative immunogenic antigens to produce a continuous immunogenic score.

Tech Tool Accelerates Language Development for Children Who are Deaf or Hard of Hearing

Jareen Meinzen-Derr, PhD, MPH

Susan Wiley, MD

PUBLISHED JAN. 15, 2021
Pediatrics

For young children who are deaf or hard of hearing (DHH), language development can be challenging—up to 40 percent of DHH children under 6 develop language gaps that make it harder for them to function socially and succeed academically.

Now, an intervention using a tablet with special software can help them catch up. A clinical trial led by Jareen Meinzen-Derr, PhD, MPH, shows the benefit of incorporating the tool into therapy sessions when compared to traditional therapies.

"With spoken language, messages are said or spoken out loud and then disappear," says Meinzen-Derr. "DHH children sometimes struggle to catch and process all of what is said. As a result, they may have difficulty developing language skills in the same way as their hearing peers."

The technology-assisted language intervention (TALI) allows DHH children to work with words in a way that is different than listening. When users touch images on the screen, the app announces corresponding words, phrases, and messages.

Researchers explored the effectiveness of the tool by randomly assigning 41 children to standard care or the TALI approach. After 24 weeks, the children in the TALI group demonstrated significantly greater increases in the length of phrases used to express themselves, along with improvements in the number of different words spoken and in conversational turn-taking.

When integrated with therapy sessions and used at home, TALI empowers families and providers with more therapeutic intervention choices to enhance a child's language ability, communication skills, and social relationships.

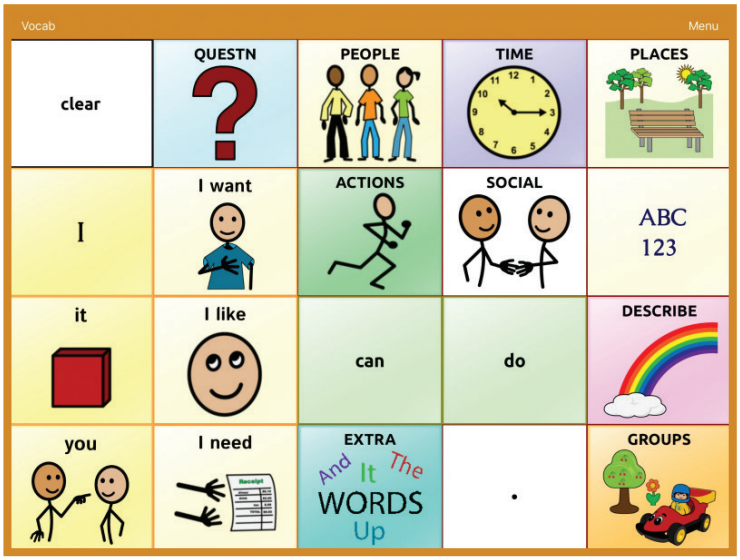
Meinzen-Derr currently has a $3 million grant from the National Institutes of Health to expand the clinical trial to a more diverse population across Cincinnati Children's and Colorado Children's hospitals.

RESEARCH & TRAINING DETAILS

Faculty	22
Research Fellows & Post Docs	2
Research Graduate Students	13
Total Annual Grant Awards	$13.1M
Total Annual Industry Awards	$22.7M

Meinzen-Derr J, Sheldon R, Altaye M, Lane L, Mays L, Wiley S. A Technology-Assisted Language Intervention for Children Who Are Deaf or Hard of Hearing: A Randomized Clinical Trial. Pediatrics. Feb 2021;147(2).

Language Learning Tool
for Deaf and Hard of Hearing



This screenshot depicts the tablet interface used by participants in the TALI clinical trial.

Under-Diagnosed TA-TMA Presents Risk to Stem Cell Transplant Patients

Christopher Dandoy, MD, MSc

Sonata Jodele, MD

RESEARCH & TRAINING DETAILS

Faculty	16
Joint Appointment Faculty	3
Total Annual Grant Awards	$2.6M
Total Annual Industry Awards	$1.1M

Dandoy CE, Rotz S, Alonso PB, Klunk A, Desmond C, Huber J, Ingraham H, Higham C, Dvorak CC, Duncan C, Schoettler M, Lehmann L, Cancio M, Killinger J, Davila B, Phelan R, Mahadeo KM, Khazal S, Lalefar N, Vissa M, Myers K, Wallace G, Nelson A, Khandelwal P, Bhatla D, Gloude N, Anderson E, Huo J, Roehrs P, Auletta JJ, Chima R, Lane A, Davies SM, Jodele S. A pragmatic multi-institutional approach to understanding transplant-associated thrombotic microangiopathy after stem cell transplant. Blood Adv. Jan 12 2021;5(1):1-11.

PUBLISHED DEC. 23, 2020
Blood Advances

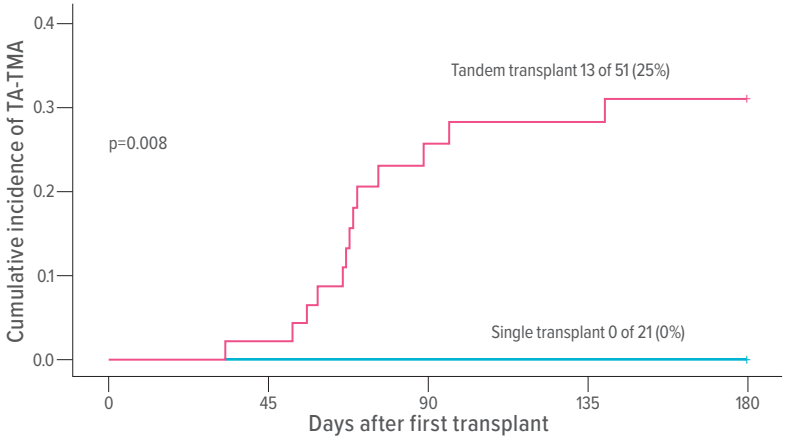
One of the most dangerous complications of hematopoietic stem cell transplantation (HSCT) is transplant-associated thrombotic microangiopathy (TA-TMA). Children with this complication often suffer kidney and heart damage as well as other dangerous effects and frequently spend more time in intensive care than those without TA-TMA. Now, a 13-center study led by first author Christopher Dandoy, MD, MSc, and senior author Sonata Jodele, MD, helps define the true incidence of TA-TMA while supporting the need for ongoing systematic screening. Co-authors from Cincinnati Children's and the University of Cincinnati also included Anna Klunk, Catherine Desmond, John Huber, Hannah Ingraham, Kasiani Myers, Greg Wallace, Adam Nelson, Pooja Khandelwal, Ranjit Chima, Adam Lane, and Stella Davies.

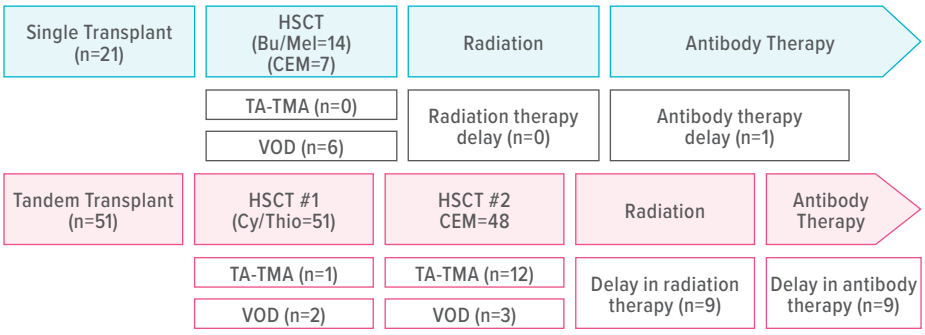
Worldwide, clinicians perform more than 50,000 stem cell transplants a year to restore healthy blood cell production in conditions including leukemias, multiple sclerosis, sickle cell disease and severe combined immunodeficiency. However, before this project, many centers were inconsistent in screening for signs of TA-TMA. Of 614 patients receiving a standardized set of tests, 98 (16%) were diagnosed with TA-TMA. Patients with underlying immune deficiencies showed increased risk for developing TA-TMA, notably those with primary hemophagocytic lymphohistiocytosis and Hurler syndrome. Also, patients with neuroblastoma who received combination carboplatin/etoposide/melphalan chemotherapy faced higher risk of TA-TMA.

"TA-TMA had been considered an infrequent complication of HSCT until the last five years," Jodele says. "This study plays a significant role in raising our awareness about TA-TMA's impact."

The good news: In many cases a complement blockade treatment of eculizumab significantly improved outcomes.

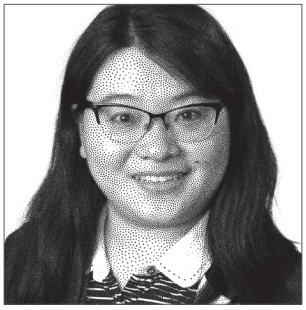
"We believe that it is very important to identify high-risk patients early in the disease process, so that targeted intervention can be used," Dandoy says.



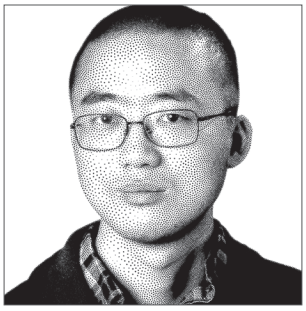


Of 72 patients with neuroblastoma receiving HSCT, 13 who were scheduled to undergo a tandem transplant developed TA-TMA. Nine patients had a delay in receiving radiation and nine patients had a delay in antibody therapy.

Bone Marrow 'Map' Opens Path to Organoid-like Blood Stem Cell Production



Qingqing Wu, PhD



Jizhou Zhang, MD

RESEARCH & TRAINING DETAILS

Faculty	25
Joint Appointment Faculty	10
Research Fellows & Post Docs	28
Research Graduate Students	29
Total Annual Grant Awards	$13M
Total Annual Industry Awards	$926,111

Zhang J, Wu Q, Johnson CB, Pham G, Kinder JM, Olsson A, Slaughter A, May M, Weinhaus B, D'Alessandro A, Engel JD, Jiang JX, Kofron JM, Huang LF, Prasath VBS, Way SS, Salomonis N, Grimes HL, Lucas D. In situ mapping identifies distinct vascular niches for myelopoiesis. Nature. Feb 2021;590(7846):457-462.

PUBLISHED FEB. 10, 2021
Nature

Imagine a day when clinicians treating people with leukemia or multiple myeloma can ask laboratories to custom-produce specific types of blood cells to replace those affected by the disease.

That day became one step closer to reality with this study led by senior author Daniel Lucas, PhD, and first authors Jizhou Zhang, MD, and Qingqing Wu, PhD, from the Division of Experimental Hematology and Cancer Biology.

"We finally have the tools to directly observe bone marrow cell differentiation," Lucas says.

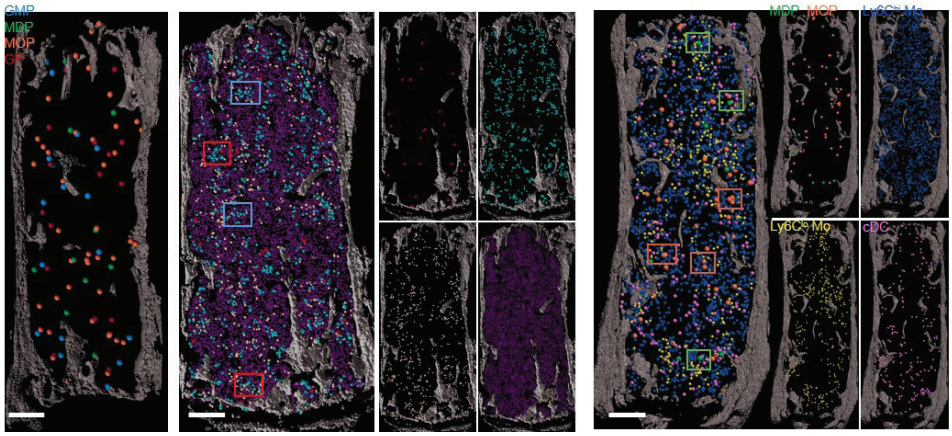
The team used a combination of cell-by-cell analysis techniques to build the first "atlas" of bone marrow tissue. The findings shed new light on how tiny blood vessels organize the bone marrow and regulate blood production.

Making the bone marrow atlas required developing novel methods. Until now, tracing cell lineages through stages of development required destroying the tissue. In this project, the team achieved unprecedented imaging resolution and a method to trace unique progenitors within the larger mass of bone marrow cells without destroying the tissue structure.

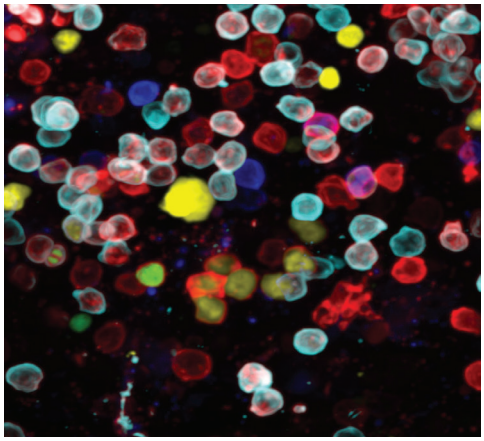
One potential goal for further study would be supporting future development of blood "organoids" that could produce blood cell populations with specific genetic variations. Scientists could use such organoids to study disease, and perhaps as a form of treatment.

"This certainly has implications for generating blood organoids," Lucas says. "The groups working on blood organoids have been trying to produce organoids that can maintain or expand stem cell production. Our data indicates that additional structures are needed to produce mature blood cells in a balanced manner."

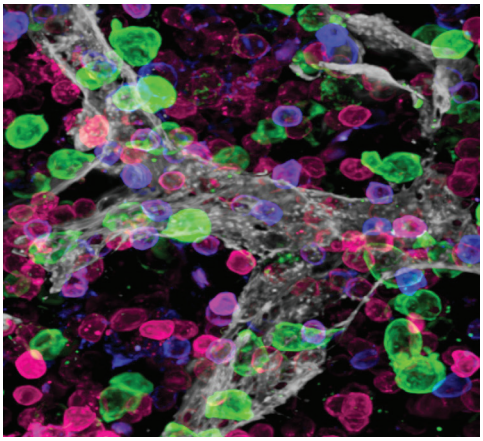
Mapping Blood Cell Production in Bone Marrow



These images pinpoint the location of blood progenitors and their differentiating offspring in mouse bone marrow. This is the first study to image blood production at this level of detail, say co-authors of the findings published Feb 10, 2021, in Nature.



Fate-mapping blood production: This image shows a thin slice of bone marrow tissue in confetti mice where cells can be coded using green, red, blue, and yellow fluorescent proteins to trace their offspring.



This image shows a sinusoid (white) supporting production of blood cells expressing different cell surface markers green: CD117, pink: CD11b, blue: CD115

Study led by senior author Daniel Lucas, PhD

Registry Helps Team Discover 7th Gene Linked to Rare Blood Disorder

Katie Seu, PhD

Theodosia Kalfa, MD, PhD

RESEARCH & TRAINING DETAILS

Faculty	14
Joint Appointment Faculty	1
Research Fellows & Post Docs	1
Research Graduate Students	1
Total Annual Grant Awards	$3.7M
Total Annual Industry Awards	$431,170

Seu KG, Trump LR, Emberesh S, Lorsbach RB, Johnson C, Meznarich J, Underhill HR, Chou ST, Sakthivel H, Nassar NN, Seu KJ, Blanc L, Zhang W, Lutzko CM, Kalfa TA. VPS4A Mutations in Humans Cause Syndromic Congenital Dyserythropoietic Anemia due to Cytokinesis and Trafficking Defects. Am J Hum Genet. Dec 3 2020;107(6):1149-1156.

PUBLISHED NOV. 12, 2020
American Journal of Human Genetics

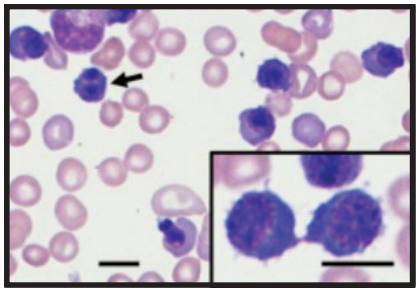
Congenital dyserythropoietic anemia (CDA) is so rare that specialists in blood disorders rarely encounter a patient. But thanks to a recently launched registry covering all of North America, scientists have gathered enough data to identify a seventh gene associated with the disease. People with CDA cannot produce red blood cells normally, which results in anemia, excessive iron levels, and organ damage. Previous studies have identified six gene variants associated with the condition. But these explain about half of known cases.

By exploring the Congenital Dyserythropoietic Anemia (CDA) Registry—launched in 2016 with funding from the Cincinnati Children's Center for Pediatric Genomics—a team led by first author Katie Seu, PhD, and senior author Theodosia Kalfa, MD, PhD, found three unrelated people with mutations of the gene *VPS4A*, but none of the other six CDA-associated genes. This gene helps regulate cellular processes, including cell division and endosomal vesicle trafficking. In CDA, the variant resulted in red blood cell precursors with distinctive double nuclei and cytoplasmic bridges that bound cells together even after they divided.

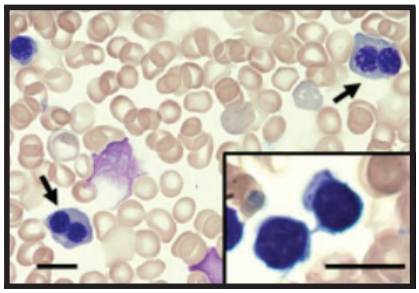
Two of the three affected children with *VPS4A* variants in the ATPase domain were born with microcephaly and significant brain development dysfunctions. The third child carrying *VPS4A* variants in another domain showed milder symptoms. Analyzing the genomic data required numerous steps, ultimately including whole-exome sequencing and deriving induced pluripotent stem cells (iPSCs) to model the syndrome. With this process established, researchers hope to find more variants linked to CDA or other rare blood disorders, the co-authors say.

"Our findings demonstrate that normal function of *VPS4A* is essential for human erythropoiesis," Kalfa says. "*VPS4A* mutations cause cytokinesis and trafficking defects leading to a human disease with detrimental effects to neurodevelopment and red cell production."

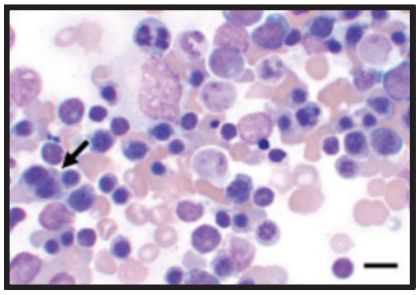
Case 1



Case 2



Case 3



These bone marrow aspirate smears, collected from a patient registry launched in 2016, show erythroid hyperplasia and dysplasia associated with a variant of the gene *VPS4A*. Erythroblasts (blue stain) show megaloblastoid changes and include cells with binucleation (arrows) and cytoplasmic bridges joining erythroblasts post-division, noted especially in probands 1 and 2 (insets).

Cincinnati Children's co-authors contributing to this study included Lisa Trump, Sana Emberesh, Robert Lorsbach, Haripriya Sakthivel, Nicolas Nassar, Wenying Zhang, and Carolyn Lutzko.

Mirdametinib Shows Benefit Against NF1-Related Tumors in Phase II Trial

Brian Weiss, MD

Nancy Ratner, PhD

RESEARCH & TRAINING DETAILS

Faculty	27
Joint Appointment Faculty	9
Research Fellows & Post Docs	11
Research Graduate Students	4
Total Annual Grant Awards	$3.3M
Total Annual Industry Awards	$952,126

Weiss BD, Wolters PL, Plotkin SR, Widemann BC, Tonsgard JH, Blakeley J, Allen JC, Schorry E, Korf B, Robison NJ, Goldman S, Vinks AA, Emoto C, Fukuda T, Robinson CT, Cutter G, Edwards L, Dombi E, Ratner N, Packer R, Fisher MJ. NF106: A Neurofibromatosis Clinical Trials Consortium Phase II Trial of the MEK Inhibitor Mirdametinib (PD-0325901) in Adolescents and Adults With NF1-Related Plexiform Neurofibromas. J Clin Oncol. Mar 1 2021;39(7):797-806.

PUBLISHED MARCH 1, 2021
Journal of Clinical Oncology

Years of studying NF1 nerve tumors at Cincinnati Children's continue to translate into medications that appear to show benefit for children and adults coping with painful, disfiguring and sometimes lethal plexiform neurofibromas (PNs).

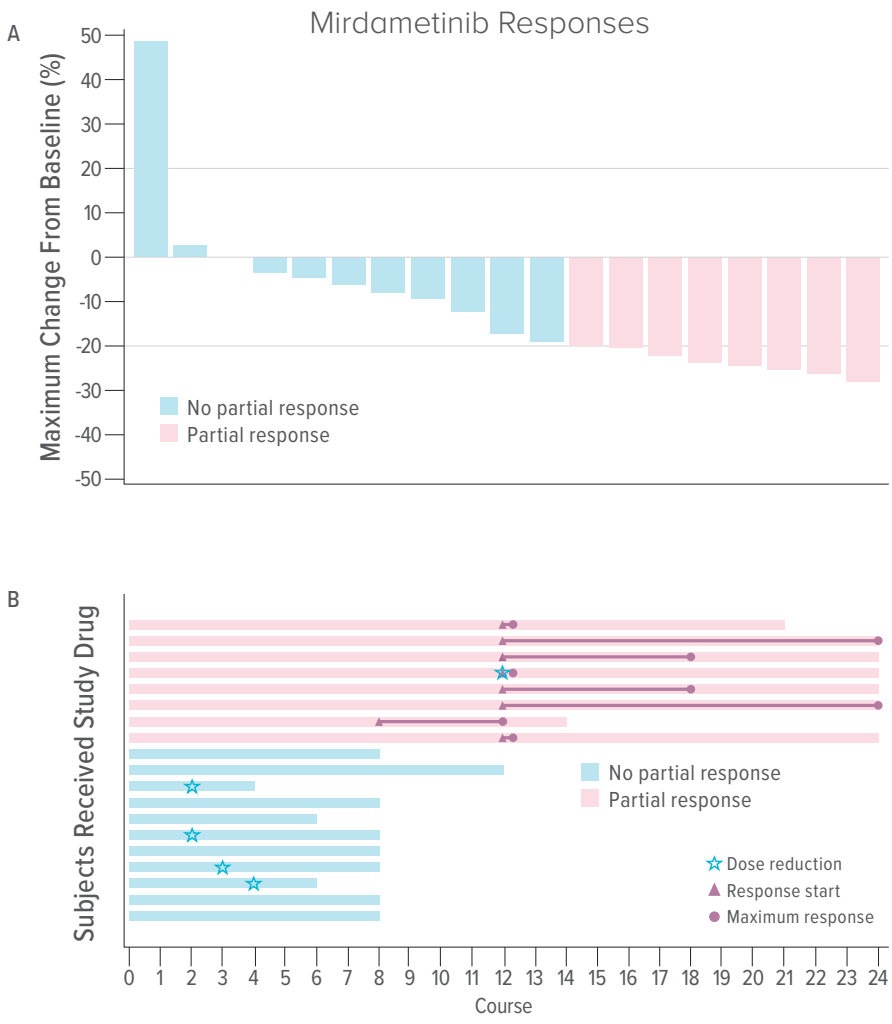
Brian Weiss, MD, Nancy Ratner, PhD, and several colleagues here are part of the 15-center Neurofibromatosis Clinical Trials Consortium (NFCTC) funded by the U.S. Department of Defense Neurofibromatosis Research Program. Among their latest projects: a phase II clinical trial of the MAPK/ERK kinase inhibitor, mirdametinib.

Nineteen patients with PNs, ages 16-39, received up to 24 four-week courses of the medication. The consortium observed "significant and durable" pain reductions. They also reported that 42% of participants achieved partial tumor volume reductions by course 12, and 53% achieved stable disease. One patient developed progressive disease, despite treatment.

"To our knowledge, this analysis represents the first characterization of the activity and pharmacokinetics of mirdametinib in patients with NF1 and PNs and is the first published response study for MAPK/ERK kinase inhibitors in adults with NF1 and PNs," according to Weiss, lead author of the study.

Cincinnati Children's breakthroughs in NF1 research date back to 1992, when Ratner helped developed an important mouse model to study the genetic and molecular factors driving the condition. By 2012, Ratner and colleagues demonstrated that MEK inhibitors shrunk NF1 tumors in mice, and in human cells under lab conditions. By 2018, the drug selumetinib had received orphan drug approval from the U.S. FDA as the first treatment for NF1.

Along the way, Weiss has played central roles in several clinical studies of NF1 treatments. Co-authors from Cincinnati Children's also included Chie Emoto, Tsuyoshi Fukuda, Elizabeth Schorry and Alexander Vinks.



Each patient is represented by a single bar. Blue bars did not achieve a partial response (PR). Red bars achieved a PR. (A) Waterfall plot of maximal tumor volume change by patient. (B) Swimmers plot of duration of exposure, time to PR, and time to maximum response. Length of bar represents duration of exposure. Magenta triangles represent the time a PR was first observed, and magenta circles represent the time of maximum tumor volume change from baseline. Green stars represent time of dose reduction.

‘Massively Parallel’ Gene Screening Tool Can Accelerate Research for Nearly Any Disease

Leah Kottyan, PhD

Matthew Weirauch, PhD

PUBLISHED MARCH 12, 2021
Nature Communications

As part of an ongoing exploration of systemic lupus erythematosus (SLE), a 16-member research team has developed a new type of “massively parallel” genetic screening tool that could shed new light on many conditions.

“This study not only provides several critical new discoveries about lupus, it also provides a blueprint for dissecting the genetic mechanisms of many complex human diseases,” says Leah Kottyan, PhD, interim director of the Center for Autoimmune Genomics and Etiology.

Massively parallel reporter assays (MPRAs) help scientists quantify the regulatory capacity of thousands of pieces of DNA in a given cell type. Such DNA sequences control how much, when, and where particular gene products are made.

“More than 95% of the genome does not code for genes, but instead is involved in other processes, such as controlling gene expression levels,” Weirauch says. “Understanding more about this information is vital because these regions of the genome also happen to be where genetic risk concentrates for complex diseases such as lupus.”

In this study, the authors used an MPRA to examine the effect of every known lupus genetic variant on gene expression levels. For people battling lupus, this study boiled down more than 3,000 potentially important genetic variants at 91 risk loci to just 51 of significant interest at 27 risk loci.

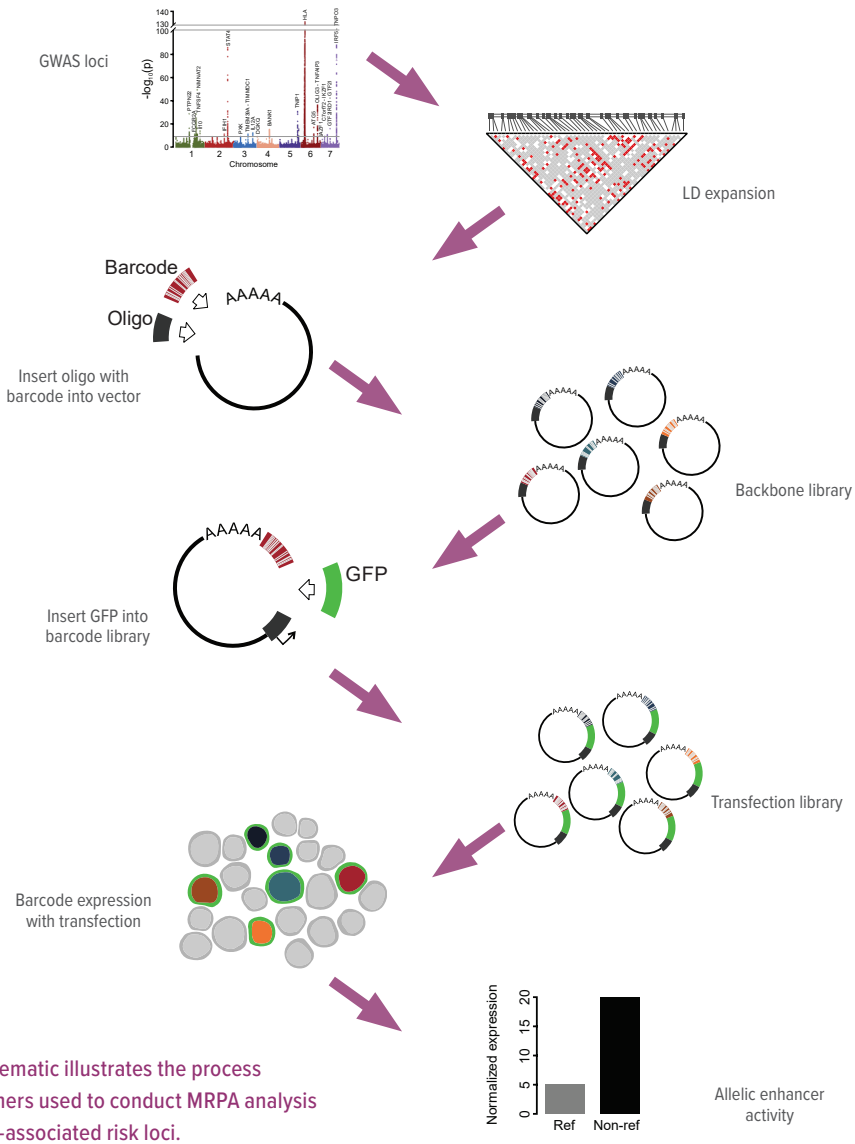
Many of the high-interest variants appear related to B cell function, which suggests some fresh ideas for preventing lupus-related complications that could be developed quickly, Kottyan says. Beyond lupus, the research team has begun using the MPRA technology to further explore atopic dermatitis, eosinophilic esophagitis, and multiple sclerosis.

RESEARCH & TRAINING DETAILS

Faculty	8
Joint Appointment Faculty	4
Research Fellows & Post Docs	12
Research Graduate Students	15
Total Annual Grant Awards	$8.5M

Lu X, Chen X, Forney C, Donmez O, Miller D, Parameswaran S, Hong T, Huang Y, Pujato M, Cazares T, Miraldi ER, Ray JP, de Boer CG, Harley JB, Weirauch MT, Kottyan LC. Global discovery of lupus genetic risk variant allelic enhancer activity. Nat Commun. Mar 12 2021;12(1):1611.

Massively Parallel Reporter Assay Workflow



This schematic illustrates the process researchers used to conduct MRPA analysis of lupus-associated risk loci.

Precision Dosing Technology Poised to Spread Beyond Academic Medical Centers

Tomoyuki Mizuno, PhD

Min Dong, PhD

PUBLISHED JULY 2020
British Journal of Clinical Pharmacology

For many years, the ability to employ model-informed precision dosing in real-world clinical settings has been limited to a select set of medications for a limited menu of health conditions managed almost exclusively by specialists working at the largest academic medical centers.

Applications have focused on preventing rejection of transplanted organs, walking the tightrope between effective cancer chemotherapy and dangerous side effects, constantly re-calculating doses for younger patients receiving off-label drug treatments for rare diseases, and so forth.

More recently, however, a convergence of improved precision dosing models, wider use of electronic medical records, and more user-friendly decision support software suggests that once-theoretical concepts like pharmacogenetics are becoming increasingly ready for day-to-day clinical practice. That's the conclusion drawn from a wide-ranging review article produced by five scientists at Cincinnati Children's. The paper details four successful implementations of model-informed precision dosing (MIPD):

- Customizing doses for children ranging from newborns to teens in clinical trials evaluating the drug sirolimus in multiple conditions.
- Helping doctors find the maximum tolerated dose of hydroxyurea within days instead of months for children coping with sickle cell anemia.
- Managing toxicity risk when cancer patients receiving high-dose methotrexate experience delays clearing the drug from their bodies.
- And introducing a decision support tool called NeoRelief that helps care teams more precisely manage morphine doses for neonates experiencing pain.

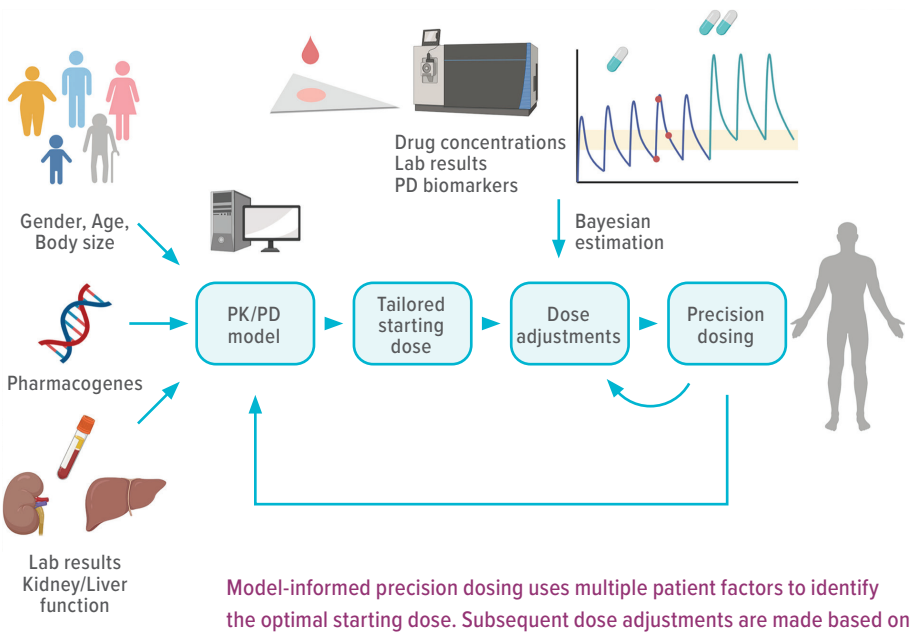
"Our overarching vision is that integrating a pharmacokinetics and pharmacodynamics (PK/PD) profile or prediction into prescribing clinicians' workflows will improve the safety and efficacy of many medications," the co-authors state.

RESEARCH & TRAINING DETAILS

Faculty	4
Joint Appointment Faculty	4
Research Fellows & Post Docs	1
Research Graduate Students	5
Total Annual Grant Awards	$435,757

Mizuno T, Dong M, Taylor ZL, Ramsey LB, Vinks, AA. Clinical implementation of pharmacogenetics and model-informed precision dosing to improve patient care. Br J Clin Pharmacol. 2020.

Steps involved in PK/PD-Informed Precision Dosing



Model-informed precision dosing uses multiple patient factors to identify the optimal starting dose. Subsequent dose adjustments are made based on clinical feedback.

Contributing co-authors from Cincinnati Children's also included:
Lisa Ramsey, PhD, Zachary Taylor, MS, and Alexander Vinks, PharmD, PhD.

PCSK9 Gene Plays Key Role in Poor Outcomes for Pediatric Septic Shock Patients

Mihir Atreya, MD, MPH

Hector Wong, MD

RESEARCH & TRAINING DETAILS

Faculty	17
Joint Appointment Faculty	1
Research Fellows & Post Docs	3
Research Graduate Students	1
Total Annual Grant Awards	$2.4M

Atreya MR, Whitacre BE, Cvijanovich NZ, Bigham MT, Thomas NJ, Schwarz AJ, Weiss SL, Fitzgerald JC, Allen GL, Lutfi R, Nowak JE, Quasney MW, Shah AS, Wong HR. Proprotein Convertase Subtilisin/Kexin Type 9 Loss-of-Function Is Detrimental to the Juvenile Host With Septic Shock. Crit Care Med. Oct 2020;48(10):1513-1520.

PUBLISHED OCTOBER 2020
Critical Care Medicine

Septic shock—the most serious manifestation of sepsis, a severe response to an infection—causes organ failure and dangerously low blood pressure. Among critically ill children, septic shock is associated with major morbidity and mortality.

Despite decades of research, care for patients with septic shock remains limited primarily to antibiotics and intensive care. Biological heterogeneity and host developmental differences are key barriers to identifying the right treatment for the right patient.

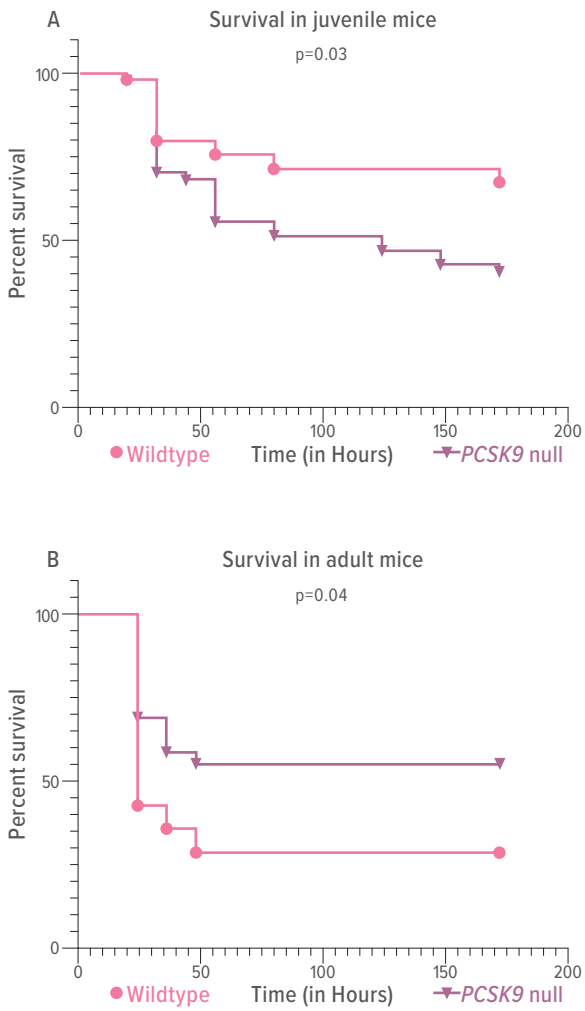
In adults, loss of function in the proprotein convertase subtilisin/kexin type 9 (*PCSK9*) gene—a key lipid regulator—is associated with improved sepsis outcomes. As commercially available *PCSK9* inhibitors are being tested for their efficacy against sepsis, researchers led by first author Mihir Atreya, MD, MPH and senior author Hector Wong, MD, investigated the influence of the *PCSK9* gene on pediatric septic shock outcomes.

In a large cohort of over 500 pediatric septic shock patients and in mouse models of sepsis, the team found that *PCSK9* loss-of-function is associated with poor survival and increased organ dysfunction, contradicting the data for adults.

"Our data support the long-standing contention that developmental age is a crucial determinant of host response to sepsis," says Mihir Atreya, MD, MPH. "We found that the detrimental effects of *PCSK9* loss-of-function in the pediatric host are not mediated by changes in serum lipoprotein concentrations, which have previously been positively correlated with sepsis survival in adults. Our data suggest that pleiotropic effects of *PCSK9* may play a crucial role in the pediatric host response to sepsis."

These results provide strong evidence to exclude pediatric sepsis patients from clinical trials of *PCSK9* inhibitors. Further studies may enable the identification of mechanistic pathways and targeted sepsis therapeutics specific to children.

PCSK9 Gene Needed for Sepsis Survival



Loss of proprotein convertase subtilisin/kexin type 9 (*PCSK9*) shows opposite effects on survival between juvenile and adult mice with sepsis.

International Experts Develop Guidelines for Best Treatment of Epidermolysis Bullosa During the COVID-19 Pandemic

Anne Lucky, MD

PUBLISHED JULY 16, 2020

Journal of the American Academy of Dermatology

For patients with epidermolysis bullosa (EB), a genetic condition that causes the skin to blister and erode very easily, the COVID-19 pandemic exacerbated physical and emotional challenges. To promote the best outcomes for these patients, a team of international experts outlined how to care for them during the pandemic.

In patients with EB, minor injuries and friction—such as rubbing or scratching—cause blisters to form. Depending on the type of EB, blisters and erosions may form on the skin, but other organ systems are also affected. The disease can range from a minor inconvenience to completely disabling or even fatal.

Due to severe systemic complications, patients with EB are a particularly vulnerable population. In addition to concerns about the effects of COVID-19 on the body, patients and families face fears about how they will be perceived on admission to hospitals. Because patients with severe forms of EB often appear frail and emaciated, health care workers unfamiliar with the condition could underestimate their likelihood of survival—affecting decisions about distribution of ventilators and other limited resources.

By responding to a questionnaire, 44 experts from five continents agreed on appropriate care standards for EB during the pandemic. Modifications include teledermatology rather than in-person visits, testing by local laboratories, and special ICU protocols to protect the skin and airway.

"We hope to share more detail on the protocols our Cincinnati Children's Epidermolysis Bullosa Center has developed, and eventually be able to assess how they affect outcomes for our patients," says co-author Anne Lucky, MD. "We are partnering with specialists as well as the Anderson Center at Cincinnati Children's to continually update our processes and maximize our successes."

RESEARCH & TRAINING DETAILS

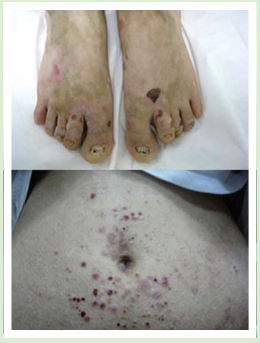
Faculty	3
Total Annual Grant Awards	$74,002
Total Annual Industry Awards	$171,558

Murrell DF, Lucky AW, Salas-Alanis JC, Woodley DT, Palisson F, Natsuga K, Nikolic M, Ramirez-Quizon M, Paller AS, Lara-Corrales I, Barzegar MA, Sprecher E, Has C, Laimer M, Bruckner AL, Bilgic A, Nanda A, Purvis D, Hovnanian A, Murat-Susic S, Bauer J, Kern JS, Bodemer C, Martin LK, Mellerio J, Kowaleski C, Robertson SJ, Bruckner-Tuderman L, Pope E, Marinkovich MP, Tang JY, Su J, Uitto J, Eichenfield LF, Teng J, Aan Koh MJ, Lee SE, Khuu P, Rishel HI, Sommerlund M, Wiss K, Hsu CK, Chiu TW, Martinez AE. Multidisciplinary care of epidermolysis bullosa during the COVID-19 pandemic-Consensus: Recommendations by an international panel of experts. J Am Acad Dermatol. Oct 2020;83(4):1222-1224.

Management of Epidermolysis Bullosa (EB) During COVID-19 Pandemic

MASKS
patient, caregivers, nurses, doctors

Low-risk for internal dz & SCC
EBS, JEB, DDEB



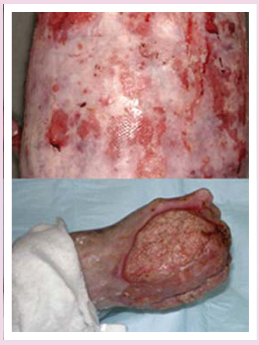
Telehealth-photos, bloods
Level 1 PPE-pt, caregivers

EB Nurses
Not in contact with COVID patients

Newborn with EB

Liaise with local hospital
Keep away from COVID hospitals if possible

High risk of internal dz
RDEB, JEB



Live visits for SCC checks
Transfusions, infusions

Telehealth for planning lx, referrals, management
At home unless procedures needed

Level 1 PPE in hospital
Photography biopsies if suspicious for SCC

If EB patient gets COVID-19
Level 4 PPE: Family can assist dressings care with nasal swabs, BP, dressings Cannulae

Pinpointing ADHD Symptoms in Children with Down Syndrome

Anna Esbensen, PhD

Tanya Froehlich, MD

PUBLISHED MAY 14, 2021

Journal of Developmental and Behavioral Pediatrics

Attention-deficit hyperactivity disorder (ADHD) is the most common neurobehavioral disability, impacting between 6% and 8% of kids in the general population. Yet ADHD may be as high as 20% to 44% among people with Down syndrome (DS). Despite this increased prevalence, diagnosis of ADHD among kids with Down syndrome can pose a true challenge.

"It is difficult to tell if many of the problematic behaviors—such as difficulty focusing, forgetfulness, and avoidance of effortful tasks—are due to intellectual disability or if children with DS also have ADHD," says senior author Tanya Froehlich, MD, director of research, Division of Developmental and Behavioral Pediatrics.

Research led by Froehlich and first author Anna Esbensen, PhD, found several differences in how parents and teachers report potential symptoms of ADHD that varied depending on whether the child had DS.

Parents of kids with DS and ADHD tended to report more distractibility and being "on the go," while teachers tended to report higher inattention and hyperactivity as compared to kids with DS only or typically developing children with ADHD. Some teacher-reported items specifically differentiated DS + ADHD and DS - ADHD, including difficulties following through on tasks, avoiding tasks, leaving one's seat, and excessive talking.

Overall, the reporting variations highlight a need to evaluate across environments when diagnosing for ADHD. More consistent differentiation of symptoms would help clinicians determine which children with DS can benefit from ADHD treatment. Looking ahead, the team is evaluating how children with DS and ADHD respond to methylphenidate, the most common ADHD drug.

RESEARCH & TRAINING DETAILS

Faculty	20
Joint Appointment Faculty	1
Research Fellows & Post Docs	1.5
Research Graduate Students	4
Total Annual Grant Awards	$5.7M

Esbensen AJ, Epstein JN, Vincent LB, Kamimura-Nishimura K, Wiley S, Angkustsiri K, Abbeduto L, Fidler D, Froehlich TE. Comparison of Attention-Deficit Hyperactivity Disorder in Typically Developing Children and Children with Down Syndrome. J Dev Behav Pediatr. May 14 2021.

ADHD Comparison between Children with and without Down Syndrome

	Parent Report				Teacher Report			
	DS + ADHD (n=20)	DS-ADHD (n=59)	TD + ADHD (n=54)	P	DS + ADHD (n=15)	DS-ADHD (n=36)	TD + ADHD (n=43)	P
1. Careless mistake	1.9 (0.3)	1.3 (0.1)[a]	2.4 (0.1)[d]	<0.001	2.3 (0.3)	1.8 (0.1)	1.8 (0.1)	0.230
2. Keeping attention	2.0 (0.2)	1.5 (0.1)[a]	2.5 (0.1)[d]	<0.001	2.4 (0.3)	1.9 (0.1)	2.1 (0.1)	0.186
3. Not listening	1.5 (0.2)	1.1 (0.1)[a]	1.9 (0.1)[d]	<0.001	1.9 (0.3)	1.0 (0.2)	1.3 (0.1)	0.100
4. Follow through	1.2 (0.2)[b]	1.2 (0.1)[a]	2.2 (0.1)[a, b]	<0.001	1.9 (0.3)	1.1 (0.2)[a]	1.6 (0.1)[a]	0.028
5. Organize	1.5 (0.3)	1.5 (0.1)[a]	2.1 (0.1)[d]	0.002	2.4 (0.3)	1.7 (0.2)	1.8 (0.1)	0.219
6. Avoids tasks	1.7 (0.3)	1.7 (0.1)[a]	2.2 (0.1)[d]	0.002	2.4 (0.4)[b]	1.7 (0.2)	1.4 (0.2)[b]	0.022
7. Loses things	1.0 (0.3)[b]	0.8 (0.1)[a]	1.8 (0.1)[a, b]	<0.001	1.2 (0.3)	1.1 (0.2)	1.3 (0.1)	0.710
8. Distracted	2.2 (0.2)[c]	1.3 (0.1)[a, c]	2.4 (0.1)[a]	<0.001	2.6 (0.3)	1.8 (0.2)	2.2 (0.1)	0.109
9. Forgetful	1.2 (0.3)[b]	0.9 (0.1)[a]	2.0 (0.1)[a, b]	<0.001	1.4 (0.4)	1.2 (0.2)	1.6 (0.2)	0.161
10. Fidget	1.5 (0.3)	1.0 (0.1)[a]	1.7 (0.1)[d]	0.006	1.8 (0.4)	1.3 (0.2)	1.3 (0.2)	0.417
11. Leaves seat	1.4 (0.3)	0.8 (0.1)[a]	1.3 (0.1)[d]	0.016	1.8 (0.4)[c]	0.6 (0.2)[c]	1.0 (0.2)	0.039
12. Runs/climbs	0.8 (0.3)	0.5 (0.1)	0.7 (0.1)	0.426	0.9 (0.3)	0.4 (0.1)	0.4 (0.1)	0.266
13. Playing quietly	0.9 (0.3)	0.5 (0.1)	0.8 (0.1)	0.375	0.9 (0.4)	0.6 (0.2)	0.6 (0.2)	0.805
14. On the go	1.4 (0.3)[c]	0.4 (0.1)[a, c]	1.0 (0.1)[d]	0.001	0.9 (0.4)	0.6 (0.2)	1.0 (0.2)	0.357
15. Talks too much	1.3 (0.3)	0.5 (0.1)[a]	1.5 (0.1)[d]	<0.001	1.2 (0.4)	0.6 (0.2)[d]	1.2 (0.2)[d]	0.036
16. Blurts	0.8 (0.3)	0.3 (0.1)[a]	1.4 (0.1)[a]	<0.001	1.1 (0.4)	0.5 (0.2)	1.0 (0.2)	0.098
17. Waiting	1.2 (0.3)	0.8 (0.1)[a]	1.4 (0.1)[a]	0.013	1.6 (0.4)	0.6 (0.2)	1.1 (0.2)	0.056
18. Interrupts	1.2 (0.3)	1.0 (0.1)[a]	1.7 (0.1)[a]	0.001	1.3 (0.4)	0.7 (0.2)	1.0 (0.2)	0.387

[a]Significant group difference between DS – ADHD and TD + ADHD.
[b]Significant group difference between DS + ADHD and TD + ADHD.
[c]Significant group difference between DS + ADHD and DS – ADHD.
ADHD, attention-deficit hyperactivity disorder; DS, Down syndrome; TD, typically developing.

Comparison between children who have DS with and without ADHD, and typically developing (TD) children with ADHD on the Vanderbilt ADHD Diagnostic Parent Rating Scale and Vanderbilt ADHD Diagnostic Teacher Rating Scale.

How Clock Genes Drive Healthy Spinal Formation

Oriana Zinani, PhD

Ertugrul Ozbudak, PhD

PUBLISHED DEC. 23, 2020
Nature

When healthy, vertebrae of developing zebrafish project a regimented, evenly spaced set of spines. This outcome depends heavily on sets of co-expressed genes working in concert, like clocks. Now it appears that achieving balanced outcomes also can require that key clock genes be located in close proximity, not just functioning at the same time, according to research led by first author Oriana Zinani, PhD, and senior author Ertugrul Ozbudak, PhD.

In zebrafish, the team used CRISPR-Cas9 to disrupt a paired gene set known to play a role in spine formation: *her1* and *her7*. They tracked the effects using single-cell transcript counting, real-time imaging, and computational modeling. The transparent embryos of zebrafish made them an ideal model for observing skeletal formation.

Normally, the *her1* and *her7* genes are expressed on the same chromosome. When functional genes are on different homologous chromosomes, the zebrafish became more likely to develop misshaped vertebrae with irregularly protruding spines even though the genes themselves remained functional.

The team found that embryos developing in unusually cold water exhibited similar dysfunctions, suggesting that environmental stresses can interfere with development by scattering closely paired genes. The team also reports that gene pair co-location is a commonly seen process for many paired genes in humans and may be at work in other conditions, such as developmental disorders and some cancers.

"We anticipate gene pairing is similarly advantageous in other systems, and could enable engineering of precise synthetic clocks in embryos and organoids," Ozbudak says.

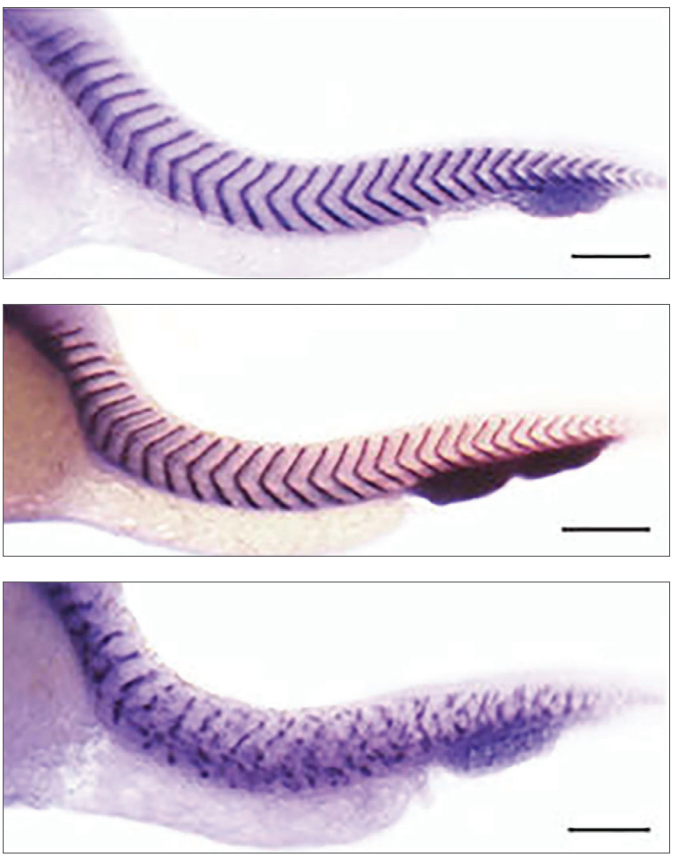
Since publication in *Nature*, the research team also has published a review in *Trends in Genetics*, highlighting widespread gene pairing and clustering of co-expressed genes across organisms. Ozbudak plans to present more findings at an upcoming Gordon Research Conference and Keystone Symposium.

RESEARCH & TRAINING DETAILS

Faculty	22
Joint Appointment Faculty	26
Research Fellows & Post Docs	19
Research Graduate Students	60
Total Annual Grant Awards	$7.7M

Zinani OQH, Keseroglu K, Ay A, Ozbudak EM. Pairing of segmentation clock genes drives robust pattern formation. Nature. Jan 2021;589(7842):431-436.

How Gene Pairing Affects Spine Development



Gene-paired embryos, showing typical vertebrae development and genes *her1* and *her7*, unpaired, showing vertebral variations.

Experts Develop Consensus Definitions for Persistent, Refractory, and Biphasic Anaphylaxis

Timothy Dribin, MD

David Schnadower, MD, MPH

RESEARCH & TRAINING DETAILS

Faculty	46
Joint Appointment Faculty	3
Research Graduate Students	1
Total Annual Grant Awards	$6.4M
Total Annual Industry Awards	$60,000

Dribin TE, Sampson HA, Camargo CA, Jr., Brousseau DC, Spergel JM, Neuman MI, Shaker M, Campbell RL, Michelson KA, Rudders SA, Assa'ad AH, Risma KA, Castells M, Schneider LC, Wang J, Lee J, Mistry RD, Vyles D, Vaughn LM, Schumacher DJ, Witry JK, Viswanathan S, Page EM, Schnadower D. Persistent, refractory, and biphasic anaphylaxis: A multidisciplinary Delphi study. J Allergy Clin Immunol. Nov 2020;146(5):1089-1096.

PUBLISHED AUG. 24, 2020
The Journal of Allergy and Clinical Immunology

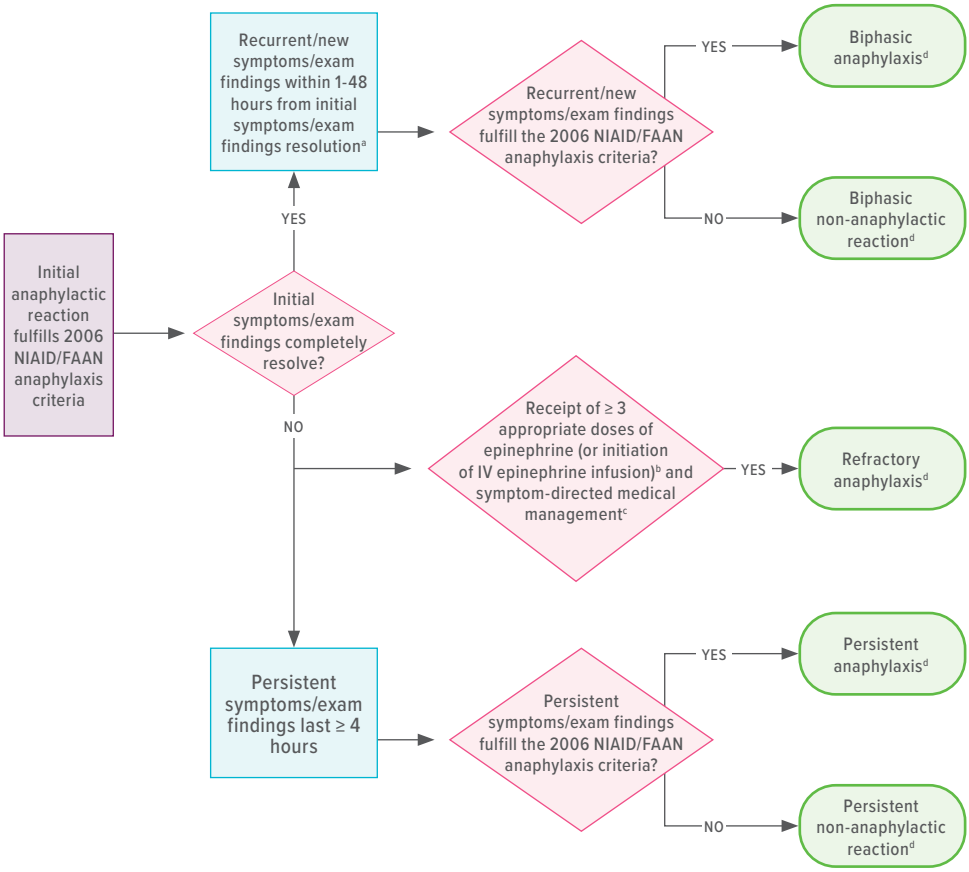
In the past decade, pediatric emergency department visits for anaphylaxis tripled. The clinical courses for patients with anaphylaxis varies—some children experience complete symptom resolution after treatment with epinephrine, while others experience persistent or recurrent symptoms. However, there are no consistent definitions for these outcomes, hindering clinical practice and research efforts.

To address this need, researchers in the divisions of Emergency Medicine and Allergy and Immunology collaborated with national anaphylaxis experts to develop consensus anaphylaxis outcome definitions. Using Delphi methodology—a structured group consensus technique—the 19-member multidisciplinary panel of experts completed online surveys to achieve consensus for the definitions of persistent, refractory, and biphasic anaphylaxis, as well as for persistent and biphasic non-anaphylactic reactions.

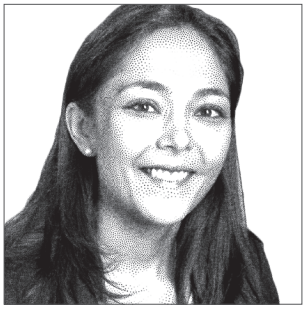
"These definitions will help standardize the language used in clinical care to delineate clinically important anaphylaxis outcomes, as well as provide a foundation for researchers to evaluate the epidemiology of anaphylaxis," says lead author Timothy Dribin, MD. "Ultimately, we hope they will aid in the development of optimal care strategies to reduce the burden of anaphylaxis on patients, families, and the U.S. healthcare system."

Currently, Dribin's research team is applying these definitions in a multi-site retrospective study of over 6,000 children with anaphylaxis to evaluate the incidence and risk factors for persistent, refractory, and biphasic anaphylaxis. The research team also is enrolling a prospective cohort of children with anaphylaxis in the emergency department at Cincinnati Children's.

Algorithm for Applying the Anaphylaxis Outcome Definitions in Clinical Care and Research



Arterial Stiffness and Heart Rate Variability Help Identify Cardiovascular Risk in Youth with Type 2 Diabetes



Amy Shah, MD, MS

Elaine Urbina, MD, MS

PUBLISHED JULY 16, 2020
Journal of Diabetes and its Complications

When a child is diagnosed with type 2 diabetes (T2D), their risk for cardiovascular disease increases; however, some are at higher risk than others. How can providers identify these patients to improve outcomes? A link between two early cardiovascular markers could provide important clues. Research led by first author Amy Shah, MD, MS, Division of Endocrinology, in collaboration with Elaine Urbina, MD, MS, Director of Preventive Cardiology, discovered a relationship between increased artery stiffness and lower heart rate variability (HRV) in patients with T2D, resulting in a worse cardiovascular risk profile.

Using data from the SEARCH for Diabetes in Youth study, researchers examined characteristics of 185 young adults with youth-onset T2D. Cardiovascular risk factors and heart rate variability were compared between those with and without arterial stiffness. The team's findings highlighted distinct differences between the two groups. Participants with T2D and arterial stiffness were more likely to be more overweight, have higher blood pressure, and higher cholesterol. Stiffer arteries were also associated with abnormalities in heart rate variability.

Measurements of the arteries are noninvasive tests that predict future risk for morbidity and mortality in cardiovascular disease. These findings show that arterial stiffness and heart rate variability in youth with T2D are key indicators of risk that could help steer early interventions.

"These findings stress that teens are showing early markers of cardiovascular disease," says lead author Amy Shah, MD, MS. "What we need to do now is understand why some teens with obesity develop T2D, and whether treating blood pressure and cholesterol early and aggressively can prevent future diabetes-related complications."

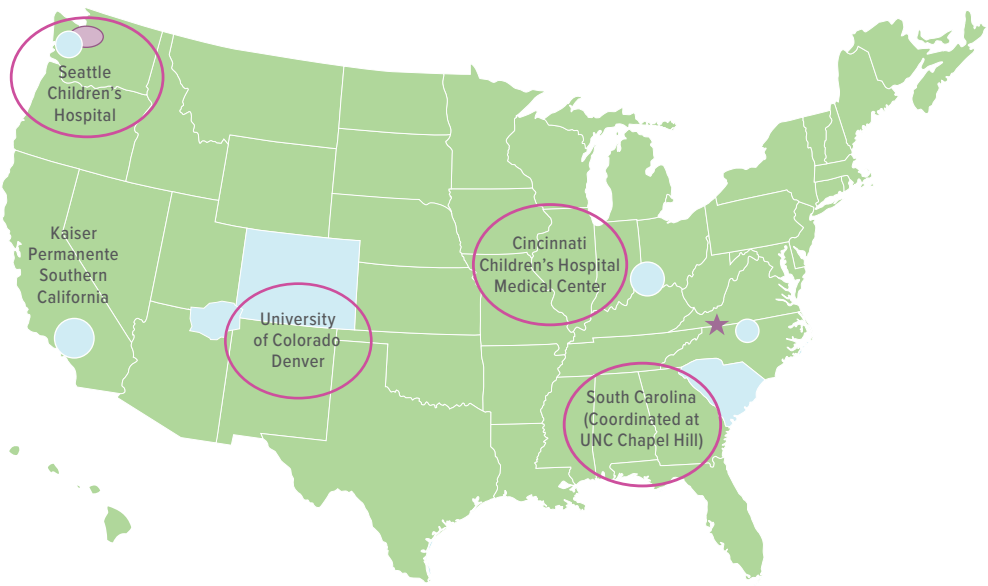
While the SEARCH study has stopped collecting prospective data, researchers will continue utilizing previous data and blood samples collected over 20 years to examine complications of diabetes emerging in young adulthood.

RESEARCH & TRAINING DETAILS

Faculty	18
Joint Appointment Faculty	2
Research Fellows & Post Docs	1
Total Annual Grant Awards	$2.7M
Total Annual Industry Awards	$1,787

Shah AS, Jaiswal M, Dabelea D, Divers J, Isom S, Liese AD, Lawrence JM, Kim G, Urbina EM. Cardiovascular risk and heart rate variability in young adults with type 2 diabetes and arterial stiffness: The SEARCH for Diabetes in Youth Study. J Diabetes Complications. Oct 2020;34(10):107676.

Locations of SEARCH for Diabetes in Youth Study Sites



Co-Parenting Program Improves Outcomes for Low-Income Families

Robert Ammerman, PhD

Judith Van Ginkel, PhD

PUBLISHED JUNE 24, 2021
Journal of Family Psychology

For families living in poverty, home visiting programs provide support in raising young children. While these programs welcome participation by fathers, they primarily target mothers—few involve systematic efforts and curriculum development that works with both parents.

To better reflect the essential role fathers play in raising children, the Every Child Succeeds team developed a clinical trial of Family Foundations, a program that works with both mothers and fathers to support co-parenting. Among this population of families living in poverty, the program was associated with broad improvements in mothers, fathers, and parenting. Participants included 150 low-income mother-father groups during pregnancy or shortly after birth. These groups received Family Foundations Home Visiting, a program consisting of 11 in-home sessions focusing on parental cooperation, collaboration, and conflict management.

Using a novel analytic approach called complier average causal effect (CACE) analysis, researchers determined the benefits of completing at least nine of these sessions—an important factor, as families often struggle to receive the full complement of services. Among these mothers and fathers, the team found lower depression and posttraumatic stress disorder symptoms, improved coping with stress, and decreased psychological aggression in fathers. Both parents showed benefits in parenting their children, including increased levels of affection, engagement with their child, and sensitivity to child needs.

"Currently, there are no programs targeting co-parenting offered in home visiting," says lead author Robert Ammerman, PhD. "Our findings provide support for incorporating Family Foundations to engage fathers, promote co-parenting, and maximize outcomes for parents and children."

Next, the team will complete long-term follow-up studies, develop strategies to promote full program participation, and identify the program's most beneficial elements to create shorter but equally effective interventions.

RESEARCH & TRAINING DETAILS

Faculty	1

Ammerman RT, Peugh JL, Teeters AR, Sakuma KK, Jones DE, Hostetler ML, Van Ginkel JB, Feinberg ME. Promoting parenting in home visiting: A CACE analysis of Family Foundations. J Fam Psychol. Jun 24 2021.

CACE Results for Family Foundations Home Visiting

		Intervention Effect	
		Est. (SE)	Wald's
BDI-II	Mother	-11.41 (4.67)	-2.44*
	Father	-9.73 (2.49)	-3.90**
PCL	Mother	-22.37 (11.80)	-1.90†
	Father	-27.02 (7.84)	-3.45**
PSI-SF:PD‡	Mother	-10.04 (4.65)	-2.16*
	Father	-12.64 (4.34)	-2.91**
PSI-SF: DPCI‡	Mother	2.35 (3.27)	0.72
	Father	-3.87 (3.00)	-1.29
PSI-SF: DC‡	Mother	3.78 (2.47)	1.53
	Father	2.45 (3.08)	0.80
HOME Inventory-Total‡	Mother	-0.88 (2.13)	-0.41
CTS-2: Physical Assault	Mother received	-48.04 (47.49)	-1.01
	Father received	-32.15 (37.20)	-0.86
CTS-2: Psych Aggression	Mother received	-34.60 (15.35)	-3.45**
	Father received	-1.87 (7.35)	-0.25

CACE results for FFHV compilers compared to controls
for parent-report measures (N=150)
*p<.05, **p<.01, *p=.06, ‡Administered at post-intervention only

BDI-II= Beck Depression Inventory II
PCL= Posttraumatic Stress Disorder Checklist
CTS-2= Conflict Tactics Scale-2
PSI-SF:PD= Parenting Stress Index Short-Form-Personal Distress
PSI-SF:PCDI= Parenting Stress Index Short Form-
Parent Child Dysfunctional Interaction
PSI-DIFF= Parenting Stress Index Short Form-Difficult Child

Standard of Care Lifestyle Advice Is Not Enough to Treat Fatty Liver Disease

Stavra Xanthakos, MD

PUBLISHED JULY 23, 2020
Gastroenterology

One in 10 children experience nonalcoholic fatty liver disease (NAFLD). Among young adults with NAFLD, fatty liver during childhood is now the leading predictor of future liver transplant. Adults with NAFLD can experience cirrhosis, end-stage liver disease, and increased cardiovascular morbidity and mortality. Despite NAFLD's commonality, little is understood about outcomes for youth.

In the largest study of its kind, members of the NASH Clinical Research Network compared outcomes of children treated with placebo and standard of care lifestyle advice in two double-blind, randomized clinical trials spanning 10 years. Stavra Xanthakos, MD, director of the Steatohepatitis Center at Cincinnati Children's served as lead author.

The team reported that lifestyle counseling focusing on helping children reach a healthy weight "can reduce severity of NAFLD in some children, but only rarely leads to complete resolution of disease."

The study examined biopsies from 122 children with NAFLD, finding that half showed improvement of some histological features. However, only three (2.4%) of the children completely resolved their fatty liver disease. About a third of participants experienced worsening disease severity despite counseling—including a high incidence of type-2 diabetes. Many experienced weight gain.

"This highlights the need to develop effective pharmacological therapies for NAFLD in children," notes Xanthakos.

Nonalcoholic steatohepatitis (NASH) is a form of NAFLD that involves liver inflammation and damage in addition to excess liver fat. Although NASH progression is usually asymptomatic, this study details clinical NAFLD factors that also can increase risk of NASH progression, including worsening obesity, glycemic status, and rising levels of alanine aminotransferase and gammaglutamyl transferase.

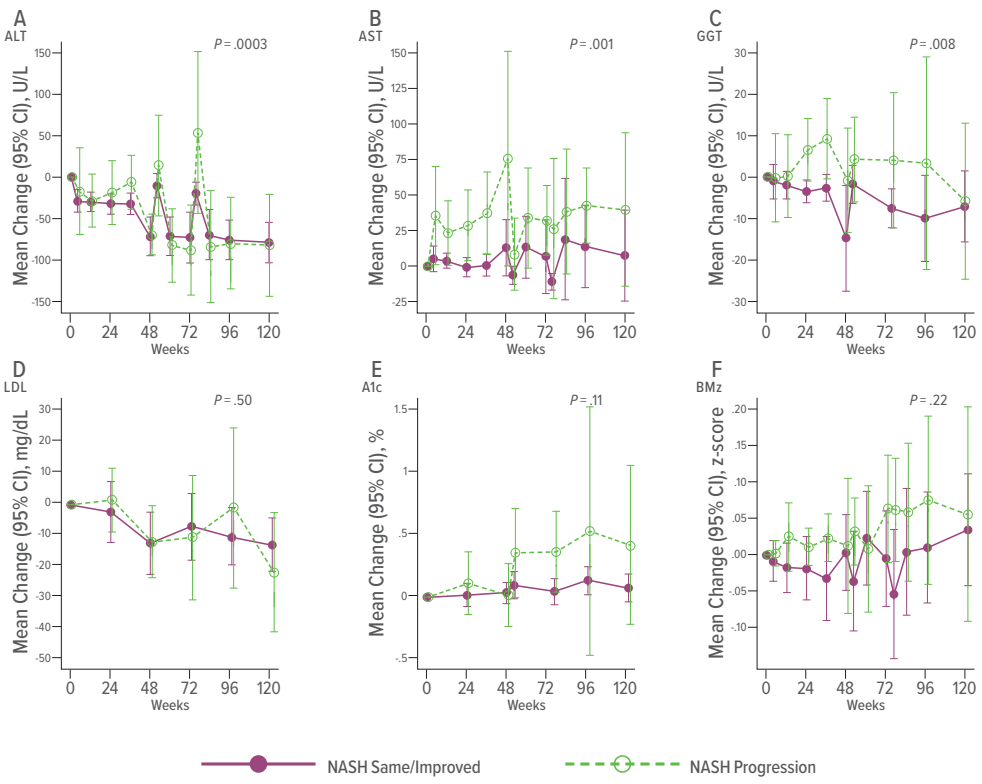
Looking ahead, the NASH Clinical Research Network plans to continue tracking children with NAFLD into their late teens and twenties.

RESEARCH & TRAINING DETAILS

Faculty	49
Joint Appointment Faculty	2
Research Fellows & Post Docs	14
Research Graduate Students	1
Total Annual Grant Awards	$9.M
Total Annual Industry Awards	$512,603

Xanthakos SA, Lavine JE, Yates KP, Schwimmer JB, Molleston JP, Rosenthal P, Murray KF, Vos MB, Jain AK, Scheimann AO, Miloh T, Fishbein M, Behling CA, Brunt EM, Sanyal AJ, Tonascia J, Network NCR. Progression of Fatty Liver Disease in Children Receiving Standard of Care Lifestyle Advice. Gastroenterology. Nov 2020;159(5):1731-1751 e1710.

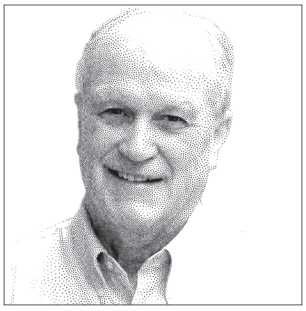
How Lifestyle Advice Affected Risk Factors for NASH



Panels show how various risk factor measures changed over time following standard fo care lifestyle advice. The factors measured were: (A) alanine transaminase (ALT), (B) aspartate aminotransferase (AST), (C) gamma-glutamyl tansferase (GGT), (D) LDL cholesterol (E) hemoglobin A1C and (F) BMI z-score. Averaged scores among those with same/improved NASH progression are denoted by black solid lines. Scores for those with NASH progression appear as dashed lines.

Early Reading Programs Improve Kindergarten Readiness

Greg Szumlas, MD



Thomas DeWitt, MD

PUBLISHED MAY 24, 2021
Pediatrics

By pairing literacy anticipatory guidance at clinic visits with more books in the home, two early reading programs have positive effects on preschool students entering kindergarten.

In the Reach Out and Read program, children receive a new book and guidance about reading at home during well-visits from newborn through age 5. Dolly Parton's Imagination Library mails new books to a child's home once a month from birth through age 5.

Researchers at Cincinnati Children's developed a unique combination of these two programs. With the participation of 23 health clinics throughout Cincinnati, the team enrolled over 3,200 children in the combined program. They analyzed the results of the kindergarten readiness assessment (KRA) literacy subtest of a sample of program participants over the course of three school years and compared them to the school district average.

Between the 2016-17 and 2018-19 school years, participants showed an increase of 15.4 percentage points, while the school district average increased by only 3.8 percent during this same time period.

"With this early study, we suggest that when combined and sustained, these two programs have the potential for effectively supporting the development of preliteracy skills of large populations of at-risk children, improving kindergarten readiness and, ultimately, success in school and life," says lead author Greg Szumlas, MD.

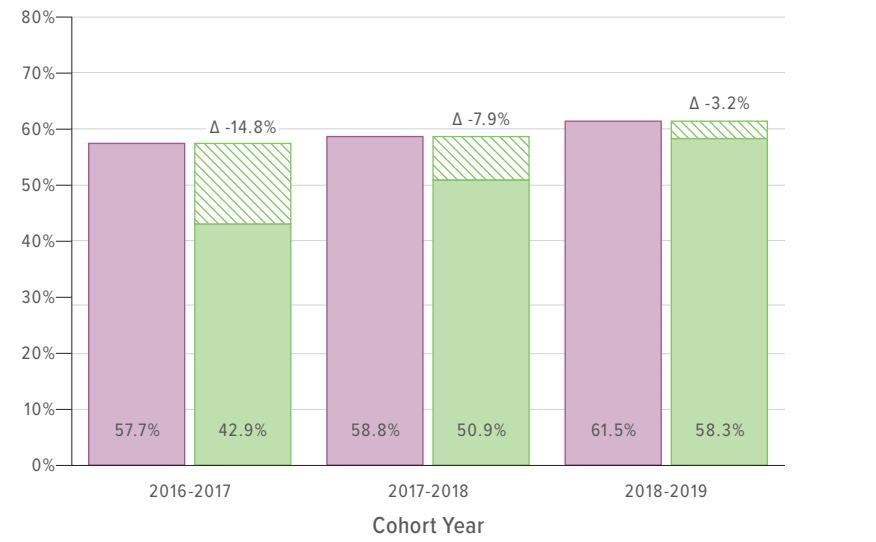
By including literacy promotion as a routine part of primary care, this study highlights the important role pediatric health care providers can play in kindergarten readiness. Cincinnati Children's and other health centers in Greater Cincinnati continue enrolling children in Reach Out and Read and Dolly Parton's Imagination Library.

RESEARCH & TRAINING DETAILS

Faculty	29
Joint Appointment Faculty	2
Research Fellows & Post Docs	4
Total Annual Grant Awards	$3.4M

Szumlas GA, Petronio P, Mitchell MJ, Johnson AJ, Henry TR, DeWitt TG. A Combined Reach Out and Read and Imagination Library Program on Kindergarten Readiness. Pediatrics. Jun 2021;147(6).

Literacy Program Participation and Kindergarten Readiness



Percentage of Reach Out and Read (ROR)/Dolly Parton's Imagination Library (DPIL) participants on-track in kindergarten readiness assessment (KRA) literacy versus Cincinnati Public Schools (CPS) district comparison. Note: District results do not exclude ROR/DPIL participants. District samples sizes for years 2016–2017, 2017–2018, and 2018–2019 were 2690, 2659, and 2718, respectively.

ABCs of Stroke Prevention Improve Outcomes for Children Using VADs

Chet Villa, MD

Angela Lorts, MD, MBA

PUBLISHED DEC. 15, 2020

Circulation: Cardiovascular Quality and Outcomes

More than 9,500 children a year are admitted to U.S. hospitals each year to treat heart failure. While pediatric ventricular assist devices (VADs) improve outcomes for many, up to 29% of patients still experience strokes as a dangerous complication of device implantation.

In 2017, Cincinnati Children's convened a group of cardiac care experts and families to form the ACTION (Advanced Cardiac Therapies Improving Outcomes Network) learning network to improve heart failure outcomes. In this study, the group dove into the factors driving stroke complications.

Before the project, anticoagulant use with paracorporeal devices was inconsistent, including use of bivalirudin, a drug with a favorable profile for use in children. But adoption of the "ABCs of Stroke Prevention" protocol (anticoagulation management, blood pressure management, and communication) resulted in sharp increases in use of the drug.

The project also improved consistency of blood pressure assessment and control as care teams worked to implement a stroke prevention checklist.

For the 86 patients involved in the updated protocol, stroke incidence was reduced to 14%. Since the work began, the number of heart centers adopting the ABCs of Stroke Prevention has grown from 20 to 44.

The stroke prevention report was compiled primarily by first author Chet Villa, MD, and senior author Angela Lorts, MD, MBA. The 30+ ACTION investigators listed as co-authors also included Cincinnati Children's experts David L.S. Morales, MD, Farhan Zafar, MBBS, Paige Krack, MBA, Lauren Smyth, MHA, and Katrina Fields, BSN, RN.

"Given the combination of low patient volumes and high complexity for this form of care, forming the ACTION network was vital to achieving collaborations with a broad range of stakeholders, including patients, families, industry regulators and clinicians of varying backgrounds such as physicians, surgeons, nurses, and care coordinators," Lorts says.

RESEARCH & TRAINING DETAILS

Faculty	53
Joint Appointment Faculty	4
Total Annual Grant Awards	$7.2M
Total Annual Industry Awards	$724,498

Villa CR, VanderPluym CJ, Investigators* A. ABCs of Stroke Prevention: Improving Stroke Outcomes in Children Supported With a Ventricular Assist Device in a Quality Improvement Network. Circ Cardiovasc Qual Outcomes. Dec 2020;13(12):e006663.

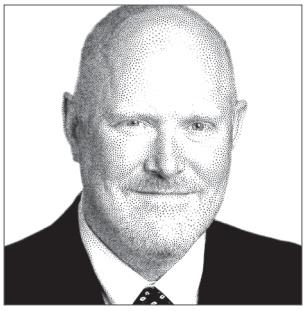
Frequency of Strokes and Strokes per Support Day Stratified by Device Type Among Patients in the ACTION Outcome Registry Database

Total number of patients implanted	Number of patients experiencing a stroke	Total device days	Stroke/Pt (%)	Stroke event/100 device days
All devices (n=86)	12	5597	14	0.23
CentriMag (n=17)	5	498	29	1.20
Berlin heart EXCOR (n=33)	4	2822	12	0.14
PediMag (n=10)	2	232	20	0.86
Rotaflow (n=3)	1	71	33	1.41
HeartWare HVAD (n=11)	0	523	0	n/a
HeartMate 3 (n=22)	0	1411	0	n/a
SynCardia TAH (n=2)	0	48	0	n/a

ACTION: Advanced Cardiac Therapies Improving Outcomes Network
TAH: total artificial heart

Externally Supported Ross Procedures Demonstrate 'Excellent' Results

Kyle Riggs, MD



James Tweddell, MD

PUBLISHED FALL 2020

Seminars in Thoracic and Cardiovascular Surgery

When children are born with aortic valve defects, many receive a Ross Procedure (usually in their teen years) to repair this potentially life-threatening condition. Dating back to 1967, this procedure involves using a child's own pulmonary valve to replace their damaged aortic valve, then replacing the pulmonary valve with donor tissue.

For children and young adults, this procedure remains the ideal option for aortic valve replacement because it provides better blood flow, poses fewer infection risks, and avoids blood clotting that can occur with mechanical and prosthetic valves. However, the procedure has long come with concerns that the re-located pulmonary valve might be too weak to withstand the pressures that the aortic valve experiences.

James Tweddell, MD, Director of Cardiothoracic Surgery at Cincinnati Children's Heart Institute, is widely credited with developing an external support technique that improves the success of the procedure. The technique involves grafting a Dacron tube around the replacement valve for enhanced support. Now, a "mid-term" study led by first author Kyle Riggs, MD, evaluates outcomes for 40 patients treated from 2005 to 2018 with Tweddell's technique.

"We have shown that, at intermediate follow-up, patients who underwent a supported Ross technique were less likely to have neoaortic root dilatation. At last follow-up, 39 patients had mild or less aortic regurgitation with median sinus z-score of 1.40," Tweddell says.

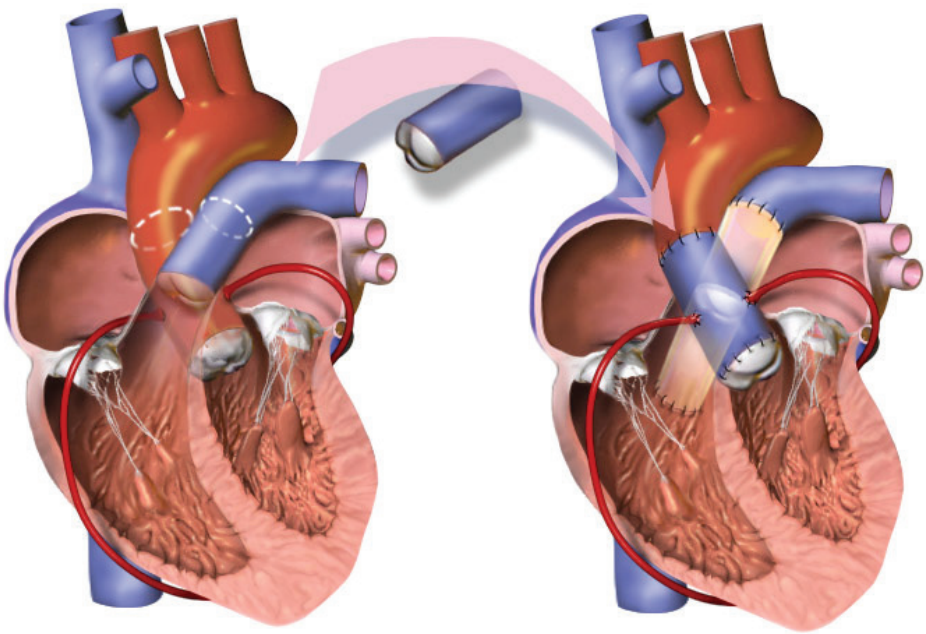
Median follow-up lasted 3.5 years, with three patients followed for more than a decade. All of the patients had survived. While five patients needed a reintervention, only one involved the aortic valve.

RESEARCH & TRAINING DETAILS

Faculty	7
Total Annual Grant Awards	$564,613
Total Annual Industry Awards	$194,665

Riggs KW, Colohan DB, Beacher DR, Alsaied T, Powell S, Moore RA, Ginde S, Tweddell JS. Mid-term Outcomes of the Supported Ross Procedure in Children, Teenagers, and Young Adults. Semin Thorac Cardiovasc Surg. Autumn 2020;32(3):498-504.

Ross Procedure



This illustration depicts the basic steps of the Ross Procedure to correct for aortic valve defects. (Source: Bruce Blaus Blausen.com staff (2014). "Medical gallery of Blausen Medical 2014". WikiJournal of Medicine 1)

Early-Life Heart Muscle and Nerve Development Depends Upon Special Set of Cells

Luis Hortells, PhD

Katherine Yutzey, PhD

PUBLISHED AUG. 17, 2020
PNAS

A research team at Cincinnati Children's has shed new light on the mechanisms at work as mammalian heart muscle loses the ability to regenerate, a discovery that may someday help scientists find effective ways to prompt damaged hearts to heal themselves.

In a study led by first author Luis Hortells, PhD, and senior author Katherine Yutzey, PhD, the team found that postnatal cardiac fibroblasts include a transient population of highly proliferative cells carrying the gene Periostin (Postn+). This population is required for cardiac nerve development and cardiomyocyte maturation soon after birth.

However, these Postn+ cells largely vanish during the first month after birth. After that, heart development shifts from hyperplasic to hypertrophic growth, and nerve development patterns change. By adulthood, the mature heart becomes largely unable to regenerate new muscle cells to replace damaged ones.

Discovering a specialized population of cells within developing heart tissue was made possible through single-cell analysis techniques that helped the team tease out new details about gene expression and cell function, including new information about crosstalk between fibroblasts, neurons and glial cells.

In adult hearts, some Postn+ cells reactivate to form post-injury scar tissue. But during the postnatal period, Postn+ cells display higher levels of expression of *Egf*, *Igf2*, and neuron growth-related genes.

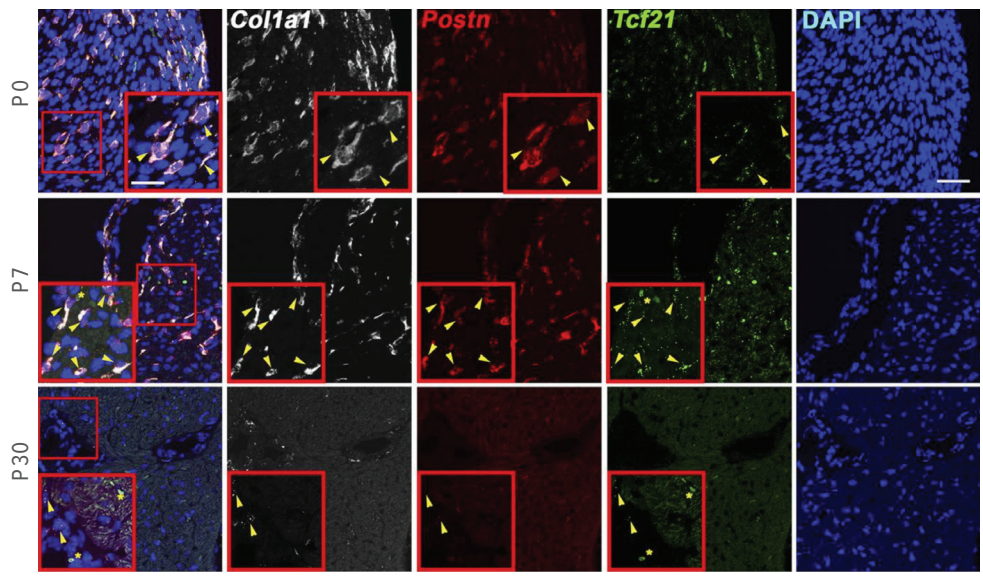
Co-authors from Cincinnati Children's also included Iñigo Valiente-Alandi, Zachary Thomas, Emma Agnew, Dan Schnell, Allen York, Ronald Vagnozzi, Evan Meyer, and Jeffery Molkentin.

RESEARCH & TRAINING DETAILS

Faculty	11
Research Fellows & Post Docs	17
Research Graduate Students	3
Total Annual Grant Awards	$8.1M
Total Annual Industry Awards	$492,045

Hortells L, Valiente-Alandi I, Thomas ZM, Agnew EJ, Schnell DJ, York AJ, Vagnozzi RJ, Meyer EC, Molkentin JD, Yutzey KE. A specialized population of Periostin-expressing cardiac fibroblasts contributes to postnatal cardiomyocyte maturation and innervation. Proc Natl Acad Sci U S A. Sep 1 2020;117(35):21469-21479.

Postn+ Cardiac Fibroblasts in the Postnatal Heart



These rows depict RNAscope measurements of cells expressing *Col1a1*, *Postn*, and *Tcf21* at 0, 7, and 30 days after birth in mice. Yellow arrowheads show positive colocalization of *Postn*, *Tcf21*, and *Col1* confirming the fibroblast identity of these cells.

Study Explores Why Post-Discharge Home Nurse Visits Led to Increased Health Care Reutilization

Sarah Riddle, MD

Katherine Auger, MD

PUBLISHED SEPTEMBER 2020
Journal of Hospital Medicine

The intent of sending nurses on home visits after children are discharged from the hospital was to reduce the need for re-admissions. But to the surprise of researchers tracking the Hospital to Home Outcomes (H2O) clinical trial, follow-up home nursing visits actually increased return visits to the hospital. To better understand this outcome, a research team led by Sarah Riddle, MD, Katherine Auger, MD, and colleagues in the Divisions of Hospital Medicine, Patient Services, and General and Community Pediatrics, developed a qualitative study of key stakeholders in the H2O trial. Their findings shed light on why patients receiving nurse home visits were more likely to return to the emergency room, urgent care, or be readmitted to the hospital.

Researchers began by conducting focus groups and interviews with parents, primary care physicians, hospital medicine physicians, and home care registered nurses (RNs) involved in the trial. Next, a multidisciplinary team coded and analyzed the transcripts using an inductive, iterative approach to identify major and minor themes.

Several themes emerged. Informing families about "red flags" may have made families hypervigilant and more likely to seek further care, whether clinically indicated or not. Nurses also may have had a low threshold for escalating care, and their affiliation with the hospital made them more likely to direct families there instead of to a primary care physician.

Recommendations for improving the intervention included better communication between physician and nursing groups, individualization of home visits to specific patient needs, and providing more detailed context for "red flags."

"Next, we aim to develop and optimize interventions to improve the transition from hospital to home for children with medical complexity and their families," says lead author Sarah Riddle, MD. "We are also working with families to adapt a patient-reported outcome measure of transition effectiveness for further study in a randomized controlled trial."

RESEARCH & TRAINING DETAILS

Faculty	54
Joint Appointment Faculty	7
Total Annual Grant Awards	$906,436

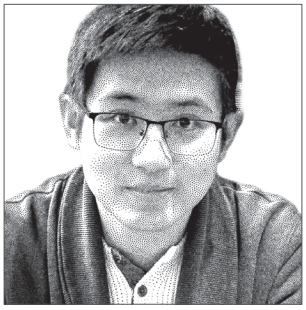
Riddle SW, Sherman SN, Moore MJ, Loechtenfeldt AM, Tubbs-Cooley HL, Gold JM, Wade-Murphy S, Beck AF, Statile AM, Shah SS, Simmons JM, Auger KA, group HOs. A Qualitative Study of Increased Pediatric Reutilization After a Postdischarge Home Nurse Visit. J Hosp Med. Sep 2020;15(9):518-525.

Reasons for Hospital Returns and Suggested Improvements

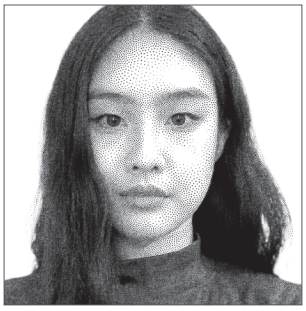
	Parents	Hospital Medicine Physicians	Primary Care Physicians	Home Health Care Nurses
Goal 1: Explanation of Reutilization Rates				
Major Themes				
Appropriation of patient reutilization	✓	✓		✓
Impact of red flags on family's reutilization decisions	✓	✓		✓
Hospital-affiliated RNs "directing traffic" back to hospital		✓	✓	
Home visit RNs had a low threshold for escalating care	✓		✓	
Minor Themes				
Families receiving visit might perceive that their child was sicker			✓	✓
Patients in the control group did not reutilize enough			✓	✓
Receiving more education drives reutilization				✓
Provider access issues				✓
Variability of RN experiences may determine whether escalated care				✓
Goal 2: Suggestions for Improving the Intervention				
Major Themes				
Need for improved post-discharge communication	✓	✓	✓	✓
Individualizing home visits — one size does not fit all	✓	✓	✓	✓
Providing context and framing of red flags			✓	✓
Minor Themes				
Streamlining discharge				✓
Improving the definition of the scope and goal of intervention		✓		
Extending inpatient team expertise post-discharge		✓		

This table shows the summary of major and minor themes by stakeholder type.

FinaleDB: New Tool Supports Developing 'Liquid Biopsies' Based on Cell-Free DNA Fragmentation



Haizi Zheng, PhD



Michelle Zhu

PUBLISHED DEC. 1, 2020
Bioinformatics

Researchers have been intrigued for several years by the potential for circulating cell-free DNA (cfDNA) in blood or urine as a potentially sensitive biomarker for diagnosing cancer and other diseases. In theory, having a blood test this powerful could replace the need for repeated invasive biopsies to track disease progression and adjust treatments.

However, the paperwork involved in gaining access to this detailed level of genomic data has made the concept excessively time-consuming. Meanwhile, differing data gathering methods have complicated the effort of consolidating existing public data sets.

Now a team of scientists at Cincinnati Children's, led by first authors Haizi Zheng, PhD, and Michelle Zhu, and senior author Yaping Liu, PhD, reports developing a database and analytic tool called FinaleDB that hosts thousands of uniformly processed and curated de-identified cfDNA whole-genome sequencing datasets across different pathological conditions.

FinaleDB also includes a sophisticated fragmentation genome browser, which allows users to integrate other 'omics data in different cell types to gain a comprehensive view of both the gene-regulatory landscape and of cfDNA fragmentation patterns.

Previously, accessing this level of data required special application processes, sometimes including data transfer agreements that can take months for organizations to arrange. This tool replaces that chore with de-indentified data from more than 2,500 paired-end cfDNA datasets across 23 different conditions, Liu says. Conditions include breast, liver, kidney, pancreatic, ovarian, colorectal, and gastric cancers as well as lupus, inflammatory bowel disease and cirrhosis.

This work was supported by a Cincinnati Children's start-up grant and Trustee Award to Liu. Producing the database also involved using the Extreme Science and Engineering Discovery Environment (XSEDE) at the Pittsburgh Supercomputing Center.

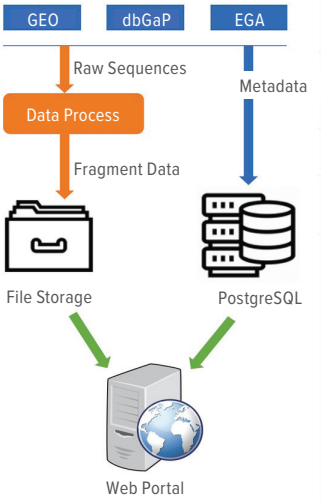
RESEARCH & TRAINING DETAILS

Faculty	28
Joint Appointment Faculty	5
Research Fellows & Post Docs	14
Research Graduate Students	4
Total Annual Grant Awards	$5.1M
Total Annual Industry Awards	$890,013

Zheng H, Zhu MS, Liu Y. FinaleDB: a browser and database of cell-free DNA fragmentation patterns. Bioinformatics. Dec 1 2020.

FinaleDB System Design

A



A. This graphic illustrates the overall system design of FinaleDB.

B. An example of the Web portal and cfDNA fragmentation browser.

Learn more about the new database at http://finaledb.research.cchmc.org.

B

Tissue Healing in the Gut Depends on Help from Friendly Bacteria

Shu-en Wu, PhD

Seika Hashimoto-Hill, DVM, PhD

PUBLISHED JULY 30, 2020
Nature

The "good" bacteria living in our guts do much more than help us digest food and build up our immune systems. Some also play vital roles in helping heal damaged intestinal tissues.

This study, led by co-first authors Shu-en Wu, PhD, and Seika Hashimoto-Hill, DVM, PhD, and corresponding author Theresa Alenghat, VMD, PhD, suggests potential new methods to repair tissue damage among people suffering from inflammatory bowel diseases. Longer term, the study opens doors to a wide range of ways to improve health by controlling the balance of bacteria living inside us.

Specifically, this study details how two opposing forces from bacteria in the gut both act on the epigenetic HDAC3: butyrate, a short chain fatty acid widely sold as a dietary supplement, and inositol phosphate 3 (IP3), a metabolite generated when bacteria break down phytates common in soybeans, nuts and other plant-based foods. In cells lining the intestine, butyrate tends to tamp down HDAC3 activity while IP3 boosts it.

Scientists have detected a number of yin-yang forces at work within our cells, but the twist in this case is that IP3 can come from bacteria, not just our own cells. In mice that had human-like intestinal inflammation, the research team found that IP3 helped damaged tissue heal. When there was not enough IP3, HDAC3 activity and tissue recovery were both impaired.

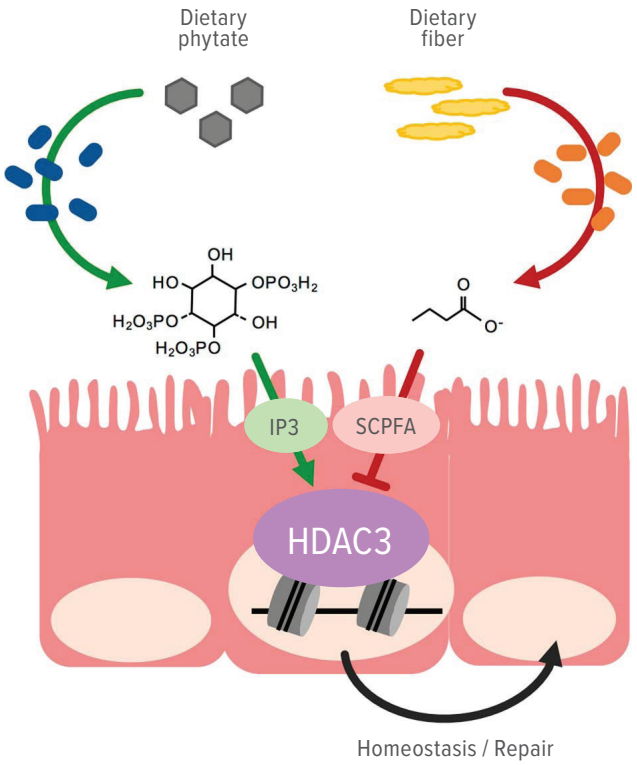
"This finding is surprising in part because it illustrates how sensitive our health is to constant interactions with organisms that normally live in our bodies. If we can influence these interactions, we may be able to control many diseases that are impacted by our microbiome or diet," Alenghat says.

RESEARCH & TRAINING DETAILS

Faculty	13
Joint Appointment Faculty	3
Research Fellows & Post Docs	17
Research Graduate Students	26
Total Annual Grant Awards	$14M

Wu SE, Hashimoto-Hill S, Woo V, Eshleman EM, Whitt J, Engleman L, Karns R, Denson LA, Haslam DB, Alenghat T. Microbiota-derived metabolite promotes HDAC3 activity in the gut. Nature. Oct 2020;586(7827):108-112.

How Intestinal HDAC3 Senses Microbiota-Derived Metabolites



Epithelial HDAC3 functions as a central hub for opposing signals generated by microbiota through metabolism of dietary fibres and phytate, which helps modulate enzymatic activity and intestinal epithelial homeostasis/repair.

Senior author Theresa Alenghat, VMD, PhD

Pfizer-BioNTech COVID-19 Vaccine Safe and Effective for Adolescents

Robert Frenck MD

PUBLISHED MAY 27, 2021
New England Journal of Medicine

It was the news that pediatricians worldwide were waiting for: The Pfizer-BioNTech vaccine BNT162b2 not only showed a favorable safety and side-effect profile, the observed efficacy in a clinical trial setting was 100% among participating teens aged 12 through 15.

Robert Frenck, MD, was lead author for the pivotal study, which supplied the data needed for the U.S. Food and Drug Administration to grant emergency use authorization (EUA) for the first vaccine for use below age 16 in the United States. Frenck was one of more than 20 key co-authors from the C4591001 Clinical Trial Group that had been evaluating the vaccine.

BNT162b2 received its initial EUA for adult use on Dec. 11, 2020. The FDA granted the EUA for ages 12 and up on May 10, 2021, acting on the data even before the full findings were published.

Overall, 2,260 teens participated; with 1,131 receiving BNT162b2, and 1,129 receiving placebo. Headache and fatigue were the most frequently reported systemic events. Severe adverse events were reported in 0.6% of vaccine recipients in the 12 to 15 age group vs. 1.7% among those 16 to 25.

This paper, one of several published as scientists tested various vaccines across age groups, generated hundreds of news articles and more than 9,000 Twitter messages from people with a combined following of nearly 20 million people.

Frenck gave numerous interviews as parents asked questions about the vaccine. He stressed that no corners were cut on safety even though results from the clinical trial were rapidly gathered and communicated. Availability of the vaccine to most junior and senior high students (in addition to adult staff) helped officials re-open nearly all U.S. schools for in-person learning in fall 2021.

RESEARCH & TRAINING DETAILS

Faculty	22
Joint Appointment Faculty	2
Research Fellows & Post Docs	5
Research Graduate Students	9
Total Annual Grant Awards	$33.2M
Total Annual Industry Awards	$141,465

Frenck RW, Jr., Klein NP, Kitchin N, Gurtman A, Absalon J, Lockhart S, Perez JL, Walter EB, Senders S, Bailey R, Swanson KA, Ma H, Xu X, Koury K, Kalina WV, Cooper D, Jennings T, Brandon DM, Thomas SJ, Tureci O, Tresnan DB, Mather S, Dormitzer PR, Sahin U, Jansen KU, Gruber WC, Group CCT. Safety, Immunogenicity, and Efficacy of the BNT162b2 Covid-19 Vaccine in Adolescents. N Engl J Med. Jul 15 2021;385(3):239-250.

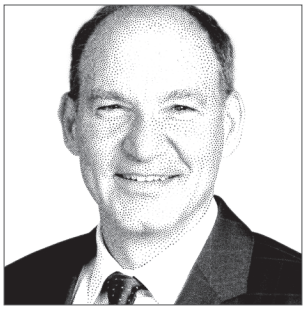
Vaccine Efficacy against Covid-19 in Participants 12 to 15 Years of Age

Efficacy End Point	BNT162b2 No. of Participants with Event/Total No.	Placebo No. of Participants with Event/Total No.	% Vaccine Efficacy (95%CI)
Covid-19 occurrence at least 7 days after dose 2 in participants without evidence of previous infection	0/1005	16/978	100 (75.3–100)
Covid-19 occurrence at least 7 days after dose 2 in participants with or without evidence of previous infection	0/1119	18/1110	100 (78.1–100)

While some teens receiving placebo in the clinical trial went on to test positive for COVID-19, none of those who received the vaccine tested positive during the study period.

Building a COVID-19 Regional Learning System from the Bottom Up

Andrew Beck, MD, MPH



Peter Margolis, MD, PhD

PUBLISHED FEB. 16, 2021
Mayo Clinic Proceedings

The sudden explosion of COVID-19 cases in the United States required nearly every healthcare organization in the country to adapt and respond to the worst public health crisis since the 1918 influenza pandemic. In the Cincinnati region, which spans 14 counties in three states, that meant building an effective response team from the leaders of 22 otherwise highly competitive hospitals, 17 local health departments, and numerous school districts, chambers of commerce, senior services, jails, shelters and other organizations. It was exactly the kind of challenge that the experts of the James M. Anderson Center for Health Systems Excellence were assembled to address.

"Although response plans existed across jurisdictions and institutions, they were insufficiently linked," says first author Andrew Beck, MD, MPH. "We quickly saw a need to use design and change management strategies and a network organizational model to organize a learning health system 'team of teams.' "

The teams co-designed responses to address hospital surge capacity and shortages of personal protective equipment. They supported shared funding for special projects, a centralized communications approach, and a regionwide data dashboard. Then they kept learning and adjusting.

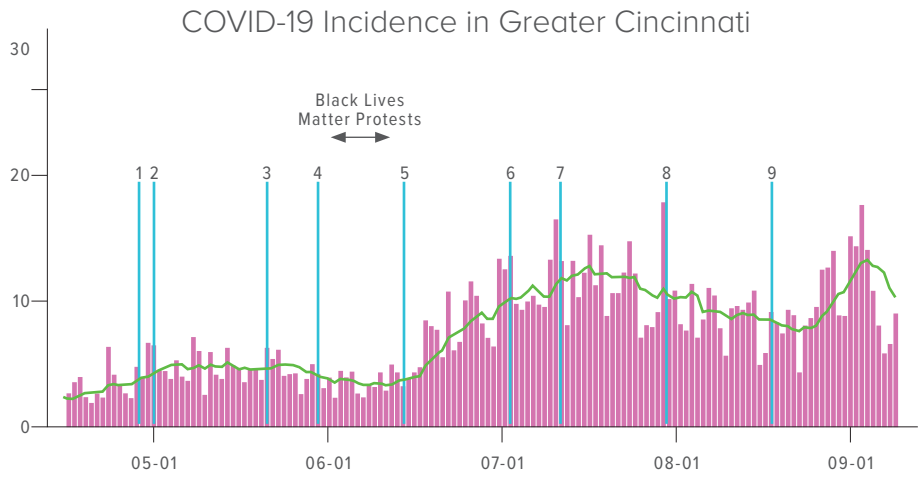
"What was appropriate on day 1 was not on day 30," says Peter Margolis, MD, PhD, Co-Director of the Anderson Center. "We employed structured improvement methods to rapidly address emerging questions such as how to establish outdoor testing sites in cold weather, where to locate sites to optimize equitable access, and how to communicate to diverse populations." The region's COVID-19 Multi-Agency Coalition ultimately navigated pandemic response throughout a highly politically charged environment with a structure that could have lasting ramifications.

"There is now an opportunity to build better national infrastructure by learning from hundreds of small-scale responses like ours," Margolis says.

RESEARCH & TRAINING DETAILS

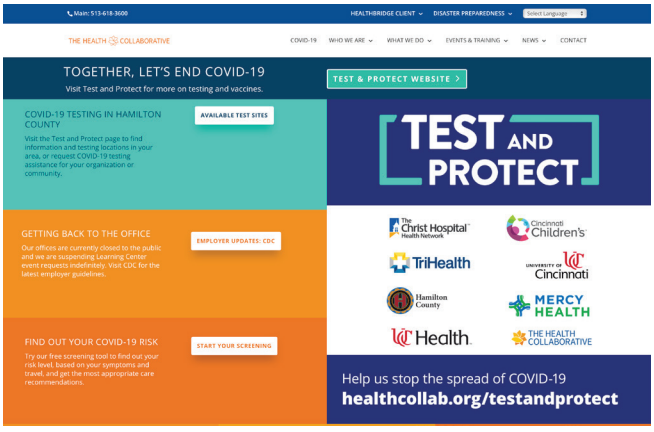
Faculty	9
Joint Appointment Faculty	27
Total Annual Grant Awards	$3M

Beck AF, Hartley DM, Kahn RS, Taylor SC, Bishop E, Rich K, Saeed MS, Schuler CL, Seid M, Cronin SC, Raney L, Zafar MA, Margolis PA. Rapid, Bottom-Up Design of a Regional Learning Health System in Response to COVID-19. Mayo Clin Proc. Apr 2021;96(4):849-855.



1. 04/30: Regional Multi-Agency Coalition (MAC) convened
2. 05/1: Reopening begins with healthcare systems
3. 05/21: Indoor dining at restaurants and bars permitted
4. 05/29-6/10: Protests for racial justice
5. 06/10: Entertainment venues opened
6. 07/2: "Masks on" campaign launch
7. 07/8: Mask mandatory in public places
8. 07/30: Hamilton county testing initiative approved
9. 08/15: Local universities and schools begin reopening

Annotated chart depicting daily case incidence, measured per 100,000 population, with a 7-day moving average. Light blue lines indicate mitigation-oriented interventions. Dark blue lines indicate background changes likely influencing viral transmission.



Developmental Delays May Present at Later Ages Following Abusive Head Trauma in Infants

Kathi Makoroff, MD

PUBLISHED JULY 30, 2020
Child Abuse & Neglect

When pediatric patients experience abusive head trauma, short- and long-term outcomes will be different for every child. Understanding these outcomes and their potential predictors could help patients receive the care they need.

For many years, researchers in the Mayerson Center for Safe and Healthy Children have been following patients in a clinic dedicated to post-injury care for abusive head trauma. Now, they are using these data to assess developmental outcomes.

Participants included infants who were admitted to a large pediatric hospital with abusive head trauma over a seven-year period. Researchers divided these patients into mild, moderate, and severe injury groups based on time spent in intensive care.

Using the Mullen Scales of Early Learning, researchers assessed patients' development at approximately six-month intervals up to 3 years of age—an average of 19 months post-injury. Around age 2, the team also assessed behavior and quality of life using the Child Behavior Checklist and PedsQL™.

Researchers found that overall cognitive development, fine motor function, and expressive language declined with age up to three years, even beyond initial assessments. Patients with at least moderate injury severity also displayed greater internalizing behaviors when compared to the mild group.

"These results show that long term follow-up of all patients following abusive head trauma is important and recommended, even if the patient is initially meeting all developmental milestones," says corresponding author Kathi Makoroff, MD.

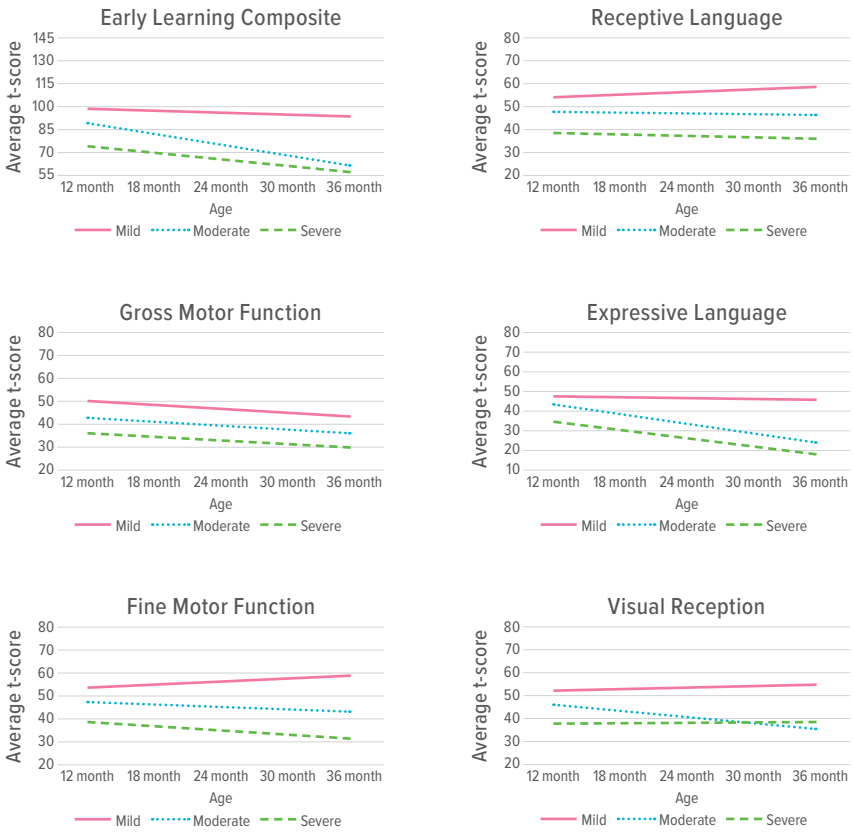
Researchers will continue to follow this patient population to assess longer-term outcomes.

RESEARCH & TRAINING DETAILS

Faculty	3
Joint Appointment Faculty	4
Total Annual Grant Awards	$355,553

Eismann EA, Theuerling J, Cassedy A, Curry PA, Colliers T, Makoroff KL. Early developmental, behavioral, and quality of life outcomes following abusive head trauma in infants. Child Abuse Negl. Oct 2020;108:104643.

Early Learning Scores After Abusive Head Trauma

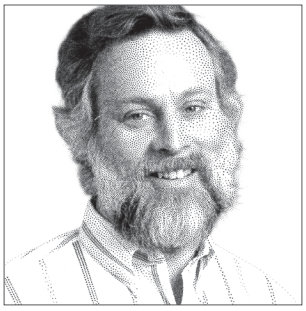


Change with age in Mullen Scales of Early Learning Scores based on injury among children following abusive trauma up to 3 years of age (n=47).

This figure demonstrates the different domains tested by a standardized developmental assessment and shows the change in development over time for patients who have been diagnosed with abusive head trauma.

First Comprehensive Atlas of Acute Kidney Injury at the Cellular Level

Valeriia Rudomanova, MD, PhD



S. Steven Potter, PhD

PUBLISHED OCT. 28, 2020

Journal of the American Society of Nephrology

Research led by developmental biologist S. Steven Potter, PhD, and colleagues has produced the most detailed "atlas" to date of transcriptional profiles related to acute kidney injury (AKI).

The research involved single cell RNA-sequencing (scRNA-seq), single molecule fluorescent *in situ* hybridization, bioinformatical analysis that demanded new algorithms, and immunofluorescent imaging. The resulting atlas has already revealed putative novel molecular and cellular targets of AKI.

"These include remarkably elevated pathologic cell-to-cell communications and several novel AKI-induced genes not previously recognized in AKI," says first author Valeriia Rudomanova, MD, PhD.

Better understanding of early-stage AKI offers a chance to detect potentially reversible changes in uninjured cells. In the murine model, injured tubules dedifferentiated dramatically, including showing elevation of renal development genes *Sox4* and *Cd24a*. (*Sox4* is implicated in renal cell cancer and *Cd24* was detected in dialysis patients with chronic kidney disease.) The study also demonstrated that while younger mice recover two weeks after unilateral renal ischemia (URI), older mice develop maladaptive fibrotic remodeling, marked by persistent *Sox4* and *Cd24a* elevation.

"Our findings might hold potential for developing targeted treatments to augment AKI and interfere with its transition to chronic kidney disease (CKD), thus substantially contributing to the field," says Rudomanova. Looking ahead, follow-up studies will focus on the functional significance of novel AKI-induced genes in *in vitro* human models and *in vivo* transgenic murine models of kidney injury.

RESEARCH & TRAINING DETAILS

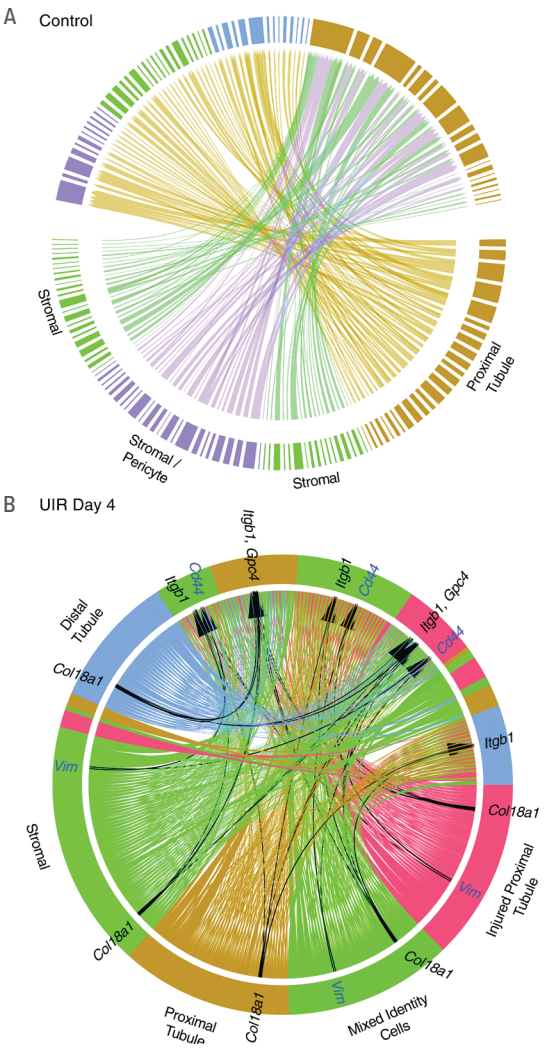
Faculty	11
Joint Appointment Faculty	5
Research Fellows & Post Docs	11
Total Annual Grant Awards	$1.5M
Total Annual Industry Awards	$1.5M

Rudman-Melnick V, Adam M, Potter A, Chokshi SM, Ma Q, Drake KA, Schuh MP, Kofron JM, Devarajan P, Potter SS. Single-Cell Profiling of AKI in a Murine Model Reveals Novel Transcriptional Signatures, Profibrotic Phenotype, and Epithelial-to-Stromal Crosstalk. J Am Soc Nephrol. Dec 2020;31(12):2793-2814.

Single-cell RNA Sequencing Identifies Novel Epithelial-to-Stromal Interactions in Adult Kidney Injury

A. Circos plot of ligand-receptor interactions between the proximal (brown) and distal (blue) tubules, the stromal cells (green), and the stromal/pericyte cells (purple) in the normal kidney.

B. Circos plot of ligand-receptor interactions between the proximal tubules (brown), injured proximal tubules (red), mixed-identity cells (green), distal tubules (blue), and the stromal cells (teal) in the UIR day-4 kidney. Populations producing the putative ligand are labeled; black arrows show *Vim-Cd44* (highlighted in blue), *Col18a1-Gpc4*, and *Col18a1-Itgb1* (highlighted in black) ligand-receptor pairs.



‘Stereo-EEG’ Shows Advantages for Epilepsy Surgery

Krista Grande, MD

Ravindra Arya, MD, DM

RESEARCH & TRAINING DETAILS

Faculty	38
Joint Appointment Faculty	2
Research Fellows & Post Docs	3
Research Graduate Students	6
Total Annual Grant Awards	$3.9M
Total Annual Industry Awards	$1.5M

Grande KM, Ihnen SKZ, Arya R. Electrical Stimulation Mapping of Brain Function: A Comparison of Subdural Electrodes and Stereo-EEG. Front Hum Neurosci. 2020;14:611291.

PUBLISHED DEC 7, 2020
Frontiers in Human Neuroscience

When children with epilepsy need surgical intervention, neurosurgeons need reliable sensors to detect abnormal electrical activity in the brain. But which techniques for collecting that data work best?

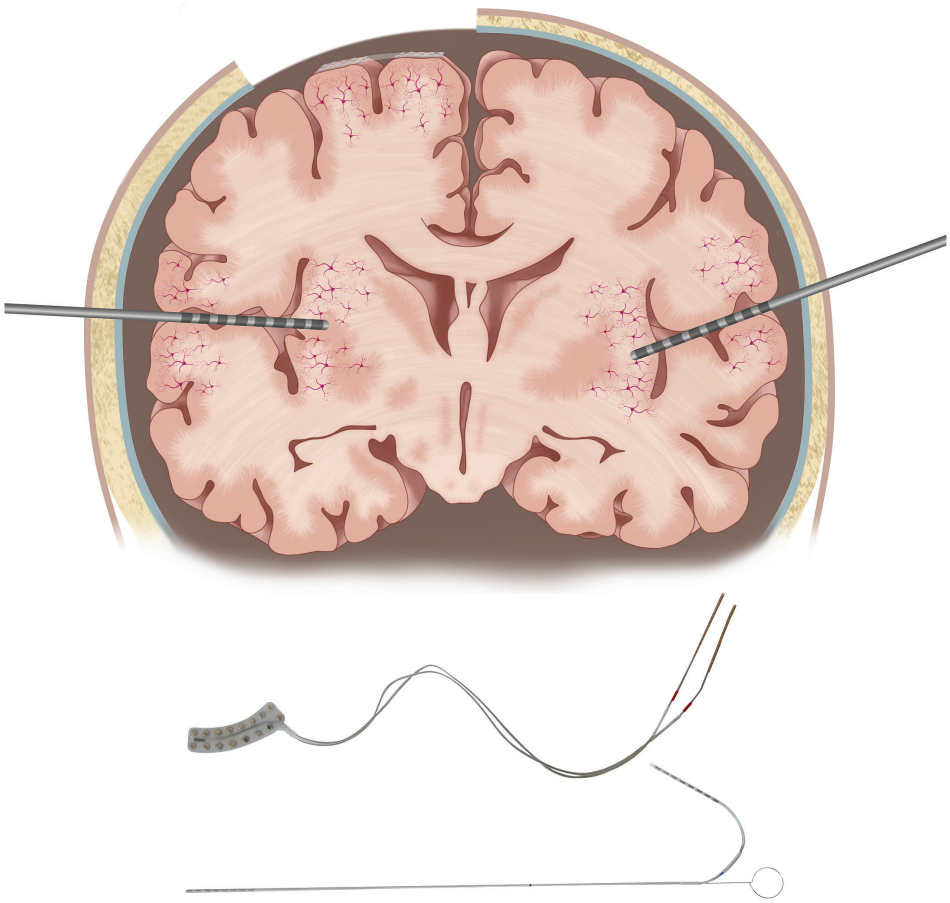
“Some patients with epilepsy, despite all the advances and treatment of epilepsy, will not respond to medicines. Some do require surgery,” says Ravindra Arya, MD, DM, a pediatric epileptologist at Cincinnati Children’s and an associate professor of computer science at the University of Cincinnati.

To prepare for surgery, patients often undergo intracranial EEG, which involves inserting electrodes on the surface of the brain to track electrical activity and localize the seizure onset zone. Over the past decade, this method has been largely replaced by stereotactic depth electrode EEG (stereo-EEG), which involves inserting probes deeper into the brain. This transition between EEG types has been a major paradigm shift in epilepsy surgery.

Another aspect of stereo-EEG evaluation is functional mapping with electrical stimulation. Prior to epilepsy surgery, neurosurgeons must determine the functions of the brain tissue they plan to remove. In subdural EEG versus stereo-EEG, “the geometry of these electrodes differs. They probably interact with different elements of the brain,” Arya says. The former rests on the surface of the brain, the latter enter at different angles and have different interactions with various cells of the brain. Arya and colleagues report that electrical stimulation mapping (ESM) with stereo-EEG may be safer. Stereo-EEG also is more feasible for mapping sensorimotor and speech/language areas, and allows for functional sampling from areas of the brain where subdural electrodes simply do not reach.

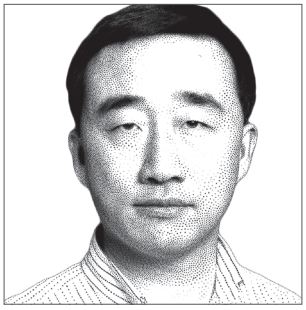
Arya plans to continue studies to develop and validate the effectiveness and safety of novel brain mapping techniques.

Comparing Sensor Methods



Subdural electrodes require a craniotomy for implantation, while stereo-EEG electrodes are implanted through burr holes. Subdural electrodes cover the crowns of gyri, nearly perpendicular to the dendrites of pyramidal cells, while stereo-EEG electrodes pass at various angles concerning pyramidal cells and passing through both gray and white matter. (Lower section: a subdural electrode grid and an stereo-EEG electrode.)

NeurDTI Imaging Helps Predict Which Prenatal Myelomeningocele Patients May Require Later Surgery



Weihong Yuan, PhD

Francesco Mangano, DO

RESEARCH & TRAINING DETAILS

Faculty	7
Research Fellows & Post Docs	1
Research Graduate Students	2
Total Annual Grant Awards	$1M

Yuan W, Stevenson CB, Altaye M, Jones BV, Leach J, Lovha M, Rennert N, Mangano FT. Diffusion tensor imaging in children following prenatal myelomeningocele repair and its predictive value for the need and timing of subsequent CSF diversion surgery for hydrocephalus. J Neurosurg Pediatr. Feb 5 2021:1-9.

PUBLISHED FEB. 5, 2021
Journal of Neurosurgery: Pediatrics

Diffusion tensor imaging (DTI) values could predict which patients receiving prenatal myelomeningocele (MMC) repair would likely later need cerebrospinal fluid (CSF) diversion surgery for MMC-associated hydrocephalus, according to a study led by experts at Cincinnati Children's.

Spina bifida occurs in about three to four babies per 10,000 live births. MMC is the most severe form of spina bifida. Among MMC patients, hydrocephalus is the most common chronic disease leading to further hospitalizations and need for care.

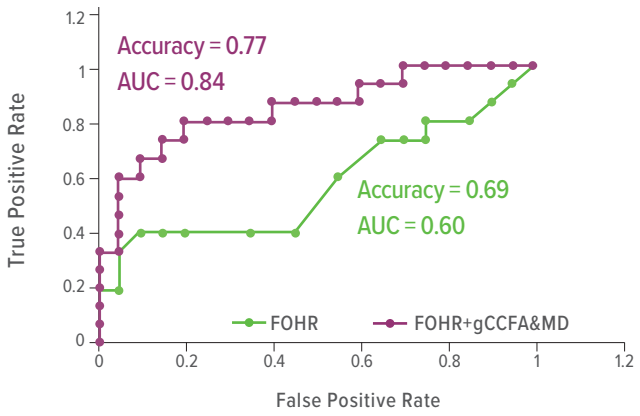
Prenatal MMC surgical repair slows the development of hydrocephalus, and ultimately can reduce the need for CSF diversion to 40% instead of 80-90% for postnatal repair. The prenatal approach also allows for more time to obtain imaging data to study white matter diffusion abnormalities, which can help determine which patients should proceed to CSF diversion.

Retrospectively analyzing data from 35 pediatric patients after prenatal MMC repair, researchers found that DTI values were more accurate as a predictor compared to fronto-occipital horn ratio (FOHR) alone. With further study, researchers believe incorporating DTI into overall management of hydrocephalus will reduce clinical bias and significantly improve therapy guidance.

"This study has generated important data to potentially support the design of a clinical trial based on both conventional clinical measures and neuroimaging biomarkers," says Francesco Mangano, DO, Director, Division of Neurosurgery and senior researcher on the study.

The team is conducting a pilot neuroimaging study to assess the application of fetal DTI in studying white matter integrity prior to fetal MMC surgery.

Determining the Need for CSF Diversion Surgery



Increasing sensitivity and specificity for predicting the need for surgery, using ventricle size (FOHR: fronto-occipital horn ratio, an index used clinically for assessing need for CSF diversion surgery) only to using both FOHR and DTI indices.

Sunlight Reaches Deep into Brain to Play Key Role in Metabolism

Kevin Zhang

Richard Lang, PhD

PUBLISHED SEPT. 2, 2020
Nature

A multi-institutional team of scientists led by Richard Lang, PhD, from Cincinnati Children's has located, in mice, certain neurons inside the brain that express the protein Opsin 5, which can detect a specific wavelength of violet light from the sun. Those neurons, in turn, send signals that influence a number of body functions—including metabolism.

This discovery of another way that sunlight affects health has wide-ranging implications that could change treatment for people with metabolic disorders, recommendations for pregnant women, or how preterm infants are cared for in hospitals.

What does this mean for human health? Since the advent of the Industrial Age and now the Digital Age, many more people are spending most of their time inside, exposed to various types of indoor lighting that nearly always lack the violet wavelengths found in outdoor sunlight.

"With the modernization of society, many of us are now exposed to artificial lighting that is neither appropriate in timing nor spectral composition. This is not how we evolved." says first author Kevin Zhang.

To further explore the questions raised by these findings, Cincinnati Children's has installed a custom-designed, programmable, full-spectrum lighting system as part of the new neonatal intensive care unit in its Critical Care Building, which opened to patients in November 2021.

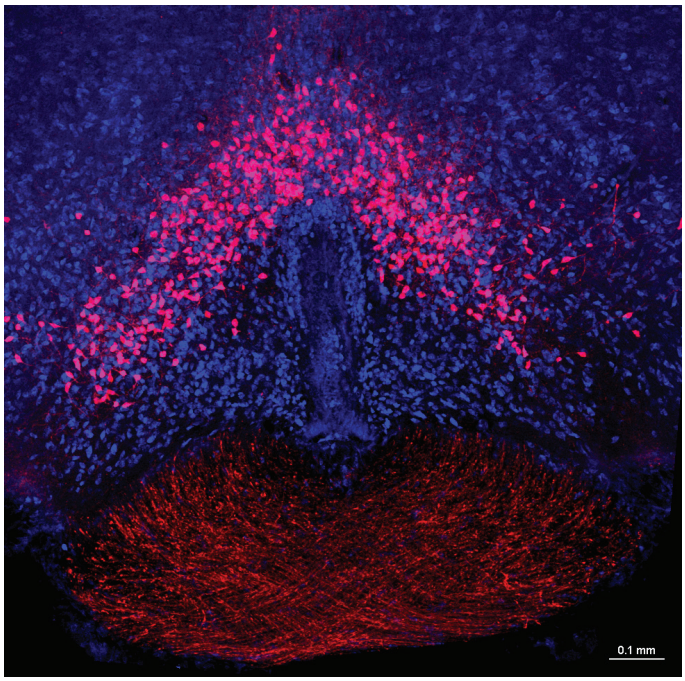
"We have a great deal more to learn about how light affects human development and influences energy metabolism and disease susceptibility," Lang says. "This may be the dawn of a new understanding of how people can live healthier lives in the modern world."

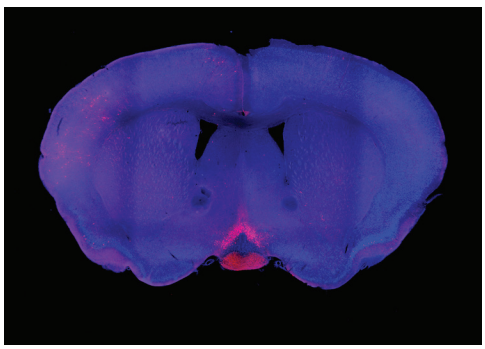
RESEARCH & TRAINING DETAILS

Faculty	1
Research Fellows & Post Docs	3
Research Graduate Students	7
Total Annual Grant Awards	$985,874
Total Annual Industry Awards	$169,280

Zhang KX, D'Souza S, Upton BA, Kernodle S, Vemaraju S, Nayak G, Gaitonde KD, Holt AL, Linne CD, Smith AN, Petts NT, Batie M, Mukherjee R, Tiwari D, Buhr ED, Van Gelder RN, Gross C, Sweeney A, Sanchez-Gurmaches J, Seeley RJ, Lang RA. Violet-light suppression of thermogenesis by opsin 5 hypothalamic neurons. Nature. Sep 2020;585(7825):420-425.

This color-enhanced confocal microscope image shows the location of sunlight-sensing neurons in the mouse brain. The bright pink dots indicate light-sensing neurons within the hypothalamus. The blue label identifies neurons in adjacent regions of the brain. The red strands at the bottom show axons from retinal ganglion cells.





This coronal view of a mouse brain shows the location of light-sensing cells relative to the rest of the brain. Uppermost in blue are the two cortical hemispheres. The light sensing cells (bright pink) are located in the Eiffel Tower-shaped patch in the hypothalamus at the base of the brain.

ROCK Group Finds Unreliable MRI Interpretations for Osteochondritis of the Knee

Andrew Zbojniewicz, MD

Eric Wall, MD

RESEARCH & TRAINING DETAILS

Faculty	16
Research Fellows & Post Docs	1
Research Graduate Students	1
Total Annual Grant Awards	$456,550
Total Annual Industry Awards	$61,608

Fabricant PD, Milewski MD, Kostyun RO, Wall EJ, Zbojniewicz AM, Research in Osteochondritis of the Knee Study G, Albright JC, Bauer KL, Carey JL, Chambers HG, Edmonds EW, Ellis HB, Ganley TJ, Green DW, Grimm NL, Heyworth BE, Kocher MS, Krych AJ, Lyon RM, Mayer SW, Nepple JJ, Nissen CW, Pennock AT, Polousky JD, Saluan P, Shea KG, Tompkins MA, Weiss J, Clifton Willimon S, Wilson PL, Wright RW, Myer GD. Osteochondritis Dissecans of the Knee: An Interrater Reliability Study of Magnetic Resonance Imaging Characteristics. Am J Sports Med. Jul 2020;48(9):2221-2229.

PUBLISHED JULY 2020
American Journal of Sports Medicine

In too many ways, assessing MRI scans to determine the prognosis of children with osteochondritis (OCD) lesions in their knees depends too much upon the eye of the beholder.

Cincinnati Children's imaging and orthopaedic surgery experts Andrew Zbojniewicz, MD and Eric Wall, MD were among several co-leading authors for an interrater study conducted by the Research in Osteochondritis of the Knee (ROCK) Study Group.

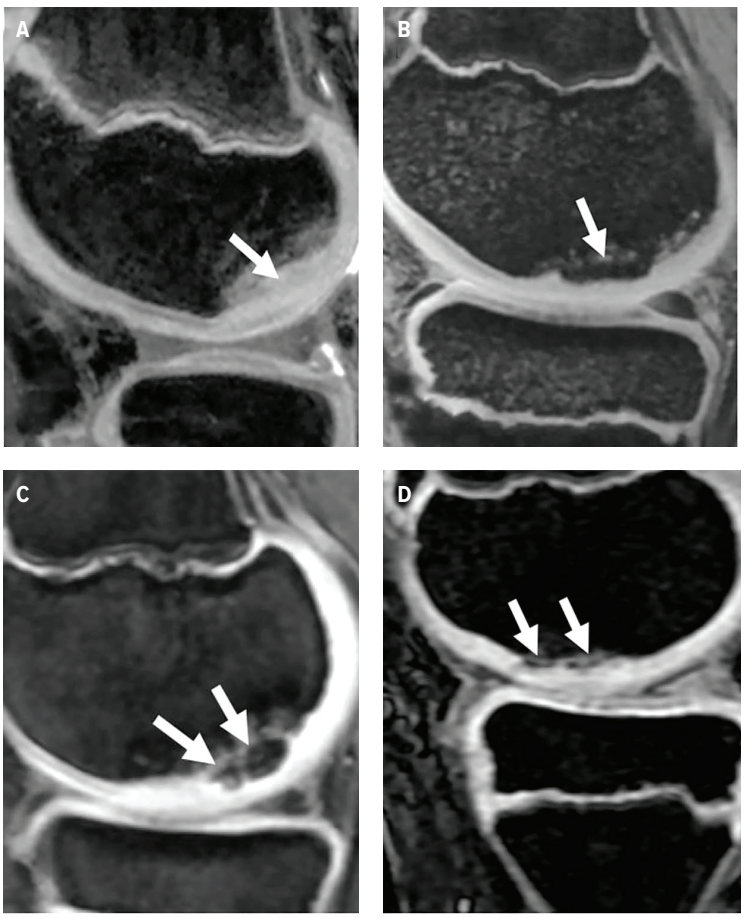
The team explored how 10 fellowship-trained orthopaedic surgeons evaluated 42 sets of MRI scans of children with OCD lesion across 31 characteristics, such as lesion size, cartilage status, and various bone features.

"Raters were reliable when the lesion was measured in the coronal plane," the team reported. "Almost perfect agreement was achieved for condylar size, substantial agreement for physeal patency, and moderate agreement for joint effusion and cartilage status."

However, reliability was "moderate at best" for other factors such as interface characteristics and progeny bone-parent bone qualities. Co-authors suggest that future developments in artificial intelligence and image scanning software may help improve the reliability of MRI data.

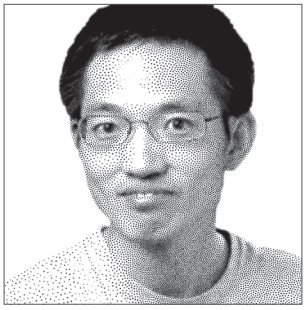
"Many MRI features of OCD that inform treatment decisions were unreliable," the team concluded. "Further work will be needed to refine the unreliable characteristics and to assess the ability of those reliable characteristics to predict clinical lesion instability and prognosis."

Progeny Bone Characteristics

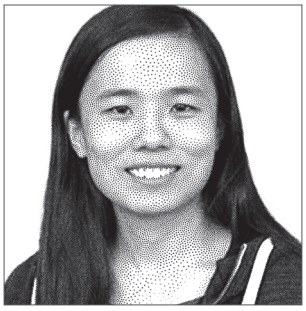


These panels illustrate progeny bone characteristics. The study found that MRI scan readers were not as consistent at evaluating these types of images compared to others, such as assessing condylar size. These sagittal images show varying degrees of mineralization within the bed of the osteochondritis dissecans site: (A) no mineralization (arrow), (B) a single discrete geographic fragment (arrow), (C) multiple distinct geographic fragments (arrows), and (D) linear mineralization (arrows).

Single-Cell Analysis Shines Light on Early Sleep Apnea Influences on Lung Development



Gang Wu, PhD



Yin Yeng Lee

PUBLISHED FEB 18, 2021
eLife

Childhood sleep apnea can have significant cardiovascular, neurological, and metabolic consequences. Now, a study detailing how specific cell types within the lung respond to the intermittent hypoxia caused by sleep apnea suggests a variety of novel targets for treatments that may limit the damage. A team of experts at Cincinnati Children's led by first authors Gang Wu, PhD, Divisions of Human Genetics and Immunobiology, graduate student Yin Yeng Lee, and senior author David Smith, MD, PhD, Division of Otolaryngology, used single-cell RNA sequencing to explore a host of gene changes occurring in 19 cell types including endothelial cells, myofibroblasts, ciliated cells and immune cells.

The team did not find comprehensive organ-wide changes in lung samples. But they did detail a series of cell type-specific changes including dysregulation of circadian gene expression and increased expression of RNAs associated with angiogenesis and pulmonary hypertension.

"Our findings suggest that circadian clock dysfunction may be an important early-stage consequence of hypoxia-driven disease and may contribute to downstream processes," the co-authors state.

Importantly, the findings also suggest potential cell type-specific approaches for improving care.

"If obstructive sleep apnea does, in fact, lead to fibrotic changes in the lung, targeting FGF pathways in alveolar epithelial cells could prevent disease progression from intermittant hypoxia," the co-authors say.

The paper includes 11 co-authors from six research divisions at Cincinnati Children's, including John Hogenesch, PhD, co-founder of the Center for Circadian Medicine, and Jeffery Whitsett, MD, co-director of the Perinatal Institute.

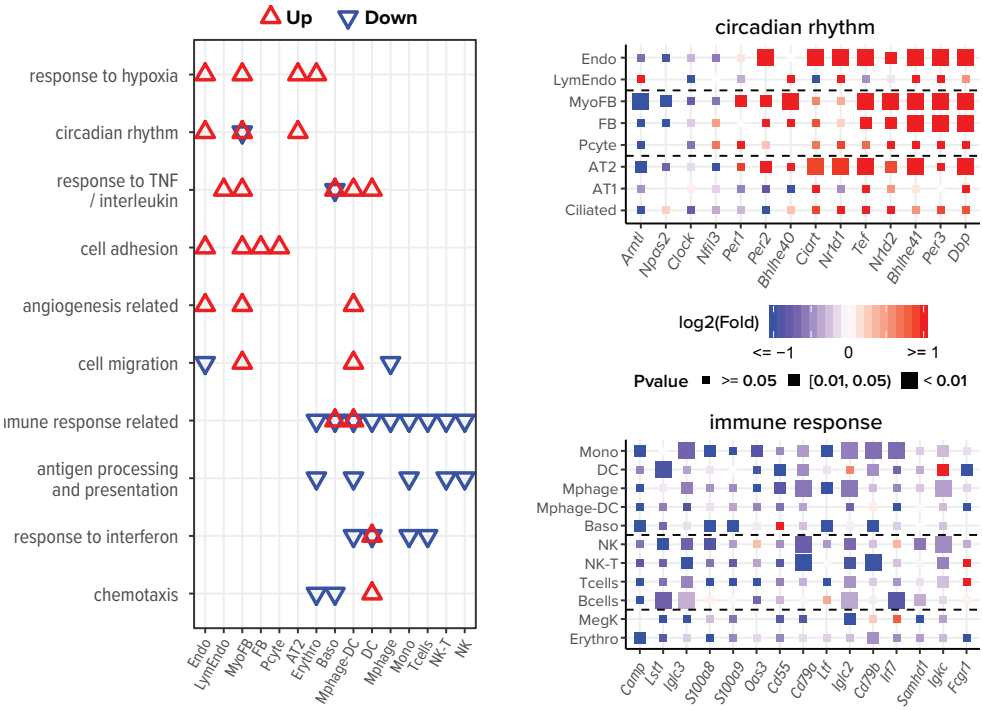
More research is planned to explore how sleep apnea-affected gene expression profiles change over time, which cell types drive disease progression from early to late IH exposure, and how early insults from hypoxia may also drive damage in other organ systems.

RESEARCH & TRAINING DETAILS

Faculty	14
Joint Appointment Faculty	2
Research Fellows & Post Docs	1
Total Annual Grant Awards	$359,748

Wu G, Lee YY, Gulla EM, Potter A, Kitzmiller J, Ruben MD, Salomonis N, Whitsett JA, Francey LJ, Hogenesch JB, Smith DF. Short-term exposure to intermittent hypoxia leads to changes in gene expression seen in chronic pulmonary disease. Elife. Feb 18 2021;10.

How Sleep Apnea Can Affect Gene Expression



Diverse expression pathways were up- and downregulated in the presence of intermittent hypoxia (IH). (A) Biological processes enriched in different cell types from lungs of mice exposed to IH vs controls. Biological processes enriched in up- and downregulated genes are indicated in red and blue triangles, respectively. (B) Expression variation of well-established genes involved in circadian rhythm for endothelial, epithelial, and mesenchymal cells. (C) Expression variation of well-established genes involved in immune response for immune-associated cells.

Chasing the Storm: Lessons from Studying Ruxolitinib as Potential Treatment for Severe COVID-19

Gang Huang, PhD

PUBLISHED JULY 2020

Journal of Allergy and Clinical Immunology

As scientists around the world raced to understand how the SARS-Cov-2 virus was causing such devastating inflammatory responses, a scientist at Cincinnati Children's made a suggestion in early 2020 to a team of doctors in China that prompted an intense look at a hopeful treatment for people with severe illness during the pandemic.

Gang Huang, PhD, Division of Pathology at Cincinnati Children's, had been part of a team that was studying the benefits of ruxolitinib as a treatment to control the cytokine storms that can occur among children with the rare disease hemophagocytic lymphohistiocytosis (HLH). He informed a colleague in China—Jianfeng Zhou, MD, PhD—about the findings, which prompted a rapidly launched clinical trial.

By July 2020, some intriguing data were published from the multicenter study, which involved 20 patients receiving ruxolitinib plus standard-of-care treatment, and 21 people receiving a placebo in addition to standard care. Doctors reported significant declines of seven cytokines in the treatment group, improvements on chest CT scans, faster recovery from lymphopenia, and minimal side effects. While three control group patients died of respiratory failure, none died of respiratory failure in the treatment group.

However, the study was too small for the observed benefits to be considered statistically significant. Over the next year, hundreds more people with COVID were treated with the drug in several larger clinical trials and compassionate use settings. The drug ultimately failed to show clear benefit in the RUXCOVID clinical trial (December 2020) and the DEVENT trial (March 2021). However, research continues to evaluate ruxolitinib in combination with other drugs.

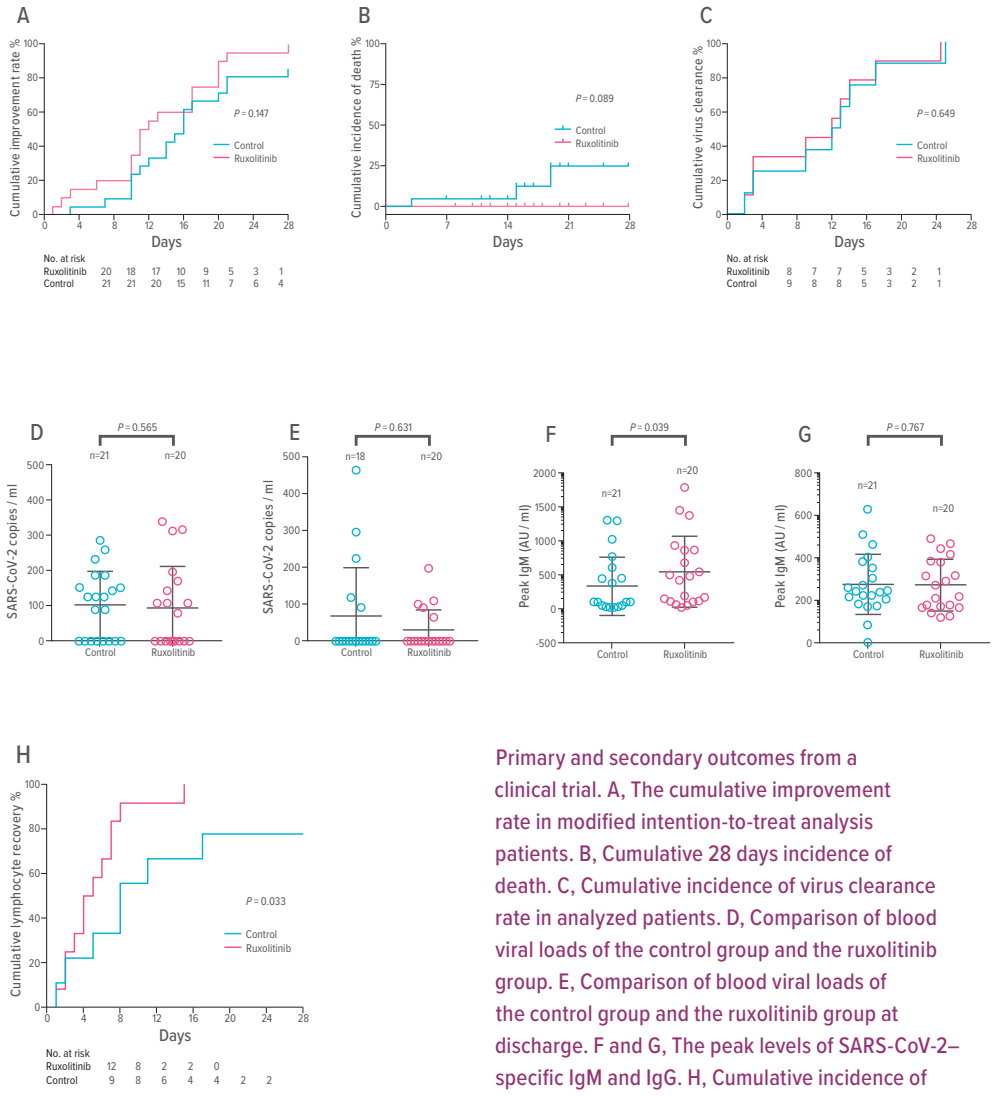
Given concerns about breakthrough infections, Huang says alternative therapies to prevent runaway inflammatory reactions may still be important for high-risk groups in addition to vaccines and other antiviral therapies.

RESEARCH & TRAINING DETAILS

Faculty	23
Joint Appointment Faculty	4
Research Fellows & Post Docs	2
Research Graduate Students	2
Total Annual Grant Awards	$1M

Cao Y, Wei J, Zou L, Jiang T, Wang G, Chen L, Huang L, Meng F, Huang L, Wang N, Zhou X, Luo H, Mao Z, Chen X, Xie J, Liu J, Cheng H, Zhao J, Huang G, Wang W, Zhou J. Ruxolitinib in treatment of severe coronavirus disease 2019 (COVID-19): A multicenter, single-blind, randomized controlled trial. J Allergy Clin Immunol. Jul 2020;146(1):137-146 e133.

Ruxolitinib and COVID-19



Primary and secondary outcomes from a clinical trial. A, The cumulative improvement rate in modified intention-to-treat analysis patients. B, Cumulative 28 days incidence of death. C, Cumulative incidence of virus clearance rate in analyzed patients. D, Comparison of blood viral loads of the control group and the ruxolitinib group. E, Comparison of blood viral loads of the control group and the ruxolitinib group at discharge. F and G, The peak levels of SARS-CoV-2–specific IgM and IgG. H, Cumulative incidence of lymphocyte recovery rate in analyzed patients.

IUDs Provide Safe, Effective Menstrual Management for Adolescents with Disabilities

Beth Schwartz

Lesley Breech, MD

PUBLISHED AUGUST 2020
Pediatrics

For patients with disabilities and their families, menstrual management is a common request. However, with little published information on treatment options, providers may not consider intrauterine devices (IUDs).

In the largest study of its kind to date, the research team demonstrates that IUDs are an effective means of stopping periods or managing symptoms associated with menstrual periods in pubertal patients with physical, intellectual, and developmental disabilities.

Unlike other hormonal methods, intrauterine devices (IUDs) have minimal systemic absorption, side effects, or interactions with other medications. Many young people with disabilities may not be able to use estrogen-containing methods due to medical comorbidities, medication interactions, or decreased mobility that may increase the risk for thrombosis.

To explore the safety and efficacy of IUDs in this population, the research team conducted a retrospective chart review of all IUDs placed at Cincinnati Children's over a 10-year period—874 in total. Of these, 227 were placed in patients with disabilities, of which 185 IUDs in 159 patients met inclusion criteria. The mean age was 16.3 years (ranging from nine to 22 years) at IUD placement, with 19% younger than 13 years.

Results showed high IUD continuation rates (95% at one year and an estimated 73% at five years), relatively high amenorrhea rates (approximately 60% throughout the duration of IUD use), and low rates of side effects and complications (3% or less).

"These data are promising and should be used to allow more accurate counseling of adolescents with special needs and their families about this highly effective, safe menstrual management and contraceptive method," says senior author Lesley Breech, MD. "Further research can allow us to prospectively assess continuation rates, outcomes, and satisfaction with levonorgestrel IUDs in this population." .

Schwartz BI, Alexander M, Breech LL. Intrauterine Device Use in Adolescents With Disabilities. Pediatrics. Aug 2020;146(2).

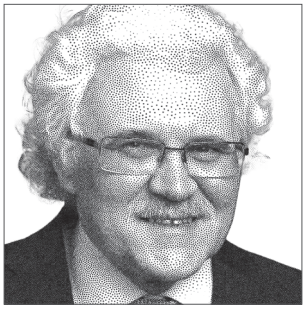
IUD Continuation Rates, Gynecologic Outcomes, and Complications Among Study Participants.

	n (%)
Amenorrhea by y	
1 (*n* = 106)	63 (59)
2 (*n* = 100)	4 (4)
3 (*n* = 66)	43 (65)
4 (*n* = 56)	34 (61)
5 (*n* = 47)	30 (64)
Side effects: pain and/or cramping by y	
1 (*n* = 124)	2 (2)
2 (*n* = 100)	1 (1)
3 (*n* = 75)	2 (3)
4 (*n* = 63)	2 (3)
5 (*n* = 52)	1 (2)
Complications	
PID[a]	0 (0)
Malposition[b]	4 (2)
Expulsion[c]	5 (3)
Uterine perforation[d]	0 (0)
Pregnancy	0 (0)

[a] PID was clinically defined; it was considered a complication of IUD use when it occurred within 20 d of insertion.
[b] Malposition was defined as incorrect positioning but within the uterus.
[c] Expulsion was defined as partial extrusion of the device through the cervix or complete expulsion from the uterus.
[d] Uterine perforation was defined as presence of the deice in the abdominal or pelvic cavity outside the uterus.

Morgan Alexander at Cincinnati Children's also contributed to this study

PARP Inhibitor Shows Promise Against Hepatoblastoma in Mice



Nikolai Timchenko, PhD

PUBLISHED MAY 26, 2021
Hepatology

Hepatoblastoma (HBL) is a devastating pediatric liver cancer that typically requires surgery to treat. These tumors grow rapidly, have a high risk of metastases, and show poor response to chemotherapy. To date, high-dose chemotherapies have produced significant neurotoxic complications.

Now, researchers in the Division of Pediatric and General Thoracic Surgery report that the chemotherapy drug Olaparib hampers tumor growth in mouse models via suppression of key molecular pathways active in aggressive HBL.

A research team led by first author Michael Johnston, MD, and senior author Nikolai Timchenko, PhD, examined the role of human chromosomal regions, called aggressive liver cancer domains (ALCDs), in HBL development. They found that these normally closed regions were open among patients with aggressive HBL, and were activated by the protein PARP1.

Next, the team used patient-derived xenografts—tumor tissue taken from patients and implanted into mice—to develop regimens targeting the PARP1 pathway. When treated with Olaparib, a PARP inhibitor, tumor growth slowed through suppression of heterochromatin-repressing genes regulated by the ALCDs.

"Our study opens the door for alternative chemotherapy regimens in the management of HBL," Johnston says. "In knowing the tumor's ALCDs, targeting and suppressing the expression of the genes key to the tumor's survival can result in significant reduction in the tumor's growth and malignancy. This can translate to improved outcomes in patients diagnosed with HBL and an alternative regimen in patients with multi-drug-resistant tumors."

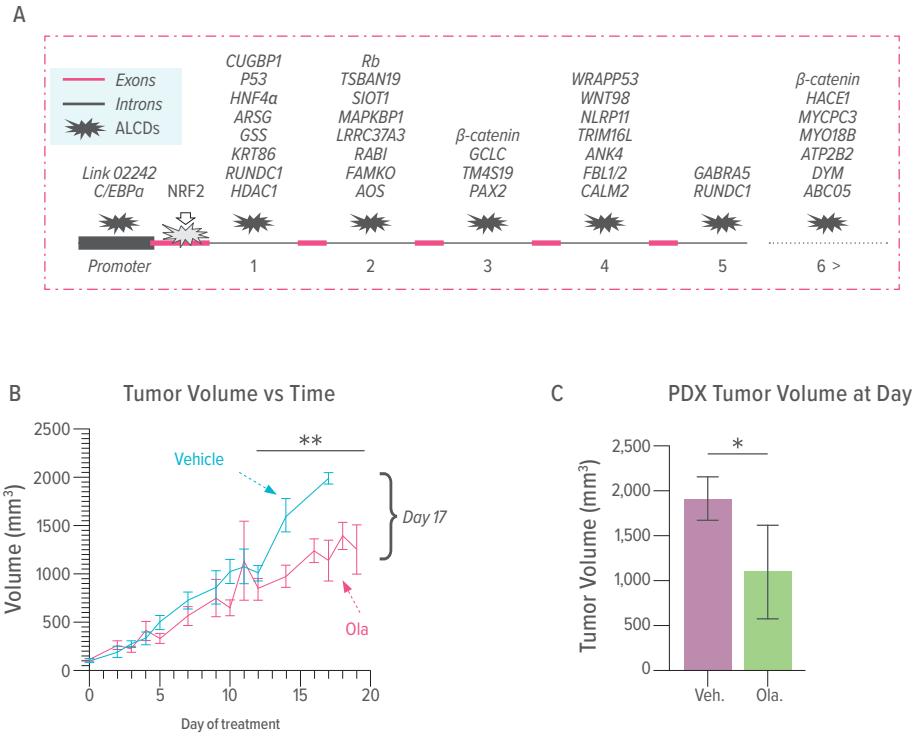
Next, the Timchenko Lab plans to study Olaparib in combination with other chemotherapies, which could help establish a regimen strong enough to treat the tumor and with reduced risk of negative side effects.

RESEARCH & TRAINING DETAILS

Faculty	22
Joint Appointment Faculty	2
Research Fellows & Post Docs	4
Total Annual Grant Awards	$3.8M

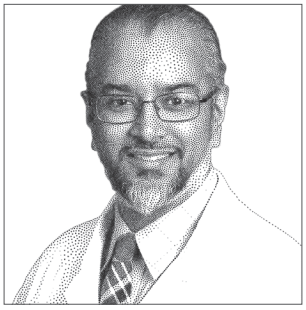
Johnston ME, 2nd, Rivas MP, Nicolle D, Gorse A, Gulati R, Kumbaji M, Weirauch MT, Bondoc A, Cairo S, Geller J, Tiao G, Timchenko N. Olaparib Inhibits Tumor Growth of Hepatoblastoma in Patient Derived Xenograft Models. Hepatology. May 26 2021.

Olaparib Hampers Tumor Growth in Mice



These graphs summarize information on the aggressive liver cancer domains (ALCDs) and effects of treatment with Olaparib on hepatoblastoma patient-derived xenografts (PDXs).

Xylitol Decreases Risk of Blood Stream Infections for Pediatric Bone Marrow Transplant Recipients



Sarat Thikkurissy, DDS, MS

Christopher Dandoy, MD, MSc

RESEARCH & TRAINING DETAILS

Faculty	8
Total Annual Grant Awards	$249,999

Badia P, Andersen H, Haslam D, Nelson AS, Pate AR, Golkari S, Teusink-Cross A, Flesch L, Bedel A, Hickey V, Kramer K, Lane A, Davies SM, Thikkurissy S, Dandoy CE. Improving Oral Health and Modulating the Oral Microbiome to Reduce Bloodstream Infections from Oral Organisms in Pediatric and Young Adult Hematopoietic Stem Cell Transplantation Recipients: A Randomized Controlled Trial. Biol Blood Marrow Transplant. Sep 2020;26(9):1704-1710.

PUBLISHED SEPTEMBER 2020
Biology of Blood and Bone Marrow Transplantation

When a child needs a bone marrow transplant, pain and low blood counts often deter regular toothbrushing. Yet poor oral hygiene can lead to bloodstream infections (BSIs) from oral bacteria, which can cause hospital readmission, and impact the success of the transplant. Is there an alternative strategy to improve oral health?

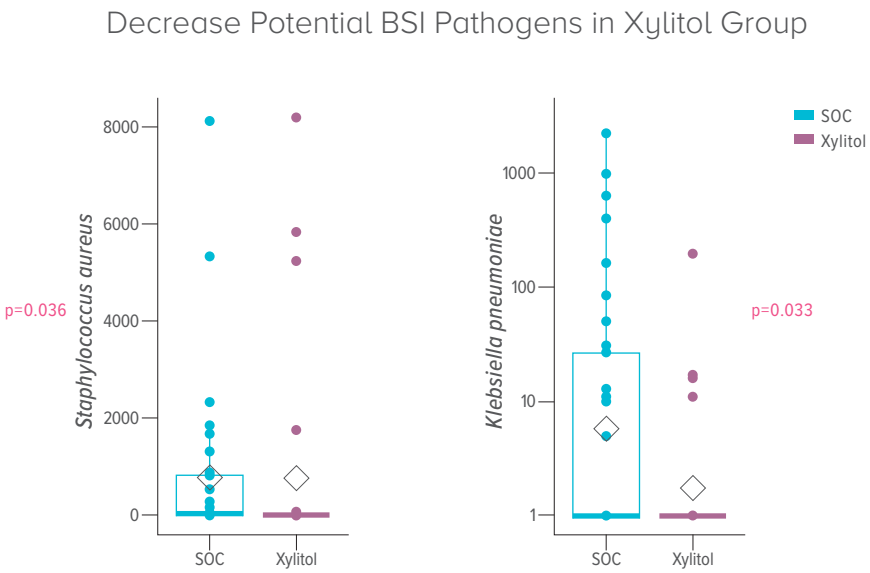
Xylitol is a commercially available, inexpensive, and non-toxic treatment that can be rapidly adopted into practice. Researchers led by first author Priscila Badia, MD, and senior authors Sarat Thikkurissy, DDS, MS, and Christopher Dandoy, MD, MSc, found that xylitol decreases BSIs from oral organisms after hematopoietic stem cell transplantation (HSCT).

To evaluate the impact of daily dental xylitol wipes, the team enrolled 35 pediatric HSCT recipients from the Cincinnati Children's Bone Marrow Transplant Unit and age-matched healthy children. Participants were randomized into a standard of care (SOC) group or xylitol group. From the beginning of chemotherapy to 30 days after transplantation, researchers measured outcomes in oral health and BSIs from oral organisms.

In the xylitol group, participants had significantly lower rates of gingivitis, oral plaque, and oral ulcers compared with the SOC group. They also had no BSI from oral organisms and significantly lower abundance of potential BSI pathogens—an overall change in the bacterial flora.

"Based on our results, xylitol can provide parents and oncology teams with a cheap and minimally invasive way to take care of the mouth pre- and post-transplant," Thikkurissy says. "This can help reduce poor outcomes and improve quality of life for children undergoing transplants."

The team is now collaborating with cardiology researchers to explore the impact of xylitol on oral bacterial infections in transcatheter pulmonary valve implantation patients.



Xylitol reduces oral bacteria among children receiving bone marrow transplants.

Split-Appendix Technique Improves Outcomes for Continent Catheterizable Channels

Michael Daugherty, MD

Brian VanderBrink, MD

PUBLISHED NOV. 13, 2020
Journal of Pediatric Surgery

In patients undergoing simultaneous urinary and fecal reconstruction, surgeons must create a continent catheterizable channel (CCC) to facilitate bladder and bowel function.

Based on the bowel segment used, there are several methods of creating CCCs—the split-appendix technique, the Monti (using part of the gastrointestinal tract), or appendix-only. Among these, which has the best outcomes?

In a six-year retrospective review of 106 patients, researchers in the Division of Urology compared perioperative and long-term outcomes of the three methods. They found that the split appendix allows for two channels to be created without having to do any bowel resectioning or anastomosis, minimizing morbidity and providing shorter operative times.

These findings contradict previous understanding of the split-appendix technique. Researchers were concerned that splitting the appendix and sharing it amongst the two channels would compromise its blood supply. However, compared to the other more established techniques, this study shows that split-appendix does not affect 30-day complications or long-term revision rates compared to other more established techniques.

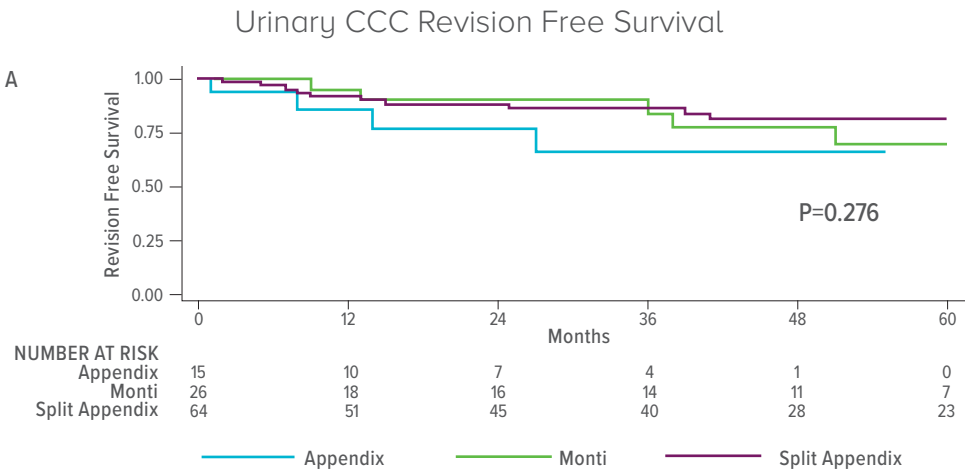
"For patients who are considering continent reconstruction, these findings can reassure them that in cases where both channels are to be created, we are able to use the appendix for both channels when technically feasible without compromising outcomes," says lead author Michael Daugherty, MD. "This decreases morbidity of an already complex surgery."

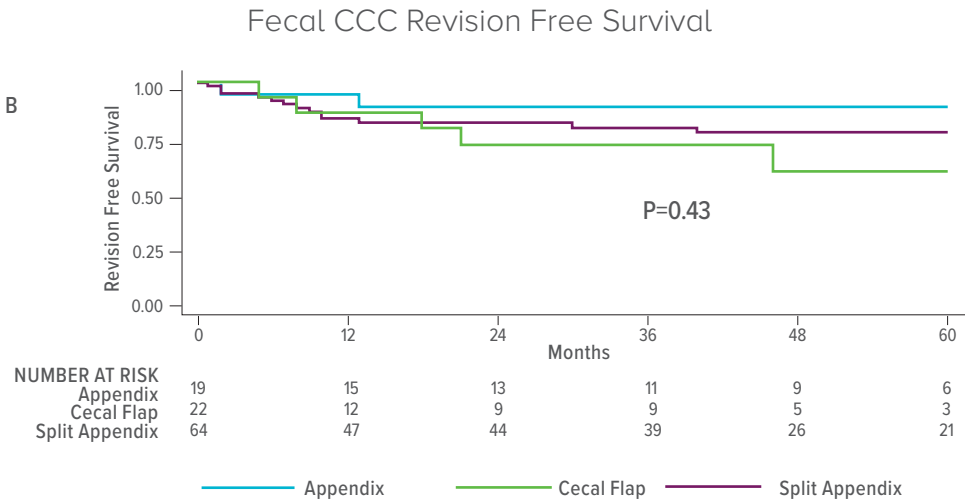
Researchers are continuing to follow patients undergoing complex reconstruction and updating the data to include longer-term outcomes. The team is participating in an Enhanced Recovery after Surgery (ERAS) protocol to expedite recovery and decrease lengths of hospital stays for these patients.

RESEARCH & TRAINING DETAILS

Faculty	6
Joint Appointment Faculty	1
Total Annual Grant Awards	$1.4M

Daugherty M, Strine A, Frischer J, DeFoor WR, Minevich E, Sheldon C, Reddy P, VanderBrink B. Outcomes according to channel type for continent catheterizable channels in patients undergoing simultaneous urinary and fecal reconstruction. J Pediatr Surg. Nov 13 2020.





These survival charts indicate that, despite concerns about compromised blood supply, a surgical technique that splits the use of appendix tissue to create continent catheterizable channels to support bladder and bowel function is feasible without compromising outcomes.

Inhaled Drug Appears to Reduce Need for Whole-Lung Lavage for People with aPAP

Bruce Trapnell, MD

PUBLISHED SEPT. 7, 2020
The New England Journal of Medicine

Most people living with autoimmune pulmonary alveolar proteinosis (aPAP) have to report to a hospital about once a year to receive a whole-lung lavage procedure to flush out waste products that their lungs cannot clear away on their own.

That routine might become less necessary based on findings from a 34-center clinical trial led by Bruce Trapnell, MD. The phase 2/3 IMPALA trial demonstrated the potential value of a daily inhaled dose of the drug molgramostim, a recombinant form of the protein granulating macrophage colony stimulating factor (GM-CSF).

The clinical trial, which involved 138 people, represented a major step for what might be the first drug that can help these patients. Autoimmune PAP affects an estimated seven to 26 people per 1 million population, or roughly 2,000 to 8,000 people in the United States.

"No drugs have been approved for treating PAP in any country, so this one could radically improve the lives of people with aPAP," Trapnell says.

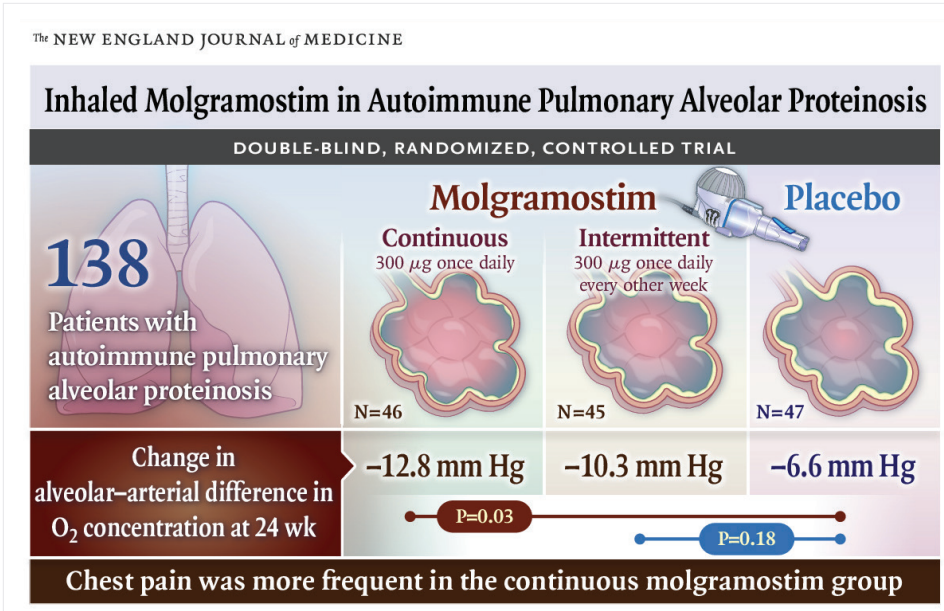
The phase II/III clinical trial results marked a key milestone in a long discovery path. Trapnell and colleagues found out nearly 20 years ago that aPAP was linked to disruption of cell regulation by GM-CSF. In research involving mouse models and patient tissue samples, the scientists learned that the immune systems of people with aPAP neutralize GM-CSF. The new drug restores GM-CSF signaling, which allows lung biology to return to a more normalized state.

Molgramostim has received Breakthrough Therapy Designation from the U.S. Food & Drug Administration. The first patient in the IMPALA-2 Phase 3 clinical trial received the drug in June 2021.

RESEARCH & TRAINING DETAILS

Faculty	63
Joint Appointment Faculty	1
Research Fellows & Post Docs	8
Research Graduate Students	10
Total Annual Grant Awards	$14.4M
Total Annual Industry Awards	$128,115

Trapnell BC, Inoue Y, Bonella F, Morgan C, Jouneau S, Bendstrup E, Campo I, Papiris SA, Yamaguchi E, Cetinkaya E, Ilkovich MM, Kramer MR, Veltkamp M, Kreuter M, Baba T, Ganslandt C, Tarnow I, Waterer G, Jouhikainen T, Investigators IT. Inhaled Molgramostim Therapy in Autoimmune Pulmonary Alveolar Proteinosis. N Engl J Med. Oct 22 2020;383(17):1635-1644.


The NEW ENGLAND JOURNAL of MEDICINE
Inhaled Molgramostim in Autoimmune Pulmonary Alveolar Proteinosis
DOUBLE-BLIND, RANDOMIZED, CONTROLLED TRIAL
138
Patients with autoimmune pulmonary alveolar proteinosis
Molgramostim
Continuous
300 μg once daily
Intermittent
300 μg once daily every other week
Placebo
N=46
N=45
N=47
Change in alveolar–arterial difference in O_2 concentration at 24 wk
−12.8 mm Hg
−10.3 mm Hg
−6.6 mm Hg
P=0.03
P=0.18
Chest pain was more frequent in the continuous molgramostim group
B.C. Trapnell et al. 10.1056/NEJMoa1913590
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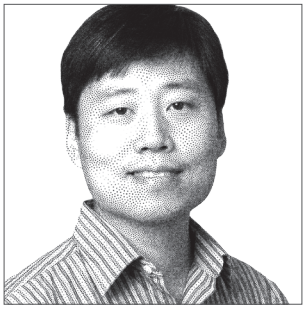
Decidua Formation Depends on Proper Cannabinoid Receptor Signaling



Xiaofei Sun, PhD

PUBLISHED SEP 29, 2020
eLife

The process of decidualization is one of the critical early stages of pregnancy. It requires a series of signaling events to support healthy embryo implantation and connection with the placenta. Now, experts at Cincinnati Children's report new findings about the molecular processes at work in a region called the primary decidual zone (PDZ).

In mice, the PDZ encircles the implantation crypt by day 5 of pregnancy to protect the embryo from maternal immune cell attack. In previous studies, the Cincinnati Children's Reproductive Sciences team led by Sudhansu K. Dey, PhD, has shown that excessive endocannabinoid signaling and lack of endocannabinoid signaling can disrupt the early stages of pregnancy. This study delves into how abnormal signaling can play havoc with blood vessel formation in the PDZ.

Females lacking expression of the genes *Cnr1* and *Cnr2* fail to receive key endocannabinoid signals that help regulate vascular remodeling. Thus, they form defective PDZs during pregnancy, which in turn compromises decidualization. The healthy process appears to require induction of CB1 membrane receptors in decidual cells (encoded by *Cnr1*) and CB2 receptors in endothelial cells (encoded by *Cnr2*). The combined role these receptors play in successful pregnancy has not been previously reported, the co-authors state.

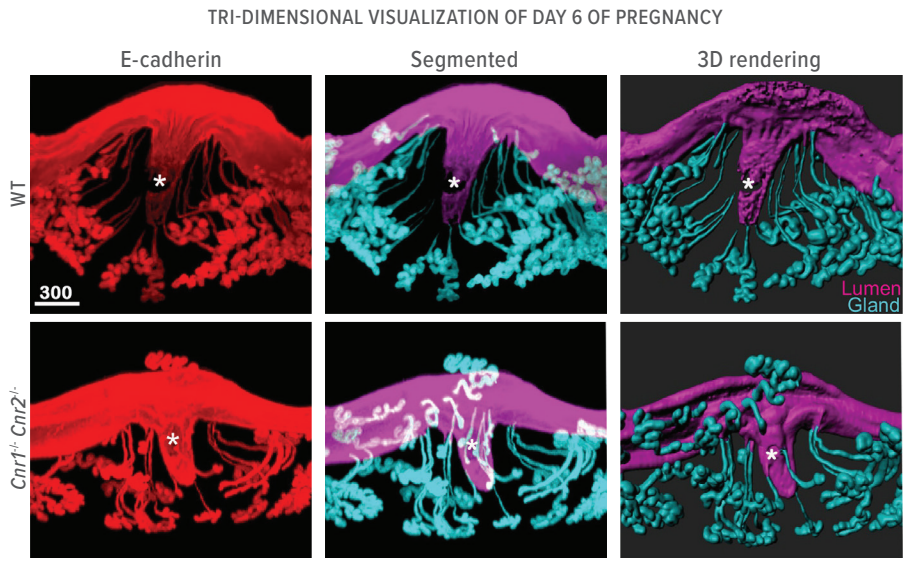
"This investigation reveals that CB1 actions in decidual cells, combined with angiogenic activities driven by CB2, facilitate the formation of the avascular PDZ, which is critical for pregnancy success," the co-authors state. "Taken together, our study illuminates a major responsibility for endocannabinoid signaling in modulating vascular remodeling and integrity."

RESEARCH & TRAINING DETAILS

Faculty	5
Joint Appointment Faculty	1
Research Fellows & Post Docs	6
Total Annual Grant Awards	$1.2M

Li Y, Dewar A, Kim YS, Dey SK, Sun X. Pregnancy success in mice requires appropriate cannabinoid receptor signaling for primary decidua formation. Elife. Sep 29 2020;9.

Structure of Implantation Sites



By day 6 of pregnancy, decidual responses in wild type (WT) mice promote the uterine lumen to form an arch shape, whereas in *Cnr1*-/-*Cnr2*-/- implantation sites, the lumen remains flat. These flattened structures are less likely to support a successful pregnancy.

A Novel Surgical Solution for Craniosynostosis

David Lobb

Jesse Skoch, MD

PUBLISHED APRIL 2021
Neurosurgical Focus

In about one in every 2,500 births, a baby will experience craniosynostosis (premature fusion of cranial sutures). Left untreated, an abnormal head shape can increase intracranial pressure, impair intellectual development, and cause psychosocial anxiety.

Although partial fusions occur in about a third of patients with craniosynostosis, surgical literature does not include clear guidance for optimal management. Now, a novel treatment strategy is available, a technique that senior co-author Jesse Skoch, MD, describes as "taking a small surgery and making it even smaller for patients."

Surgeons used ultrasound in the operating room to define where bone needed to be cut before opening the scalp. The surgery itself is similar to a traditional, minimally invasive, complete suturectomy, except with bone removed without endoscope and only at the point of suture fusion. Less cutting of bone, less bleeding and shorter surgery times can be achieved with this technique, all of which contributes to lower risk of longer-term consequences like failed or abnormal bone healing. This less intensive surgery was paired with postoperative helmet therapy, applied on postoperative day 4, worn for 23 hours per day for 6 to 9 months.

Five patients, average age 2.8 months, were selected for the study. Each had relatively contiguous fused regions of their cranial suture that comprised less than half the full suture. The remaining suture gaps were similar in size to the infant's own nonpathological sutures.

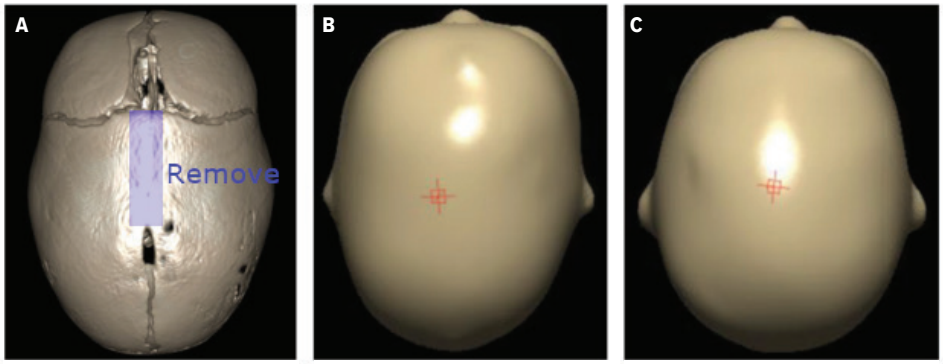
Skoch says more patients need to be studied to identify the best candidates for this type of surgery. Further research will also be required to ensure the absence of relapse remains constant, but thus far, partial suturectomy with helmet therapy is suitable for very young patients and offers a less-invasive alternative to complete suturectomy with similar outcomes.

RESEARCH & TRAINING DETAILS

Faculty	5
Joint Appointment Faculty	1
Research Fellows & Post Docs	1
Total Annual Grant Awards	$238,500

Lobb DC, Patel SK, Pan BS, Skoch J. Partial suturectomy for phenotypical craniosynostosis caused by incomplete fusion of cranial sutures: a novel surgical solution. Neurosurg Focus. Apr 2021;50(4):E6.

Managing Craniosynostosis



Preoperative computed tomography | Preoperative laser scan | Postoperative laser scan

A. Preoperative CT scan of patient, demonstrating partial sagittal synostosis with phenotypical scaphocephaly. B and C: Pre- (B) and postoperative (C) laser scans of the same patient who underwent partial suturectomy for an incompletely fused sagittal synostosis.

Males with Fragile X Syndrome More Likely to Experience Auditory Processing Disruptions

Elizabeth Smith, PhD

Craig Erickson, MD

PUBLISHED JUNE 2021
Journal of Psychiatric Research

Clinicians have long hoped that electroencephalography (EEG) results could be effectively used as a biomarker for tracking neurological disruptions occurring in children born with fragile X syndrome (FXS). However, differing EEG patterns among males and females with the condition have complicated the effort.

Now, research led by first author Elizabeth G. Smith, PhD, and senior author Craig Erickson, MD, at Cincinnati Children's, provides new insights that could make EEG results more useful to clinicians caring for children with FXS.

The team conducted an age- and sex-matched cluster-based analysis of children with and without FXS. The results did indicate several ways that EEG readings varied by biological sex. However, alterations in theta and low beta power measures were similar across males and females in FXS, and notably different from the control group.

"These EEG power patterns can complement research in preclinical models of FXS and may serve as a useful marker of neurobiological change in clinical trials," the co-authors say.

Meanwhile, the team shows the first clear evidence of significant correlation between auditory processing and theta power in FXS males. In the auditory attention task from the Woodcock Johnson test of neurological function, altered theta power in males with FXS was strongly associated with an inability to filter speech out of background noise.

"This finding supports conceptualization of FXS as a signal processing disorder, whereby difficulty separating signal from noise across sensory systems leads to impairments in both perceptual and cognitive development," the co-authors say.

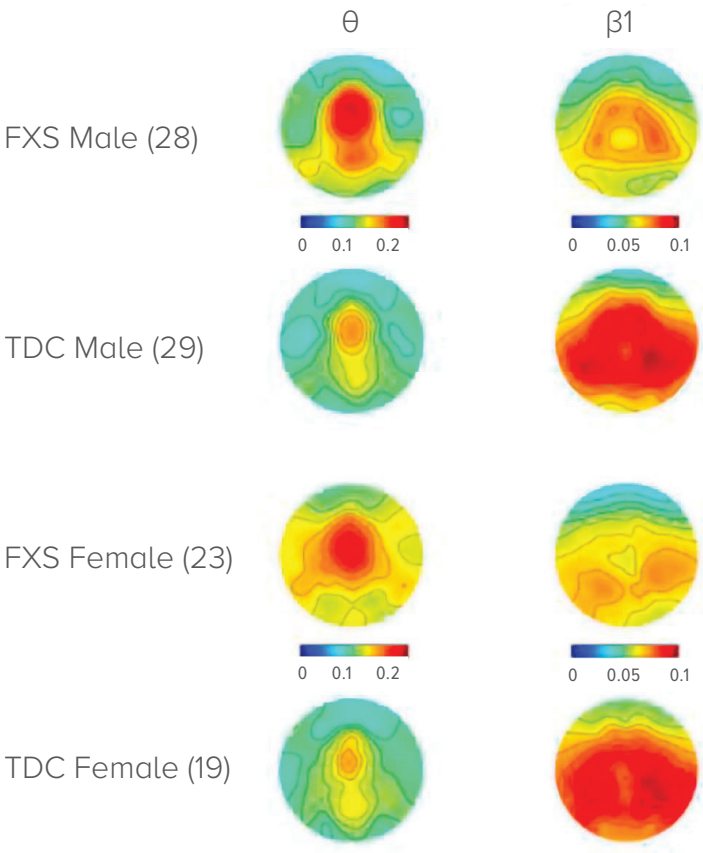
Looking ahead, the study results support continued investigation of therapeutics targeting GABAergic and glutamateric dysregulation in FXS. However, it appears likely that therapeutics targeting the E/I balance as captured by excessive gamma band activity would have different effects in males and females.

RESEARCH & TRAINING DETAILS

Faculty	24
Joint Appointment Faculty	2
Research Fellows & Post Docs	1
Total Annual Grant Awards	$4.9M
Total Annual Industry Awards	$113,967

Smith EG, Pedapati EV, Liu R, Schmitt LM, Dominick KC, Shaffer RC, Sweeney JA, Erickson CA. Sex differences in resting EEG power in Fragile X Syndrome. J Psychiatr Res. Jun 2021;138:89-95.

Potential EEG Biomarker for Fragile X Syndrome



These topographic heat plots measuring relative EEG power indicate that males and females with fragile X syndrome (FXS) show a similar differentiation pattern compared to a control group (TDC) in the theta and low beta bandwidths. Warmer colors indicate greater relative power and cooler colors represent relative power approaching zero.

Barasertib May Stop Scar Formation in Patients with Idiopathic Pulmonary Fibrosis

Satish Madala, PhD

PUBLISHED AUG. 6, 2020
EMBO Molecular Medicine

Idiopathic pulmonary fibrosis (IPF) is a chronic, progressive lung disease that is usually fatal within three to five years after diagnosis. Currently, the only cure is lung transplantation, but a new discovery suggests that a potential treatment may be within a few years of launching human clinical trials.

The pre-clinical study led by scientists at Cincinnati Children's demonstrates that in mice, the drug barasertib reverses the activation of fibroblasts that cause dangerous scar tissue to build up in the lungs of people with IPF.

"This study is the first to identify barasertib as an anti-fibrotic candidate," says Satish Madala, PhD. "That's important because so far there are no treatments for IPF that appear to reverse the underlying process that causes the disease."

In the new study, researchers found a gene expressing aurora kinase B (AURKB) at high levels within the cells of lung scar tissue (also known as fibroblasts). This gene expression appears to be driven by multiple growth factors and a transcription factor called Wilms Tumor 1, the study states.

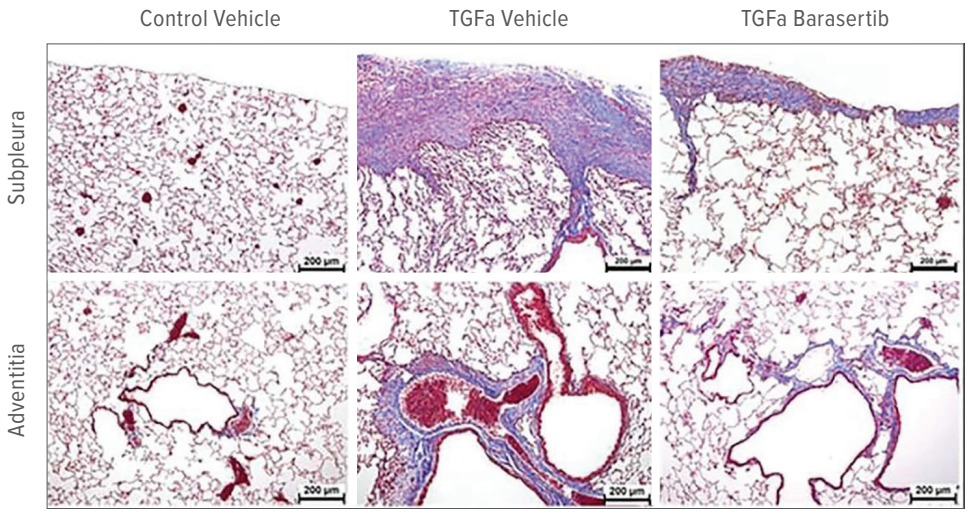
Once the team identified the involvement of barasertib, a known AURKB inhibitor, they explored the therapeutic relevance, underlying mechanisms, and target pathways related to pulmonary fibrosis. In mouse models, they found that treatment with barasertib caused faster cell death among fibroblasts, resulting in less scar tissue, improved lung elasticity, and overall better lung function.

Next, the team aims to determine whether targeting AURKB would be effective and safe enough to test in clinical trials. They also plan to explore alternative routes of administration to bypass systemic exposure and ensure targeted delivery of barasertib.

RESEARCH & TRAINING DETAILS

Faculty	36
Joint Appointment Faculty	3
Research Fellows & Post Docs	10
Research Graduate Students	5
Total Annual Grant Awards	$12.9M
Total Annual Industry Awards	$186,842

Yombo DJK, Odayar V, Gupta N, Jegga AG, Madala SK. The Protective Effects of IL-31RA Deficiency During Bleomycin-Induced Pulmonary Fibrosis. Front Immunol. 2021;12:645717.



TITLE: AURKB Inhibitor Reduces Scarring CAPTION: Representative images of Masson's trichrome-stained lung sections from the vehicle- and barasertib-treated mice. Images were obtained at 10× magnification. Scale bar: 200 µm.

International Registry Uses MRI to Learn Imaging Features of DIPG

James Leach, MD

Blaise Jones, MD

RESEARCH & TRAINING DETAILS

Faculty	51
Research Fellows & Post Docs	4
Research Graduate Students	2
Total Annual Grant Awards	$3.1M
Total Annual Industry Awards	$72,174

Leach JL, Roebker J, Schafer A, Baugh J, Chaney B, Fuller C, Fouladi M, Lane A, Doughman R, Drissi R, DeWire-Schottmiller M, Ziegler DS, Minturn JE, Hansford JR, Wang SS, Monje-Deisseroth M, Fisher PG, Gottardo NG, Dholaria H, Packer R, Warren K, Leary SES, Goldman S, Bartels U, Hawkins C, Jones BV. MR imaging features of diffuse intrinsic pontine glioma and relationship to overall survival: report from the International DIPG Registry. Neuro Oncol. Nov 26 2020;22(11):1647-1657.

PUBLISHED NOV. 26, 2020
Neuro-Oncology

In children, 80% of brain stem tumors are categorized as diffuse and poorly defined. Compared to other types of tumors, diffuse intrinsic pontine glioma (DIPG) may be relatively uncommon but they are most often lethal. Diagnosis is usually based upon imaging, but previous single-institution studies of tumor imaging have had mixed results in correlating MRI findings with survival.

Now, a report from the International DIPG Registry represents the largest and most detailed assessment of MRI findings in DIPG. This study analyzed images from 357 patients, drawing from a pool of over 1,200 patients from 116 institutions enrolled in the registry.

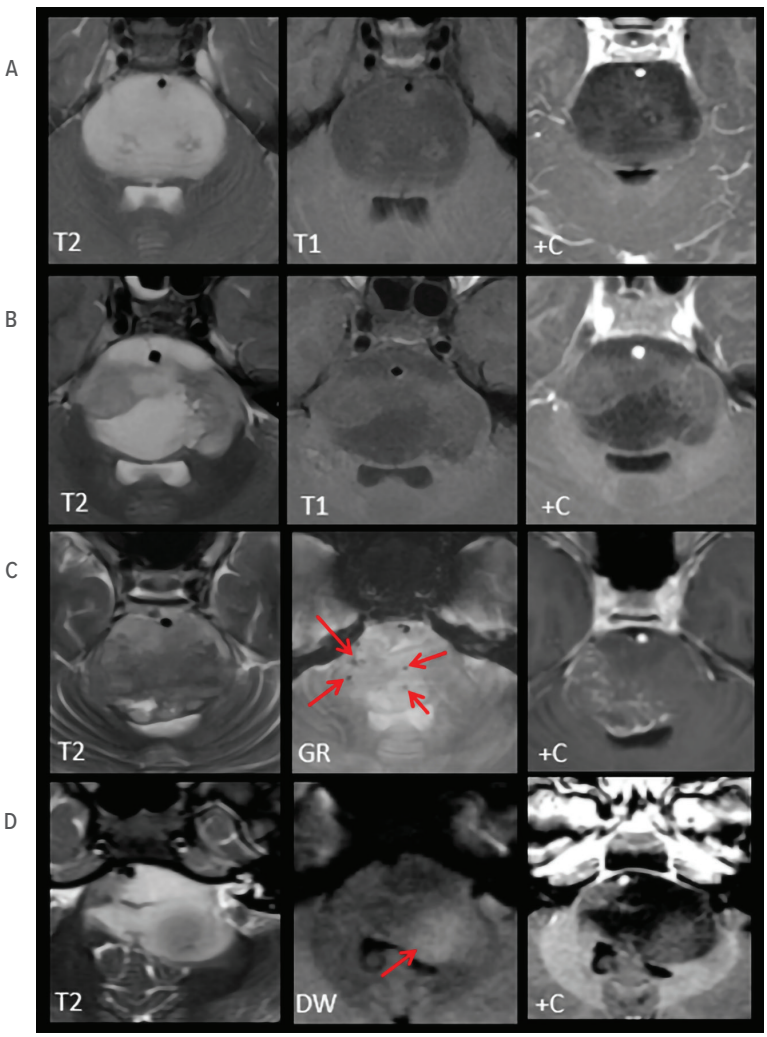
"We found that the presence of tumor necrosis, contrast enhancement, visible diffusion restriction, and most importantly, distant disease at diagnosis, correlated with worse survival in these patients," says first author James Leach, MD, a neuroradiologist at Cincinnati Children's.

On multivariable analysis, both age and distant disease were significantly associated with overall survival. Also, baseline imaging showed a 9.5% discordance in DIPG diagnosis between local and central review, which demonstrated the need for central imaging confirmation for prospective trials.

Organizing so much clinical, pathological, and imaging data from numerous institutions was a major challenge—a task met by the team's research PACS application and imaging core specialists. Research from this study has been presented at conferences of the American Society of Neuroradiology, the International Symposium on Pediatric Neuro-Oncology, and the Society for Neuro-Oncology.

Looking ahead, researchers plan to begin evaluating image changes during the course of treatment to track outcomes of differing therapy regimens.

Learn more: https://dipgregistry.org/



Examples of submitted cases classified as characteristic of DIPG. (T2: T2-weighted, T1: T1-weighted, +C: post contrast T1-weighted, GR: Gradient recalled echo, DW: Diffusion weighted). A. Classic infiltrative pontine lesion with minimal enhancement. B. More heterogenous signal on T2 but characteristic. C. Spotty minimal areas of hemorrhage on GR (GR, arrows), with patchy enhancement. D. Mildly heterogenous with more localized area of diffusion restriction (DW, arrow) and relative T2 hypointensity.

Electronic Health Record Data Reveals Patterns of Care for Children with Cerebral Palsy

Brad Kurowski, MD, MS

PUBLISHED MARCH 25, 2021
Developmental Medicine & Child Neurology

For children with cerebral palsy (CP)—the most commonly seen motor disability in children—care involves providers from many different specialties. Coordination of care among these groups is essential to improving outcomes.

By characterizing the patterns of care for children with CP, Brad Kurowski, MD, MS, and colleagues are providing a foundation for understanding how care could be improved.

The team began by extracting electronic health record data for more than 6,000 children with CP over a 10-year period. Across 34 specialties, a total of nearly 4 million in-person visits and care coordination notes were identified. Per child, the duration of care averaged five years and five months, with five specialty interactions and 22 in-person visits each year. Overall, the ratio of in-person to care coordination visits was one to five, meaning that most interactions with care teams occurred outside of in-person visits.

Using hierarchical clustering, a machine learning algorithm that groups similar objects, the team also identified seven clusters of care—musculoskeletal and function, neurological, high-frequency/urgent care services, procedures, comorbid diagnoses, development and behavioral, and primary care.

"These care patterns help us gain a better understanding of where care can be optimized," says Kurowski. "Medical informatics, machine learning, and big data approaches provide unique insights to inform the development of precision care models for individuals with CP."

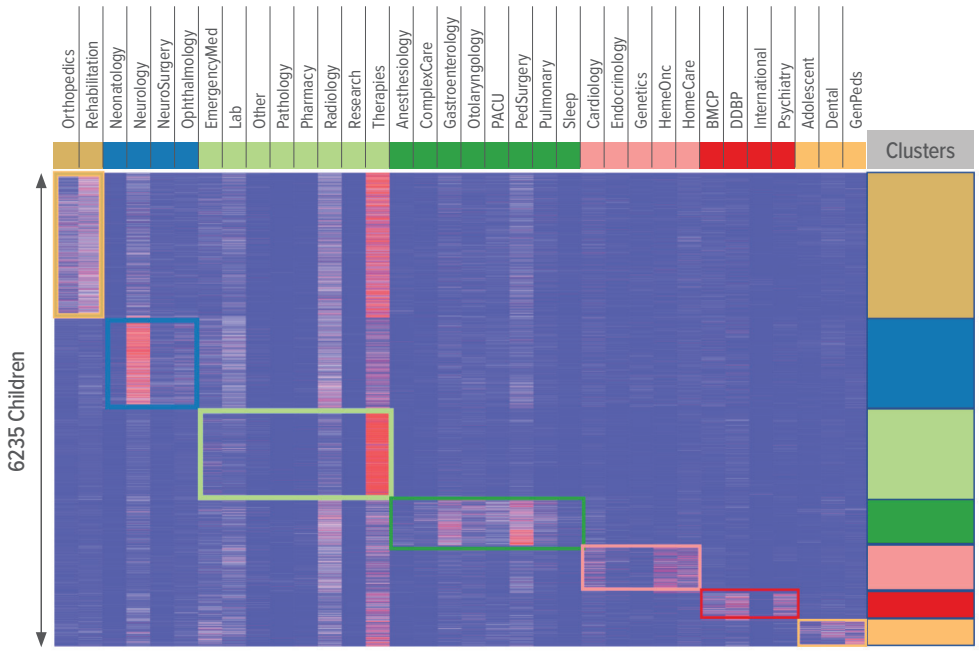
Next, researchers will use these insights to develop clinical dashboards and identify areas for intervention.

RESEARCH & TRAINING DETAILS

Faculty	10
Research Fellows & Post Docs	1
Research Graduate Students	6
Total Annual Grant Awards	$1.7M

Kurowski BG, Greve K, Bailes AF, Zahner J, Vargus-Adams J, McMahon MA, Aronow BJ, Mitelpunkt A. Electronic health record and patterns of care for children with cerebral palsy. Dev Med Child Neurol. Mar 25 2021.

Care Clusters in Cerebral Palsy



This graph shows clusters of care for children with cerebral palsy. Clusters of specialties are shown on the x-axis and individuals with cerebral palsy are shown on the y-axis. Each row represents the visits of one child across all specialties at one tertiary medical center. Each column represents the number of visits to a specialty over 10 years. The number of visits was normalized using the mean of each column. Clusters were created using unsupervised hierarchical clustering applied to both rows and columns. PACU, post-anesthesia care unit; BMCP, Behavioral Medicine and Clinical Psychology; DDBP, Division of Developmental and Behavioral Pediatrics.

CLUSTERS (# OF CHILDREN)
- Musculoskeletal and Function (1877)
- Neurological (1226)
- High Frequency Services (1156)
- Procedures (648)
- Comorbid Diagnoses (629)
- Development and Behavior (362)
- Primary Care (337)

Web-Based Tool Helps Manage Methotrexate Toxicity Risk

Zachary Taylor

Laura Ramsey, PhD

PUBLISHED SEPT 2020
Clinical Pharmacology & Therapeutics

Some children and adults with acute lymphoblastic leukemia (ALL) face a risk of toxicity from high-dose treatment with methotrexate (MTX) because their bodies are slower than others at clearing the drug from their systems.

Severely delayed MTX clearance is seen in up to 1% of pediatric patients with ALL. If this metabolic difference is not detected and managed, patients can experience life-threatening kidney, liver and intestinal damage in addition to their cancer. While folinic acid often helps the kidneys to eliminate MTX, sometimes patients need a more powerful drug, glucarpidase. This rescue agent can eliminate 90% of MTX concentrations within 15 minutes, so it should be administered only when MTX concentrations exceed specific parameters. Otherwise, there's a risk of cancer relapse because too much MTX can be neutralized.

"There has been a lack of clinical tools to identify patients likely to experience delayed MTX clearance. As a result, response tends to be reactive," says corresponding author Laura Ramsey, PhD. "Now we have a tool that can be used early in a course of treatment."

To address this concern, a team of researchers with the Division of Research in Patient Services used data from 772 children receiving MTX to develop a new pharmacokinetic (PK) model that better defines the clearance curves for patients based on several clinical factors. That model now supports a web-based clinical decision support tool called MTXPK.org.

"This tool can help clinicians optimize the administration of glucarpidase, which is indicated only when both the MTX concentration and an increase in creatinine levels reach specific targets," says first author Zachary Taylor, then a graduate student in Ramsey's lab.

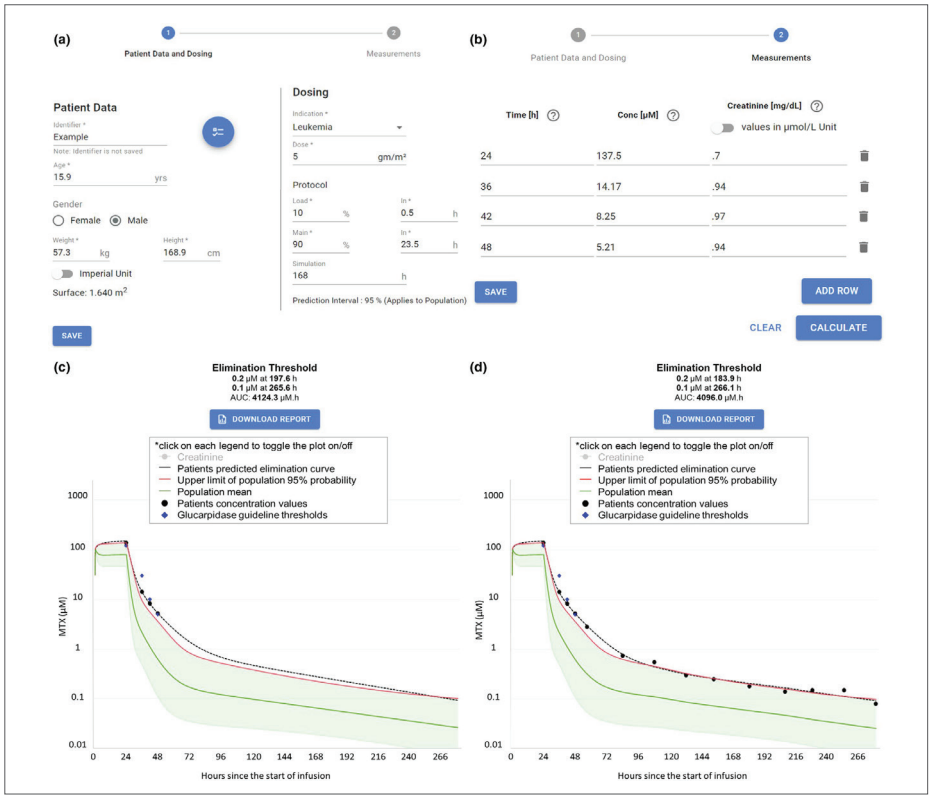
The new tool blends individualized demographics, with serum creatinine measures, and real-time drug concentrations to predict a patient's MTX elimination profile. The free tool is available at https://mtxpk.org.

RESEARCH & TRAINING DETAILS

Faculty	6
Joint Appointment Faculty	10
Research Fellows & Post Docs	1
Research Graduate Students	6
Total Annual Grant Awards	$2.5M
Total Annual Industry Awards	$124,500

Taylor ZL, Mizuno T, Punt NC, Baskaran B, Navarro Sainz A, Shuman W, Felicelli N, Vinks AA, Heldrup J, Ramsey LB. MTXPK.org: A Clinical Decision Support Tool Evaluating High-Dose Methotrexate Pharmacokinetics to Inform Post-Infusion Care and Use of Glucarpidase. Clin Pharmacol Ther. Sep 2020;108(3):635-643.

How the MTXPK.org Decision Support Tool Works



Once patient demographics, plasma methotrexate (MTX) concentrations and serum creatinine levels are loaded, the tool calculates an individualized pharmacokinetic (PK) concentration-time curve. In this demonstration case, the first screen (c) shows a patient that meets indications for glucarpidase. The second screen (d) shows the same patient after administering glucarpidase, demonstrating the accuracy of the predicted curve. Black line shows the individual elimination curve; green line shows population elimination curve; red line shows 2 standard deviations above the population curve and the purple diamonds show glucarpidase guideline thresholds.

Rapid Research Establishes Key Diagnostic Tool for COVID-Related MIS-C

Jackeline Rodriguez-Smith, MD

Grant Schulert, MD, PhD

PUBLISHED JUNE 8, 2021
Lancet Rheumatology

Early in the COVID-19 pandemic, the impact on children was relatively small compared to older adults. But for the children who did suffer severe illness, one of the most serious concerns was multisystem inflammatory syndrome (MIS-C).

Initially, this condition appeared similar to the inflammatory disorders Kawasaki disease and macrophage activation syndrome (MAS), both of which were familiar to experts at Cincinnati Children's. So what was different about MIS-C and could this form of hyperinflammation be diagnosed and controlled with similar approaches? A team led by first author Jackeline Rodriguez-Smith, MD, and Grant Schulert, MD, PhD, was quickly assembled to find out.

Between April 30, 2019, and Dec. 14, 2020, the team enrolled 19 patients with MIS-C and nine with Kawasaki disease. While both groups displayed similar levels of several inflammatory biomarkers, including S100 proteins and Interleukin-18, those with MIS-C had significantly higher median concentrations of IFNγ-induced CXCL9—1730 pg/mL vs. 278 pg/mL. The MIS-C patients with elevated CXCL9 also tended to have signs of shock, acute kidney injury, altered mental status, myocardial dysfunction and other biomarkers of severe illness.

This set of symptoms more closely resembled MAS, which is also an IFNγ-driven disorder, and suggests more-specific approaches for diagnosis and management.

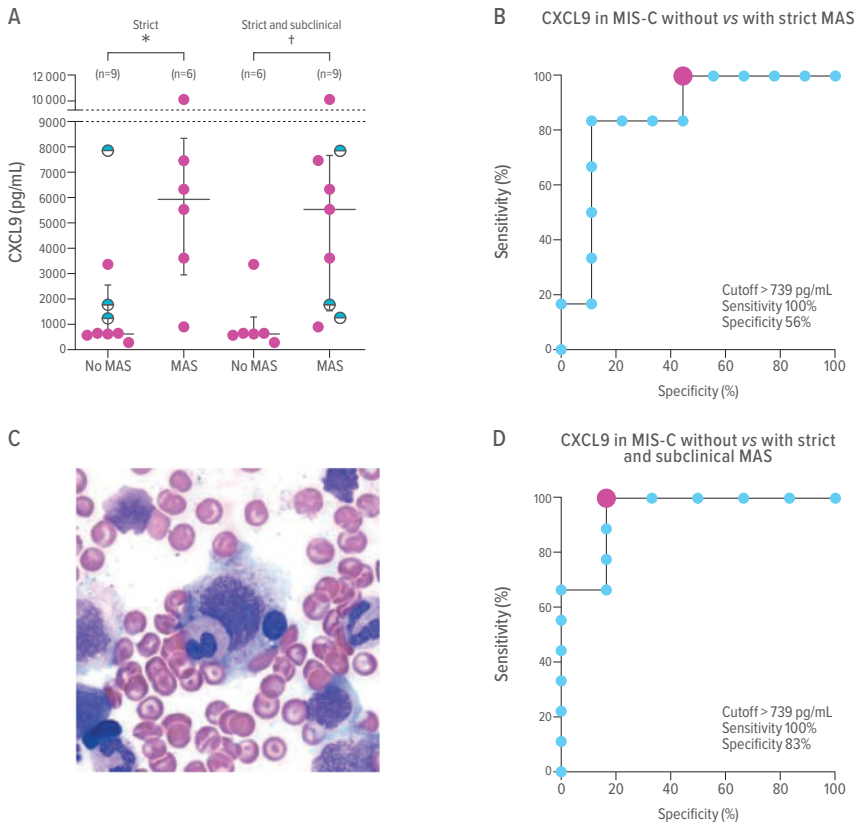
"These findings have two key implications," Schulert says. "First, diagnosing MIS-C will become harder with more people having prior COVID infection and the disease becoming more endemic. Checking CXCL9 levels, especially if the turnaround time is short, may be very helpful. Second, this tells us that treatment approaches used in macrophage activation syndrome—such as blocking key inflammatory cytokines—may be very helpful in the most severe MIS-C cases."

RESEARCH & TRAINING DETAILS

Faculty	11
Total Annual Grant Awards	$2.1M
Total Annual Industry Awards	$482,084

Rodriguez-Smith JJ, Verweyen EL, Clay GM, Esteban YM, de Loizaga SR, Baker EJ, Do T, Dhakal S, Lang SM, Grom AA, Grier D, Schulert GS. Inflammatory biomarkers in COVID-19-associated multisystem inflammatory syndrome in children, Kawasaki disease, and macrophage activation syndrome: a cohort study. Lancet Rheumatol. Aug 2021;3(8):e574-e584.

Differential CXCL9 Concentrations in MIS-C with and without MAS



Panel (A) shows CXCL9 concentrations in patients with MIS-C based only on strict MAS classification criteria (left) and including subclinical MAS (right). The subclinical MAS data appears as half-filled black circles. Panel (B) shows ROC curves for CXCL9 differentiation based on strict criteria. The red dot indicates the optimal cutoff point. Panel (C) A bone marrow biopsy smear of a patient with MIS-C shows haemophagocytosis with an ingested lymphocyte and a myeloid precursor in the process of being ingested by a histocyte. Panel (D) a ROC curve for CXCL9 differentiation that includes subclinical MAS. The red dot indicates the optimal cutoff point. ROC=receiver operating characteristic. MAS=macrophage activation syndrome. MIS-C=multisystem inflammatory syndrome in children.

Biofeedback System Reduces Risk of Anterior Cruciate Ligament Injury in Adolescent Female Athletes

Gregory Myer, PhD

PUBLISHED NOV. 1, 2020
Journal of Sport Rehabilitation

For adolescent female athletes, risk of anterior cruciate ligament (ACL) injury is high. Existing prevention programs have failed to reduce the rates of these injuries. Can mind-body therapy help?

Using biofeedback—a technique that teaches individuals how to better control their body's functions—researchers led by Gregory Myer, PhD, in the Division of Sports Medicine designed a new system to reduce the risk factors associated with ACL injuries. The innovative system works by simultaneously providing real-time, interactive, visual feedback about a wider range of biomechanical variables (knee, trunk, and hip) than previous approaches (knee only).

In a kinetics laboratory, researchers tested the system with 20 adolescent females. Participants performed sets of bodyweight squats in several training blocks for a total of 110 squats. Half of the participants were randomly assigned to receive a real-time feedback block first, while the other half received a control (sham) feedback block first.

Compared with performance when participants squatted with the sham stimulus, heat map analysis revealed that interaction with the real-time feedback improved squat performance. These results show the system's significant impact on movement biomechanics during performance of a bodyweight squat.

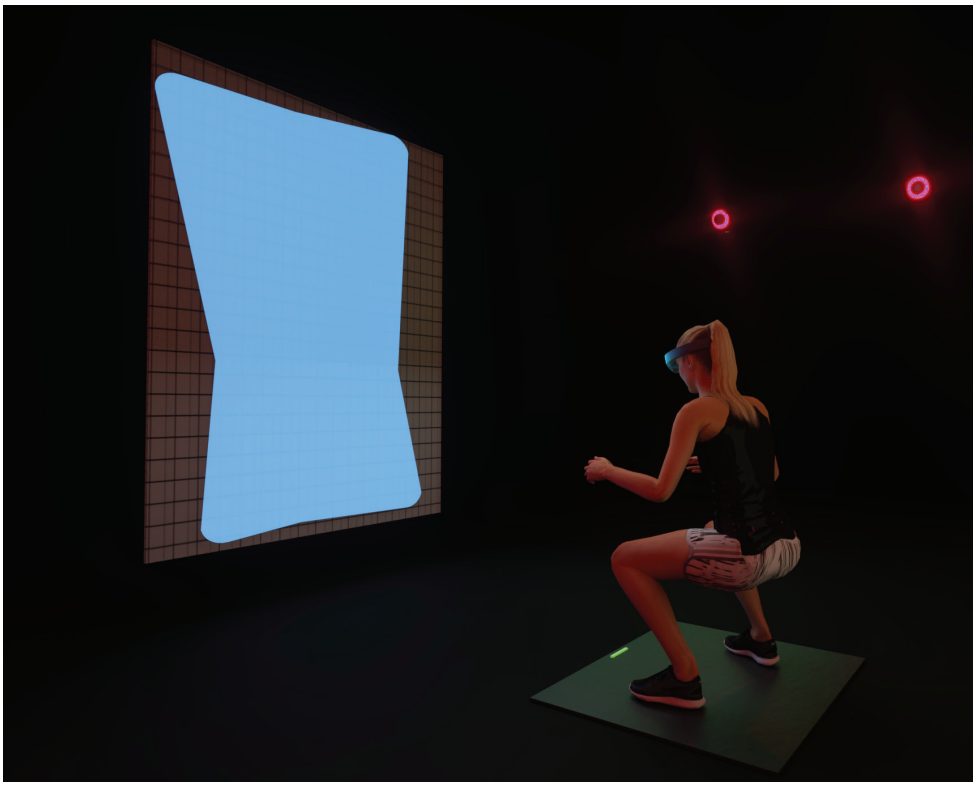
"Stopping ACL injuries in adolescent females reduces the chances of ending of an athletic career and other associated trauma, including significant pain, depression, decreased athletic identity, and lower academic performance," says lead author Scott Bonnette, PhD. "This may also greatly reduce the associated amplified risk of a subsequent ACL injury, likelihood for long-term disability, and risk of early osteoarthritis and chronic pain."

Next, researchers plan to develop the system from a research tool to a clinic-ready platform, preventing ACL injuries on a wide scale.

RESEARCH & TRAINING DETAILS

Faculty	6
Total Annual Grant Awards	$142,327
Total Annual Industry Awards	$25,000

Bonnette S, DiCesare CA, Kiefer AW, Riley MA, Barber Foss KD, Thomas S, Kitchen K, Diekfuss JA, Myer GD. Injury Risk Factors Integrated Into Self-Guided Real-Time Biofeedback Improves High-Risk Biomechanics. J Sport Rehabil. Nov 1 2019;28(8):831-839.

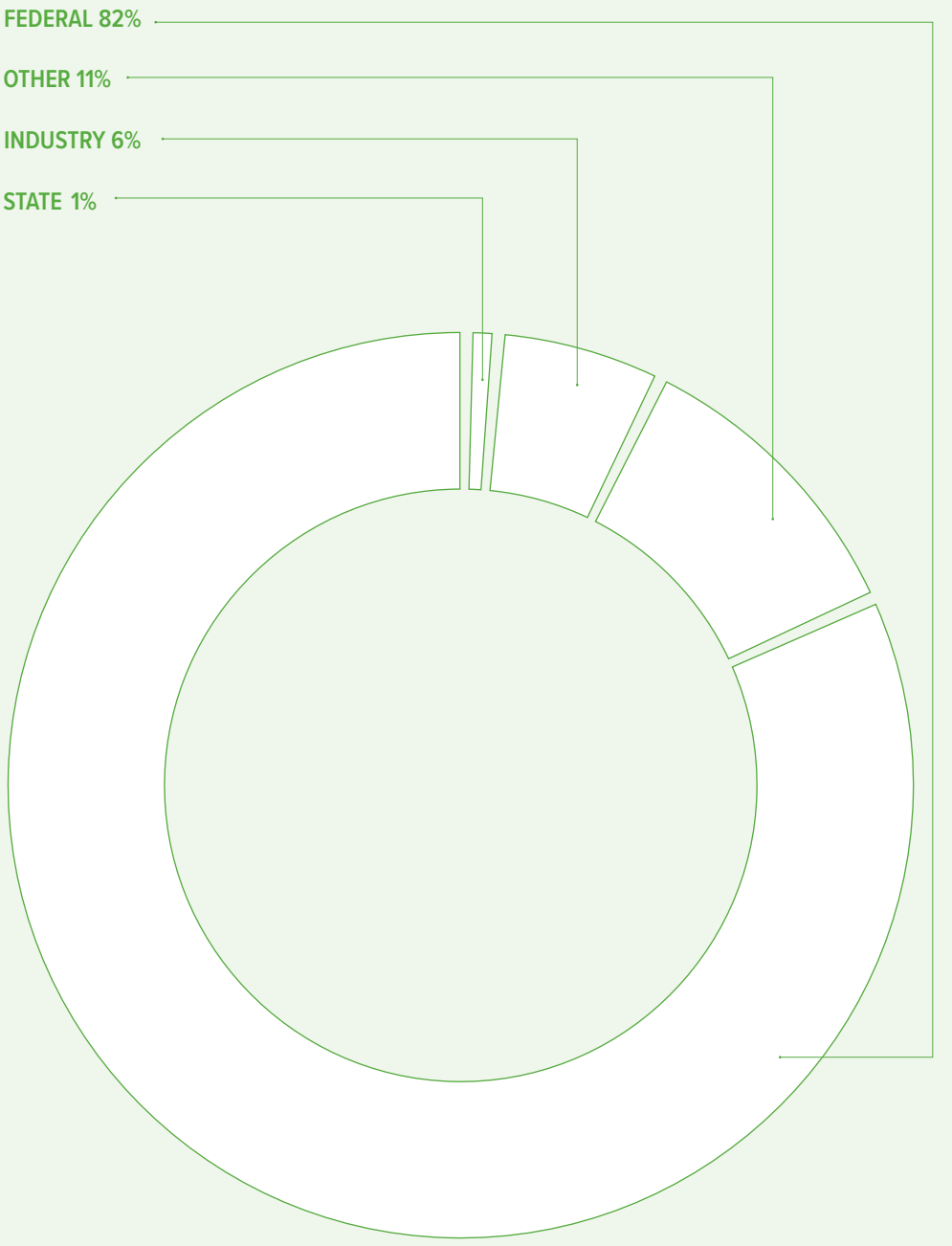


An athlete performs a squat exercise during the biofeedback study.

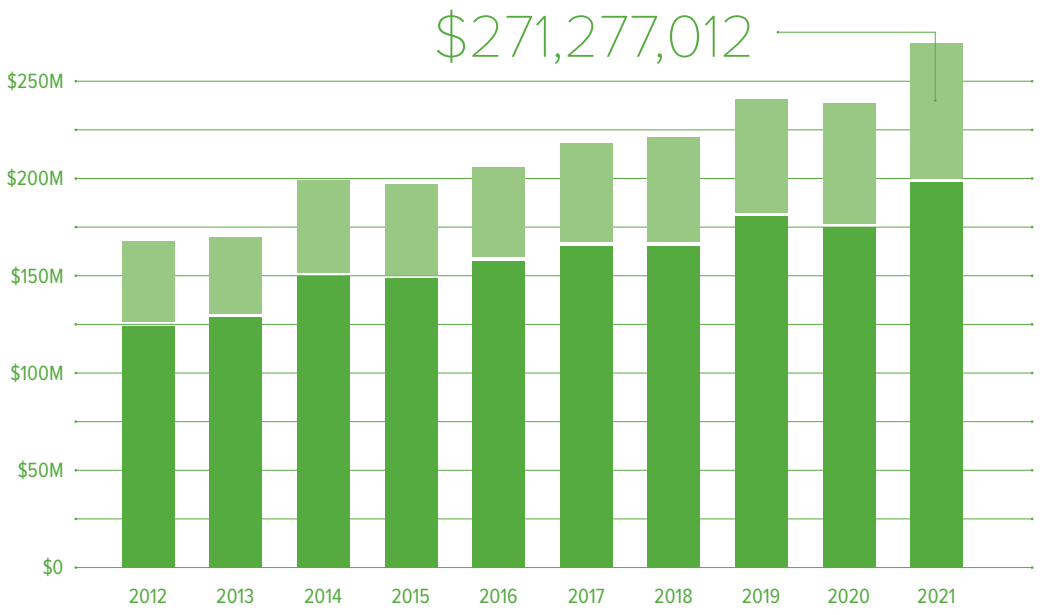
By the Numbers

Funding & Awards
Faculty, Fellows, and Staff

Sources of External Funding

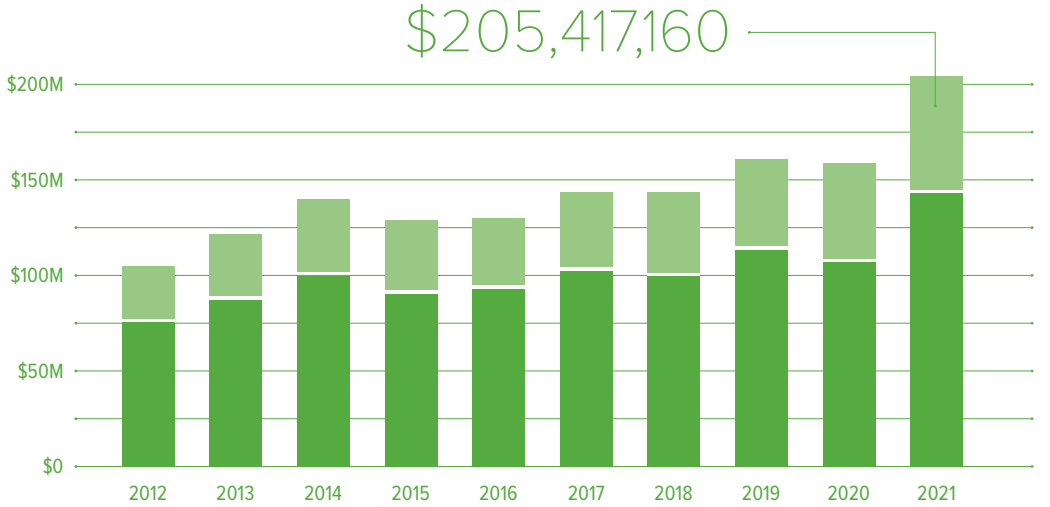


Sponsored Program Awards



Sponsored program award figures include funding awarded for direct and indirect costs, but exclude fee-for-service contracts.

National Institutes of Health Awards



Indirect Funds

Direct Funds

Child Health Research Career Development Awards

This program provides $93,000 grants to support training physician-scientists and stimulate pediatric research across a variety of disciplines.

Anna Peters, MD
Gastroenterology

Meredith Schuh, MD
Nephrology

Sonya Girdwood, MD
Hospital Medicine

Strauss Fellows

The Arnold W. Strauss Fellow Award is a one-year $10,000 award instituted in 2014 in honor of Dr. Strauss' tireless championship of higher education at Cincinnati Children's.

Ryan Brady, MD
Endocrinology

Francis Leblanc, MD
Cancer and Blood Disease Institute

Naomi Shakked, MD
Nephrology and Hypertension

Alexandra Power-Hays, MD
Hematology/Oncology

Zheyi Teoh, MD
Infectious Disease

Natalia Arias, PhD
Neonatology and Pulmonary Biology

Tafadzwa Chihanga, PhD
Oncology/CBDI

Christian Paese, PhD
Developmental Biology

Place Outcomes Research Awards

This program, administered by the James M. Anderson Center for Health Systems Excellence, provides $60,000 grants to stimulate the development of health services and quality improvement research at Cincinnati Children's and to ensure optimal implementation of clinical and operational innovations in the care delivery system.

Robert Ammerman, PhD, ABPP
Behavioral Medicine and Clinical Psychology

Meera Kotagal, MD, MPH
Pediatric General and Thoracic Surgery

Vanessa Olbrecht, MD, MBA
Anesthesia

Matthew Zackoff, MD, MEd
Critical Care Medicine

Roger Cornwall, MD
Orthopaedic Surgery

Sources of Federal Funding

National Institutes of Health (NIH)	$205,417,160
Health Resources & Services Admin	$6,872,974
Centers for Disease Control and Prevention	$3,120,840
Department of Defense	$2,025,311
Department of Defense Army	$1,899,702
Agency for Healthcare Research and Quality	$1,453,237
Administration for Community Living	$1,208,455
Department of Health and Human Services	$920,526
US Department of Education	$776,854
Center for Medicare and Medicaid Services	$425,617
Food and Drug Administration	$172,295
Department of Veteran Affairs	$152,572
National Science Foundation	$104,874
Maternal & Child Health Bureau	$90,500
US Department of Agriculture	$68,618
US Department of Housing & Urban Development	$28,483
Department of Justice	$15,000
Cincinnati VA Medical Center	$6,645
TOTAL	**$224,759,663**

State & Other Funding Sources

State and Other Funding	$16,290,043
Cystic Fibrosis Foundation	$5,155,732
Patient-Centered Outcome Research Inst.	$2,610,556
American Heart Association - National	$2,241,724
University of Cincinnati	$1,834,711
Children's Hospital of Philadelphia	$1,116,748
Ohio Department of Health	$1,047,718
The Leona M & Harry B Helmsley Charitable Foundation	$927,260
American Society of Hematology	$708,311
Boston Children's Hospital	$672,108
The New York Stem Cell Foundation	$600,000
Dr. Ralph & Marian Falk Med Res Trust Aw	$600,000
TOTAL	**$33,804,911**

Philanthropic Gifts for Research

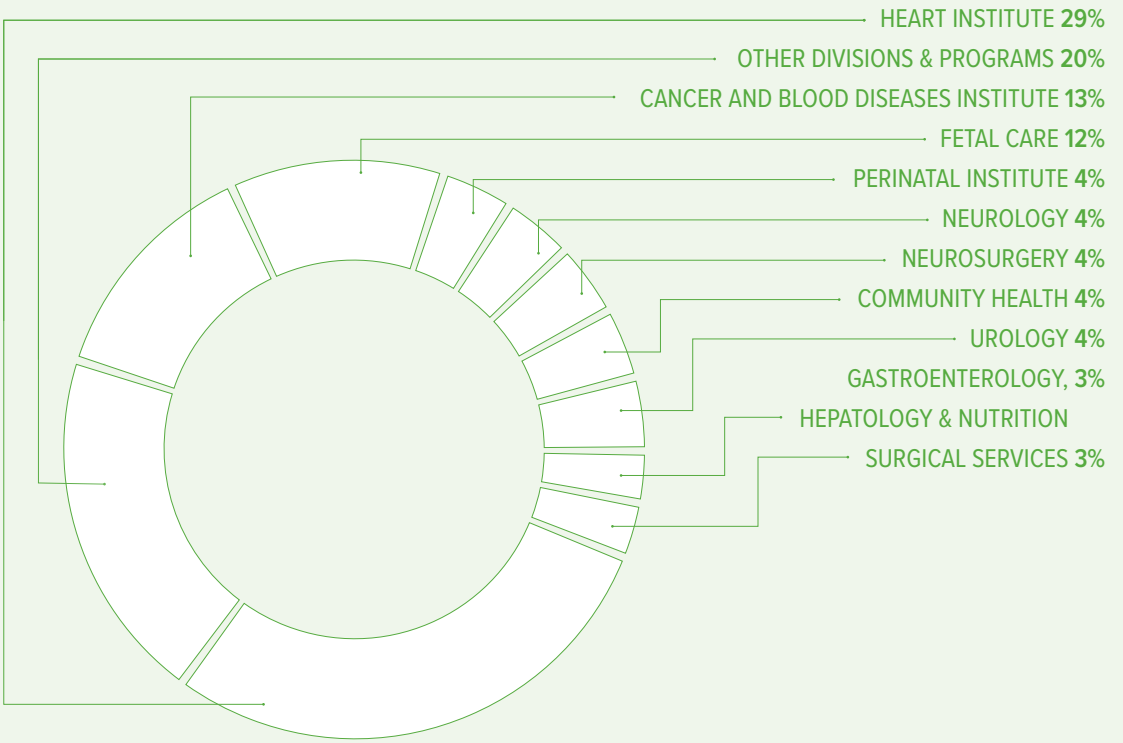
Our commitment to improving care for children through the application of research discovery is the backbone of Cincinnati Children's. And as a nonprofit hospital and research center, private donors play an important role in this work.

OF THE $53 MILLION RAISED THROUGH PHILANTHROPY IN 2021, 50% SUPPORTED THE WORK OF OUR RESEARCHERS.

We are profoundly grateful to those who have chosen to partner with Cincinnati Children's to advance scientific innovation and build better futures for kids. Together, we will never stop moving forward to make a difference for children — here in our community and beyond.

$26,690,829

DONATED TO RESEARCH IN 2021



Trustee Awards

This program provides research funds ranging from $30,000 to $75,000 for junior faculty to support rapid achievement of independent, sustained extramural funding.

Ziyuan Guo, PhD
Developmental Biology

Tamara Tilburgs, PhD
Immunobiology

Rana Herro, PhD
Immunobiology

Jason Tchieu, PhD
Developmental Biology

John Robinson, MD, PhD
Experimental Hematology and Cancer Biology

Mingxia Gu, MD, PhD
Pulmonary Biology

Mattia Quattrocelli, PhD
Molecular Cardiovascular Biology

Procter Scholars

This program supports faculty members from the Departments of Pediatrics, Surgery, Radiology, Patient Services, and Anesthesia who are pursuing academic research careers

David Smith, MD, PhD
Pediatric Otolaryngology and Pulmonary Medicine

William Zacharias, MD, PhD
Pulmonary Biology

Neha Santucci, MD
Gastroenterology

Maria Barnes-Davis, MD, PhD
Neonatology and Pulmonary Biology

Fifth Third Bank / Charlotte R. Schmidlapp Women Scholars

This program provides $50,000 grants to support the academic career development of women faculty who have demonstrated academic potential and leadership skills as they progress toward the ranks of associate and full professor.

Elisa Boscolo, PhD
Division of Experimental Hematology and Cancer Biology

Megan McGrady, PhD
Behavioral Medicine and Clinical Psychology

CCTST Program Awards

Cincinnati Children's partners with the University of Cincinnati and other institutions to support programs funded through the Center for Clinical and Translational Science and Training (CCTST). These faculty received grants ranging from $10,000 to $100,000 to support translational research, build core capabilities, develop innovative research methods, or collaborate with community partners.

June Goto Nakamura, PhD
Neurosurgery

Hee Kim, MD
Radiology

Theodosia Kalfa, MD, PhD
Hematology/Oncology

Nicholas Ollberding,PhD
Biostatistics and Epidemiology

Yan Xu, PhD
Pulmonary Biology

Emily Miraldi, PhD
Immunobiology and Biomedical Informatics

Elaine Urbina, MD, MS
Cardiology

Md Nasimuzzaman, PhD
Experimental Hematology and Cancer Biology

Gang Huang
Pharmaceutical Sciences

Vivian Hwa, PhD
Endocrinology

Daniel Prows, PhD
Human Genetics

H. Leighton Grimes, PhD
Immunobiology

Rana Herro, PhD
Immunobiology

Ian Lewkowich, PhD
Immunobiology

Bin Huang, PhD
Biostatistics and Epidemiology

Xueheng Zhao
Pathology

Mina Busch
Nicolas Nassar, PhD
Rick Ittenbach, PhD
Biostatistics and Epidemiology

Sang Hoon Lee, MD, MEd
Emergency Medicine

Tanya Froehlich, MD, MS,
Developmental and Behavioral Pediatrics
& Nichole Nidey, MS, PhD
Biostatistics and Epidemiology

Laura Olexa, RN, BSN,
& Linda Helms
Veggies via Vespa/North Fairmount Community Center

Dena Cranley, MA,
& Barbara Lynch
Chairs, First Ladies for Health

MEDICAL RESIDENTS
209

Research Graduate Programs

Biomedical Informatics	Immunology Program	MSTP Program	BRT Graduate Program - MS	MDB Graduate Program - PhD
51 Students (23 PhD/28 GC)	43 Students (37 PhD/6 MS)	70 Students	10 Students	54 Students

Administrative Staff

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Vice President
Research Operations

Our Faculty

Pediatrics
804 total [746 full time / 58 part time]

Surgery
104 total [99 full time / 5 part time]

Anesthesia
63 total [42 full time / 21 part time]

Radiology
51 total [43 full time / 8 part time]

Patient Services
13 total [5 full time / 8 part time]

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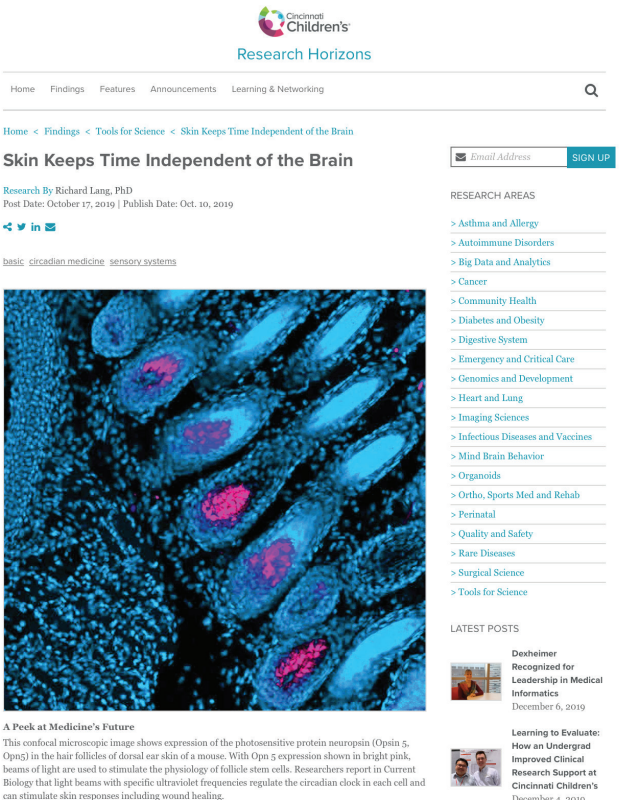

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