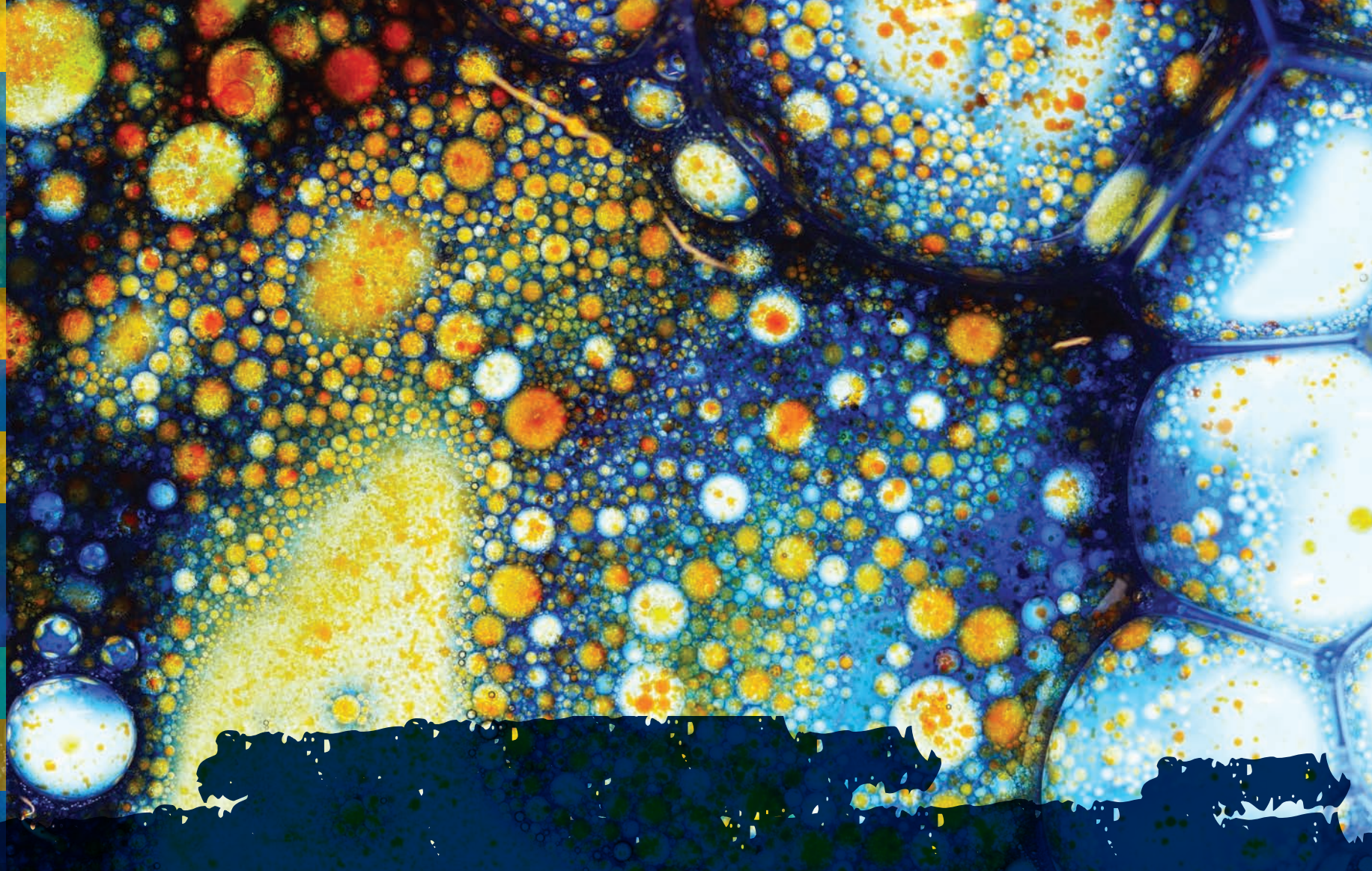


MichiganAnswers™ FOR KIDS

C.S. MOTT CHILDREN'S HOSPITAL
UNIVERSITY OF MICHIGAN HEALTH

RESEARCH HIGHLIGHTS FROM C.S. MOTT CHILDREN'S HOSPITAL

What is a Michigan Answer?

It is a lifelong pursuit.

A dedication stretching through years, decades, and (for us) over a century.

Every mention of “incurable” or whisper of “unbeatable” calls us to attention.

Every diagnosis is a rally cry.

Kids are waiting. Their families are waiting.

So, we innovate and iterate. We push and challenge the unknown.

We hypothesize and collaborate until new breakthroughs bloom.

Because answers must be found.

Answers must be created.

And we’ll push and persevere until every question has a Michigan Answer.

You can learn more about the nationally ranked clinical services and programs of C.S. Mott Children’s Hospital at **www.mottchildren.org**.

How can we use 3D printing to improve care for children?

Ten years ago, University of Michigan Health C.S. Mott Children’s Hospital kicked off a new frontier in children’s health. Pediatric otolaryngologist Glenn Green, M.D., and pediatric cardiothoracic surgeon Richard Ohye, M.D., implanted a 3D-printed splint in a child’s airway to treat a life-threatening condition.

Incredibly, that child is thriving, and Green continues to use these splints to treat critically ill children with severe lower airway collapse. And the medical 3D-printing revolution led by Green and pediatric otolaryngologist **David Zopf, M.D., M.S.**, shows no signs of slowing.

Zopf is piloting a new device, developed with biomedical engineer Jeff Plott, Ph.D., to treat severe upper airway obstruction that conditions like cerebral palsy and hypotonic airway collapse can cause. The device is non-surgically placed in the nose. It extends down the airway, bypassing upper airway collapse, to help these medically complex kids avoid invasive surgeries, such as tracheostomies. It’s been an instant sigh of relief for families as kids almost immediately start to breathe easier.

Now, there’s a clinical trial underway, which received $3 million in NIH support, to test this specially designed device developed using 3D printing. It’s garnered strong national interest from clinicians desperate to help seriously ill children. With support from the U-M Coulter Translational Research Partnership Program, Zopf is also seeing remarkable promise treating extremely common adult obstructive sleep apnea with the same technology.

In addition, Zopf’s 3D-printing labs are producing teaching tools, including high-fidelity medical and surgical simulators. These printed pieces replicate actual patient anatomy — this is particularly valuable with pediatric procedures where cadaveric models aren’t an option.

During the pandemic, Zopf and his colleagues developed a whole anatomy dissection course using 3D-printed simulators instead of traditional cadaveric dissection. They sent 3D-printed kits across the country, facilitating a virtual video session between 35 surgeons in training and 25 expert surgeons.

Zopf is using the same approach globally, most recently working with a group of surgeons in Burundi, Africa to expand craniofacial surgical education there.

As for what’s next, Zopf says there’s no limitation — any medical specialty could utilize these tools in a variety of creative ways to continue breaking barriers and making meaningful advancements for children.

How can children's hospitals work together to address key research questions for children with congenital heart disease?

University of Michigan Health C.S. Mott Children's Hospital is one of the nation's best and most experienced centers caring for children with congenital heart disease. Although congenital heart disease is the most common birth defect, specific types of heart defects can be relatively rare. In these cases, collaboration across institutions is necessary to study the best treatments and therapies.

One of the newest and most innovative research projects to date is the COMPASS trial, which will be the first ever multicenter randomized clinical trial to compare a catheter-based procedure and a surgical procedure in congenital heart patients. In the trial, infants with ductal-dependent pulmonary blood flow will be randomized to receive either a catheter-based ductal stent or surgery to place a systemic-to-pulmonary artery shunt.

Pediatric cardiothoracic surgeon **Jennifer Romano, M.D., M.S.**, (from left), pediatric cardiologist **Sara Pasquali, M.D., M.H.S.**, and interventional pediatric cardiologist **Jeffrey Zampi, M.D.**, along with a collaborative group of investigators from other prominent congenital heart centers, designed this clinical trial. It's being conducted through the Pediatric Heart Network and funded by the National Heart, Lung, and Blood Institute. The trial received FDA approval and will begin enrollment in spring of 2022.

Several types of congenital heart defects can have ductal-dependent pulmonary blood flow, including tetralogy of Fallot with pulmonary atresia as well as some types of single ventricle heart defects like tricuspid atresia. Newborns with these conditions do not have adequate blood flow to the pulmonary arteries and lungs. Because of this, not enough oxygen is picked up from the lungs, and these children will not survive without intervention.

Traditionally, a surgical shunt is placed to supply pulmonary blood flow. More recently, newer less-invasive procedures that involve placement of a stent during a cardiac catheterization have been developed. Both procedures can be successfully performed, but studies to date have not been able to determine which is the best option in the long run.

With the COMPASS trial, investigators expect to enroll 300 infants across 23 heart centers around North America. Health outcomes such as mortality, subsequent days in the hospital, a need for repeat procedures and other complications will be monitored over time. In addition, those who do not qualify or cannot be enrolled in the trial will be studied in a registry.

This novel trial was made possible in part through a unique initiative U-M supports to promote sharing of congenital heart data and collaborative research across the country. This effort, known as Cardiac Networks United, brings together data across multiple research networks to foster collaborative research not possible within individual centers or research registries. The Congenital Heart Center at Mott serves as the Data Coordinating Center, housing the most comprehensive collection of congenital heart data worldwide, now spanning more than two thirds of the nation's congenital heart programs.

Why do certain gene mutations cause children to develop epilepsy?

When basic scientists and clinicians work together, there's a chance to develop new precision medicine therapies for some of the body's most perplexing conditions.

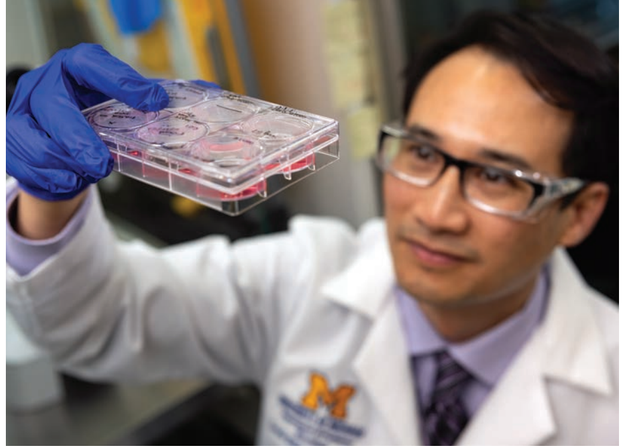
That's the ultimate hope of **Louis Dang, M.D., Ph.D.**, and his collaborators studying epilepsy and other conditions affecting the developing brain.

Epilepsy is most often diagnosed in children. It causes chronic seizures, plus it is associated with a host of issues that can severely disrupt childhood, including learning, behavioral and sleep problems, ADHD and psychiatric comorbidities.

In recent years, scientific discovery has been able to isolate which gene mutations can cause epilepsy. But the function of many of those genes still isn't well understood, so it's unclear how these gene mutations can cause epilepsy or what can be done about it.

Dang and his colleagues focus on human stem cell-based models to probe this issue.

A recent study used skin cells from patients with polyhydramnios, megalencephaly and symptomatic epilepsy (PMSE) syndrome, a neurological condition marked by an unusually large brain, frequent seizures and intellectual disability. With cell samples from these patients, Dang and colleagues generated stem cells and derived them into neural cultures.



This is a relatively new technology that lets researchers take stem cells and make them into small 3D balls of cells that have a structural resemblance to the developing human brain. It allows for studying the structural aspects of a developing human brain in a laboratory setting.

In Dang's study, the neural cultures demonstrated upregulated activity in the mTOR pathway, as expected from the gene mutation. The mTOR pathway is considered a master regulator of metabolism but its role in neural development is not as well known. This NIH-funded study offered a novel look at how hyperactivation of the mTOR pathway affects early developmental processes of the brain.

Dang and his collaborators are also investigating certain sodium channel mutations and how they affect neuronal function. As with the mTOR pathway work, the hope is to understand the underlying pathological processes to uncover new gene-targeted therapeutics for pediatric patients.

How can access to developmental and behavioral care be more equitable?

Connecting to follow-up care can be a challenge for any busy parent. For families facing things like transportation barriers, food insecurity, racism and financial stress, it can be that much harder.

Clinical psychologist **Sharnita Harris, Ph.D.**, is working at the University of Michigan Health's Ypsilanti Health Center to help all families find access to developmental and behavioral screenings and follow-up care as recommended.

Harris offers behavioral health care for common pediatric problems in the clinic as well as integrated developmental assessments for issues including communication, motor and adaptive skills, and problem solving. She is also researching how parents experience access to resources today and how the health care system infrastructure can improve to remove barriers.

More than any other University of Michigan Health primary care clinic, the patient population at Ypsilanti is diverse. They're more likely to have Medicaid insurance and to speak Spanish as a first language.

To understand their experience, Harris conducted brief phone interviews with 51 caregivers to assess access to developmental care referrals and follow-up resources. Of the families interviewed, 67 percent had some form of Medicaid insurance and 57 percent were Black. She also interviewed five practitioners to understand the provider perspective.

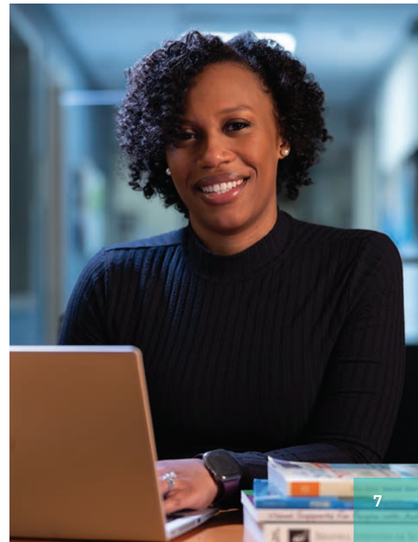
The interviews showed a need to create a more equitable infrastructure so the burden doesn't fall just to caregivers. The COVID-19 pandemic has only hastened these concerns, as families from communities of color and/or from low socioeconomic backgrounds experienced disproportionate challenges.

Next, Harris and collaborators have secured funding to hold several focus groups over the next year to go deeper into these issues. Harris will use this patient information to develop a multi-level referral toolkit.

Future changes could include logistical improvements such as allowing parents to make appointments with specialists during a clinical visit. Or providers could be given standard language to use that's shown to resonate with patients.

Parents could receive more handouts on a child's development or have more in-depth conversations around a child's developmental or behavioral concerns.

By understanding what parents want and need, health systems will be better able to provide creative solutions that make a difference, Harris says.



How can we help infants surviving preterm birth breathe easier?

In the United States, 1 in 10 babies are born prematurely, or before 37 weeks gestation. Advances in medical care have led to increased survival of extremely premature infants. Of those who are born at a birth weight less than one kilogram (about 2.2 pounds), approximately 50 percent develop bronchopulmonary dysplasia (BPD), a chronic lung disease in which lung alveoli or air sacs fail to form normally. Each year, more than 12,000 infants develop BPD in the U.S.

Many children born prematurely, especially those with BPD, develop chronic pulmonary complications, such as recurring wheezing, cough and asthma, and they need inhaled medications. Throughout childhood and early adulthood, they can have more severe respiratory illnesses and need more frequent doctor visits and hospital admissions for respiratory viral infections.

When an infant with a history of BPD is exposed to a common cold virus, such as rhinovirus, they risk an infection that can be life-threatening or can result in long-term respiratory health consequences.

Despite its severity, there is no way to prevent or modify the course of BPD, and only symptomatic treatment is available.

That's why pediatric pulmonologist **Antonia Popova, M.D.**, is studying how BPD and prematurity-related pulmonary complications develop.

Research has linked BPD development with issues associated with prematurity, such as hyperoxia (elevated inhaled oxygen levels), infection or inflammation. The goal of the Popova lab is to understand the cellular and molecular mechanisms by which early life exposures prime lung innate immune responses and lead to development of BPD and to discover new ways to combat the disease.

Popova and her team have identified several novel immune mechanisms triggered by "danger signals," or damage-associated molecular patterns (DAMPs), released from injured cells during early life exposure to hyperoxia or infection. These appear to be a priming mechanism for activation of the immune cells in the lung, triggering damaging inflammation. They also appear to regulate how the lung grows and develops over time.

Pinpointing these DAMP-induced immune mechanisms could ultimately help explain why BPD develops and how it causes long-term issues such as asthma or exaggerated immune responses to viral infections later in life. Popova's innovative NIH-funded research program uses a combination of animal models, in vitro studies and translational work to understand the disease.

The ultimate aim is to harness novel immune mechanisms to help children surviving preterm birth breathe easier and build healthy lungs.

Can a robust clinical and translational research infrastructure accelerate discovery?

The Chad Carr Pediatric Brain Tumor Center at University of Michigan Health C.S. Mott Children's Hospital is making rapid progress toward advancing treatments for these devastating diseases. A particular focus is the cancer that took 5-year-old Chad Carr's life in 2015: diffuse intrinsic pontine glioma (DIPG), one of the most aggressive and lethal types of brain tumors.

Two of the investigators leading the center's efforts are pediatric neuro-oncologist **Carl Koschmann, M.D.**, (right) and neuropathologist **Sriram Venneti, M.D., Ph.D.** They've overseen a remarkable sea change, as pediatric brain tumors have historically received much less attention, funding and research than adult brain tumors or other types of cancer.

Several initiatives have recently contributed to Mott's world-renowned expertise on high-risk brain tumors.

First, translational research is moving to clinical care faster than ever before. At U-M, some 10 active labs are working on brain tumor research with experts from pediatrics, pathology, neurosurgery, radiation oncology and other departments.

There's an internal research program at Mott that funds specific initiatives, which has helped propel many projects forward to receive NIH grant funding. Many peer-reviewed publications have resulted, including recent papers in *Cancer Cell* and *Science Translational Medicine*.

Second, investment from the Carr family has spurred growth in Mott's pediatric cancer clinical research infrastructure. Koschmann says they've been able to hit the gas pedal when it comes to opening new clinical trials. At any given time, Mott is participating in around two dozen clinical trials for pediatric brain cancer.

Mott also joined the Pacific Pediatric Neuro-Oncology Consortium (PNOC), an international consortium dedicated to pediatric brain tumors. This enables researchers at U-M to have a complete translational pipeline from drug discovery to multi-site early phase clinical trials in children with brain tumors. Multiple projects are underway.

Patients and families have taken notice: In recent years, children and young adults with high-risk brain tumors have traveled

from around the world for treatment at Mott. It's not just about work in the lab, either. Koschmann and his collaborators have established a multidisciplinary clinical and clinical research infrastructure that optimizes patient care and quality of life for the entire family.

Koschmann says pediatric brain tumors have historically been a neglected section of cancer research. They haven't been well-understood and little progress has been made toward treatments in the past two decades.

But the Chad Carr Pediatric Brain Tumor Center shows that with the right people and support, it's possible to shed light on these complex cancers.

Is newborn sleep a key to improved child cognitive development?

Sleep is a window into the newborn baby brain. But scientists haven't always been able to look inside. There is very little research about newborn sleep, and there's not a clear threshold for when newborn sleep patterns should be considered abnormal.

In her research and clinical practice, pediatric neurologist **Renée Shellhaas, M.D., M.S.**, found a specialized group of babies who could help fill in these gaps. Babies with myelomeningocele (MMC), the most severe form of spina bifida, have a high risk for abnormal sleep patterns and disordered breathing. For young adults with MMC, sleep-disordered breathing is associated with risk of death.

But babies with MMC are not regularly screened for sleep-disordered breathing, nor is it understood how treating the issue could affect long-term neurodevelopmental outcomes. Shellhaas and a multidisciplinary Mott team conducted a pilot study of babies in the NICU and found that indeed babies with MMC had much worse sleep-disordered breathing than age-matched controls.

Now, a first-of-its-kind study is underway to further probe the connection and also compare sleep in babies who received fetal surgery to address MMC with babies who had surgery after birth. Previous studies showed babies who get fetal repair for MMC are more likely to have good motor outcomes. They're more likely to walk as children, but cognitive outcomes remain abnormal.

Researchers aim to enroll 173 babies for the NIH-funded, nine center study and follow these children through age 2 to evaluate how sleep patterns change and how they relate to cognitive development.

Shellhaas believes if the research continues to find that babies with MMC have a high risk for sleep-disordered breathing, and that sleep-disordered breathing is associated with abnormal cognitive or language development, there's a clear opportunity to change the standard of care. New therapies could be developed to treat the sleep problems and improve cognitive outcomes.

Eventually, the data from this specialized patient population could be extrapolated and applied to other infants with sleep-disordered breathing.

Can wearable sensors put temperature monitoring back in patients' hands?

For cancer patients who've had a blood and marrow transplant (BMT) or chimeric antigen receptor (CAR) T-cell therapy, a fever can be a sign of danger to come.

In BMT recipients, a spike in body temperature could mean infection and/or possibly a severe complication known as graft vs. host disease, in which the donor's transplanted immune system attacks the recipient's tissues. For patients who receive CAR T-cell therapy, fever could mean a life-threatening complication, such as cytokine release syndrome.

A simple FDA-approved temperature sensor in the hospital could help. In a study of 62 adult and pediatric patients in the hospital at University of Michigan Health, researchers found a consumer-grade temperature sensing patch was able to detect fever as soon as five hours before routine temperature checks by hospital staff.

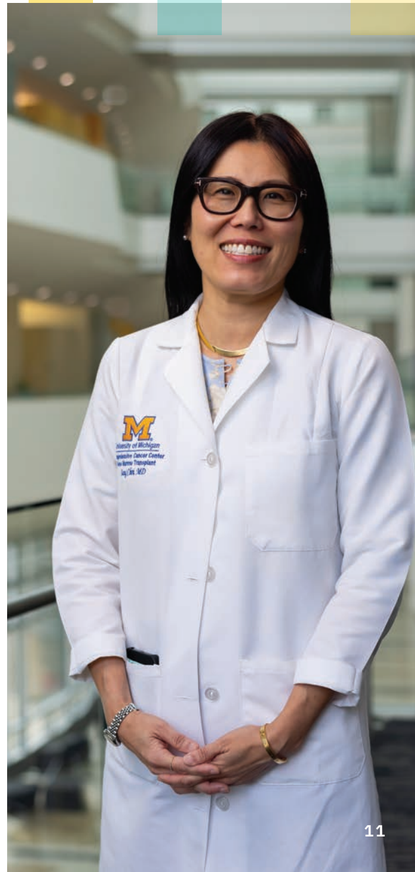
Patients put these sensing patches on below the armpit and swapped them out every 24 hours, just like a Band-Aid. The sensors send temperature readings to a smartphone every two minutes.

Pediatric oncologist **Sung Won Choi, M.D. M.S.**, is one of the co-authors of the study. She says the research team has already taken this approach to an outpatient setting and has observed that some patients were better able to care for themselves at home and get to a hospital faster than they would have doing routine checks with a thermometer.

Constant surveillance could be particularly helpful for kids with these conditions and offer parents some peace of mind.

Home health innovations are particularly important now that the COVID-19 pandemic has driven an increase in telehealth visits. Plus, because BMT and CAR T-cell therapy recipients are some of the most vulnerable or immunocompromised patients in the hospital, any tool that allows these patients to go home faster could be beneficial.

Future research into using this device will consider the technology habits of patients. It requires a smartphone to work at home, so researchers will be mindful of health equity and work to make such interventions broadly available to the patients who need them most.



Can standardizing the evaluation and management of small bowel obstruction improve outcomes?

The Division of Pediatric Surgery at University of Michigan Health C.S. Mott Children's Hospital collaborates with 10 other major children's hospitals through the Midwest Pediatric Surgery Consortium (MWPSC), which is one of the first multi-institutional research efforts of its kind, with the goal of developing best practices to improve outcomes in pediatric surgery.

One recent effort is tackling adhesive small bowel obstructions, which can happen after any abdominal surgery. Even a large institution like Mott may see only 10 to 15 adhesive small bowel obstructions per year, so working across centers allows researchers to gather data — and improve outcomes — faster.

Historically, the decision to operate on a child with a bowel obstruction has been rather arbitrary — between 35 and 75 percent of kids will receive surgery, depending on the institution and the surgeon.

To address this variability, pediatric surgeon **K. Elizabeth Speck, M.D., M.S.**, designed a prospective multi-institutional study that will assess what MWPSC centers are doing now, put a standard approach in place, and review the results. The standard approach will include a contrast challenge; these have been used in adults for decades but weren't proven safe in children until Speck and her colleague's research recently did so.

Here's how it works: If a child comes to the hospital with a history of prior abdominal surgery, symptoms of a small bowel obstruction (a distended abdomen, vomiting and pain), and dilated loops of intestine on an X-ray, their stomach is suctioned out. Then they're

given a "contrast challenge." The contrast lights up the intestine on the X-ray to diagnose the obstruction. Importantly, it can also be therapeutic, helping relieve the obstruction in some patients.

An X-ray is taken after 8 to 10 hours. If the contrast is visible in the large intestine, that's good news — the small bowel isn't obstructed anymore because the contrast made it through.

If the contrast remains in the small intestine, the child gets another X-ray at 24 hours. If the contrast is still in the small bowel, it's time to operate.

Without a contrast challenge, there's no standard to help clinicians decide when it's time to move to surgery. This study will show if contrast challenges help hospitals avoid surgery for kids who don't need it and make more timely decisions — with better outcomes — for kids who do.

How can health disparities for kids with sickle cell disease be decreased?

Sickle cell disease — a group of conditions affecting predominantly racial and ethnic minorities in the United States — is rife with inequities.

It affects nearly three times the people as cystic fibrosis, yet receives 10 times less funding per patient. There are far fewer FDA-approved medications for sickle cell disease than other rare, chronic conditions. And people living with sickle cell disease experience severe pain, but patients seeking relief in the emergency room can be inappropriately labeled as drug-seeking.

Meanwhile, persons with sickle cell disease face an average life expectancy of only 45 years, plus lifelong issues with comorbidities such as stroke, bacterial infection and pain.

Yet despite these devastating consequences, systemic barriers block access to quality care, according to research led by pediatric epidemiologist **Sarah Reeves, Ph.D., M.P.H.**, and her team at the Susan B. Meister Child Health Evaluation and Research (CHEAR) Center.

Reeves' research has shown that children with sickle cell disease receive low quality of care — across the nation, whether kids have private insurance or Medicaid coverage.

She's now leading a CDC-funded surveillance effort in partnership with the Michigan Department of Health and Human Services. The goal is to ensure that every individual living with sickle cell disease in Michigan will be able to access high-quality lifelong care. The data will also help identify patients now eligible for expanded health coverage under new Michigan legislation.

Reeves hopes to leverage data to support policy changes that help patient families and incentivize health plans to implement policies that directly improve quality of care for all children with sickle cell disease.

Changes could include expanding access to hematologists and helping kids obtain proven interventions, such as daily antibiotics for the first five years of life and an annual transcranial Doppler screening to monitor stroke risk.

Patient families are involved every step of the way.

Reeves believes the lack of access to quality care for people with sickle cell disease is a complex problem rooted in systemic racism that deserves effective solutions. The long-term surveillance project aims to document the scope of the issue and pave the way to system-level solutions.

How can we eliminate unnecessary opioid prescriptions to children and right-size the rest?

Health care can be about balance — giving patients the right interventions at the right time, not too much nor too little.

Kao-Ping Chua, M.D., Ph.D., a primary care pediatrician and health services researcher, was interested in how unnecessary health care can harm children and their families. This naturally led to an interest in improving opioid prescribing.

In 2021, Chua published a study in *Pediatrics* that reviewed how many opioid prescriptions are written to children, adolescents and young adults, and by whom. Using national data from 2019, he found that over 4 million opioid prescriptions were written to children and young adults (aged 0 to 21 years) in the United States.

About 3.5 million prescriptions were for adolescents and young adults between 12 and 21 years. Dentists wrote 42 percent of these prescriptions, and surgeons wrote 20 percent.

In another study published in 2021, Chua found that 79 percent of prescriptions from dentists to adolescents and young adults were for tooth extractions — even though Tylenol and ibuprofen are equally effective at controlling pain after this procedure.

Based on these two studies, Chua estimates that about one-third of all opioid prescriptions to adolescents and young adults could be avoided just by eliminating opioid prescribing for tooth extractions. With support from the Benter Foundation, he is conducting research on the risks and drivers of dental opioid prescribing, particularly to young people.

Concurrently, Chua is working on efforts to right-size prescriptions when opioids are needed to control moderate to severe pain. With support from the NIH National Institute on Drug Abuse, Chua and collaborators surveyed adolescents and young adults after they had their tonsils removed to find out how many opioid doses they actually took.

From that survey, he found that most patients used far fewer doses than prescribed, leading to leftover opioids that potentially could be misused. Based on these data, he changed the tonsillectomy discharge order set at Mott so that the default number of doses in opioid prescriptions reflected the amount most patients need.

Ultimately, Chua's study shows that it is possible to decrease leftover opioids without compromising pain control after surgery in young people.

Why do some patients with blood clotting diseases have worse symptoms than others?

Pediatric hematologist **Jordan Shavit, M.D., Ph.D.**, sees patients with genetic and acquired disorders of the blood and cardiovascular systems, particularly clotting. While some of his patients exhibit severe disease, others with the same condition will have mild symptoms or none at all.

To understand why these patient differences occur, Shavit employs a novel tool: zebrafish.

Leveraging CRISPR and other genome editing technologies, Shavit and his U-M laboratory collaborators study blood clotting and cardiovascular disorders in tiny zebrafish embryos. The ultimate goal is to discover novel genes that regulate these conditions and to develop new therapies.

Zebrafish have several unique characteristics that make for an ideal model. They can produce hundreds of offspring on a weekly basis, which facilitates large genetic studies. There's no pregnancy or gestation period, and they develop rapidly. By day three of life, they have every major organ system.

The embryos are also transparent with easily visualized flowing blood that can clot. This is beneficial because, in contrast to diseases like cancer that can be studied in cell cultures, blood clotting disorders require a fully intact circulatory system.

To date, one area in which Shavit's lab has made significant progress is studying estrogen-induced thrombosis (when blood clots block veins) in girls. It has been known for many years that some young women using oral contraceptives develop blood clots in their legs.

This can result in a fatal condition if the clots break off and travel up to the lungs. But the mechanism of how estrogen causes thrombosis is unknown, so it is impossible to predict which girls will be affected and how to prevent it.

With the zebrafish model, Shavit has been able to test whether FDA-approved drugs interfere with the development of these blood clots. He is currently comparing lab findings with patient data from electronic medical records to see if there is a correlation between the laboratory response in zebrafish and what's happening in adolescent patients.

Eventually, the research may help clinicians know which common over-the-counter (OTC) drugs could help prevent thrombosis in girls taking oral contraceptives. Conversely, physicians could be able to advise the same patients against using certain OTC drugs.

Either way, the zebrafish help light the path forward — if Shavit were using electronic medical record data without lab testing to suggest particular OTC medications, it would be impossible to isolate which factors were affecting patients.

In April 2020, Shavit was awarded a prestigious NIH R35 grant that will fund his laboratory's studies on both thrombosis and bleeding disorders through 2027.

How can precision medicine treat rare kidney disease?

Pediatric nephrologist **Debbie Gipson, M.D., M.S.**, has devoted her professional life to answering four essential patient questions about nephrotic syndrome: (1) What disease do I have? (2) Why do I have it? (3) What's going to happen to me? (4) What's the best treatment for me?

Much of Gipson's research and clinical care specifically focuses on glomerular disease. All types of nephrotic syndrome are rare, affecting about 7 per 100,000 children in the United States.

The disease is unpredictable. Symptoms can flare any time and include total body swelling, pain and fatigue. People with glomerular disease risk complications like increased infections, blood clots and high blood pressure. Some 60 percent cannot get the disease under control with available treatments, and many will progress to kidney failure in an average of just eight years — staggeringly fast for a child.

For those lucky enough to receive a kidney transplant, the disease will come back in one-third, setting patients down the same path of symptoms and treatment resistance all over again.

Despite the severity of glomerular disease and other kidney conditions, it's not known how many children in the United States have them. To help document the scope, Gipson is working on a new surveillance initiative of kidney disease in children.

As for why patients get glomerular disease, Gipson and her collaborators are studying disease mechanisms and biomarkers. Researchers want to understand how genetic and environmental factors work together to trigger disease.

One molecular pathway of interest is the tumor necrosis factor (TNF) pathway. A pilot clinical trial is underway at Mott to test a precision medicine approach to turning off this overactive pathway. The work is supported by the NIH-sponsored nephrotic syndrome research consortium, NEPTUNE, which is coordinated by U-M and encompasses 34 total centers across the United States and Canada.

Gipson is currently working to design the next phase of the TNF-focused trial while designing additional pathway-specific clinical trials for children with glomerular disease.

Currently, there's only one FDA-approved treatment for nephrotic syndrome. The ultimate goal is to take new precision medicine therapies all the way to FDA approval and labeling — all part of answering Gipson's big patient questions.

Can mapping fat cells help us understand why excess fat is bad for children?

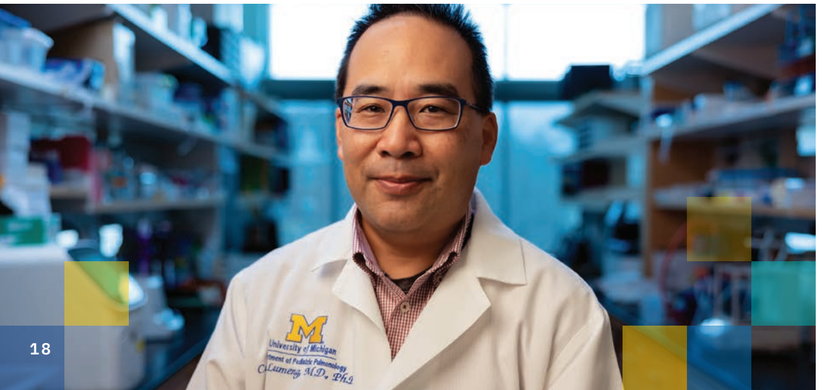
To answer big questions about disease, researchers need to think small: within single cells.

The Pediatric Networks for the Human Cell Atlas consortium is enabling scientists to do just that. Following a similar effort in adults, the international initiative is building reference maps for every cell in a child's body in both normal and disease states.

Pediatric pulmonologist **Carey Lumeng, M.D., Ph.D.**, is contributing to the work. His lab studies fat composition to understand why having too much fat is bad for children, particularly when it comes to the development of lung diseases like asthma.

For almost 10 years, Lumeng's lab has been collaborating with a bariatric surgeon to collect adult human adipose, or fat, tissue and analyze it in high-resolution. Lumeng's research was recently awarded a prestigious grant from the Chan Zuckerberg Initiative, one of the agencies funding the Human Cell Atlas work, to expand the tissue study to children.

Lumeng is now working with colleagues at U-M to generate a comprehensive atlas of changes in fat tissue in different areas of the body throughout childhood at single-cell resolution. The research team includes pediatric surgeon Samir Gadepalli, M.D., M.S., M.B.A., pediatric cardiothoracic surgeon Richard Ohye, M.D., pediatric endocrinologist Kanakadurga Singer, M.A., M.D., and pediatrician and weight management specialist Susan Woolford, M.D., M.P.H.



So far, it's been a study of paradoxes: Fat is known to be harmful, but it's also essential for healthy development. This led Lumeng to ask why fat is okay in certain situations but not in others. His current work seeks to close gaps in understanding of fat tissue biology in children, especially as kids develop through puberty.

Research has shown inflammatory cells within fat may be key. Lumeng's lab is trying to understand why these inflammatory cells develop, what they do in fat, and why they make fat unhealthy.

The end goal is to one day find medications or other approaches that can block the harmful effects of excess fat. It's all in an effort to chase Lumeng's fundamental question of how obesity impacts lung disease in different ways.

How do we better engage and support parents of critically ill newborns?

Neonatologists routinely help parents make the hardest decisions of their lives. This makes for a medical specialty rich with ethical questions.

Marin Arnolds, M.D., (left) is currently analyzing conversations between physicians and families who have to decide before birth whether to move to palliative care at delivery or attempt resuscitation in the newborn intensive care unit (NICU).

In these cases, babies are either extremely premature and at the threshold of viability, or they have complex congenital anomalies that threaten survival.

Arnolds is audio taping conversations between physicians and families and qualitatively analyzing the content. So far, the conversations have shown that physicians focus most on biomedical information while parents more often spend time on psychosocial topics, such as values and beliefs. Later, Arnolds interviews families about their impressions of these conversations and what happened next.

In these cases, it doesn't matter what a physician would decide to do for their own child. Rather, it's about making sure the physician knows enough about the family to individualize their recommendation to them, Arnolds says. The goal is to focus the conversation on what matters most to families and help them make the best decisions for their infants.

Once a family chooses NICU care, decisions can become dizzyingly complex. Neonatologist **Stephanie Kukora, M.D.**, (right) is researching these same ethical themes in the NICU after birth when there are serious goals-of-care decisions, such as when a tracheostomy may be needed.

Kukora aims to help families and providers build understanding about where the baby is headed in terms of outcomes. She also facilitates medical improv exercises to teach clinicians how to listen and respond in the moment with parents, particularly when giving bad news.

The ultimate goal is to develop decision making support tools that can be used nationwide. In the past, neonatal decision-making tools have focused on biomedical information and statistics. But current research shows this isn't the only piece — or always the most critical piece — of the puzzle.

Both projects have support from the U-M Neonatal Ethics Lab founded by **Naomi Laventhal, M.D., M.S.** Under Laventhal's leadership, Mott has become one of the top centers in the nation for scholarly and research-based ways to address neonatology's most urgent ethical questions.

What can the skin teach us about inflammation in juvenile myositis and lupus?

Children with chronic disease frequently receive a battery of invasive tests and blood draws. But for some pediatric autoimmune conditions, there might be a way to monitor disease noninvasively through the skin.

Pediatric rheumatologist **Jessica Turnier, M.D.**, is testing a novel approach to studying skin in children with juvenile myositis (JM) and lupus.

She's using tape stripping to obtain skin samples from patients to study molecular signatures of skin disease. Working with RNA and protein from skin cells, Turnier can compare genes and proteins expressed in JM versus lupus to understand why the diseases are different.

The goal is to understand the behavior of certain genes or proteins in the skin to provide insight into treatment response. Armed with this information, clinicians could one day take a precision medicine approach to treat these complex chronic conditions. Plus, the research may show if skin is better than blood for monitoring inflammation and directing clinical care.

JM and childhood-onset lupus are rare diseases that suffer from a lack of research, as do most pediatric rheumatic conditions. JM and childhood-onset lupus each affect approximately 5 in 100,000 children though the exact prevalence is unknown.

Both diseases can be devastating for children, causing muscle weakness, rash, and debilitating pain and inflammation throughout the body. This inflammation can affect multiple organ systems including the kidneys, heart and lungs. Some two-thirds of children diagnosed with these conditions will suffer from lifelong, chronic disease.

Today, there are few targeted treatments available for pediatric autoimmune diseases. Those that do exist are immunosuppressive and have many side effects that disrupt normal childhood. Clinicians lack the tools to predict which treatments will be most effective for an individual patient. Turnier's work hopes to combat these issues.

As part of her efforts, Turnier developed a juvenile myositis clinic and patient and family advisory committee and was recently nominated to the Cure JM Clinical Care Network. The children involved enjoy being part of something that is helping other kids and now see research as another part of their clinic visit. M

Where is tech design falling short for young kids?

There's a mismatch between how technology aimed at young children is designed and what children actually need, studies from developmental behavioral pediatricians **Jenny Radesky, M.D.**, (left) and **Tiffany Munzer, M.D.**, have found.

The research pushes the conversation about tech and toddlers past screen time and, instead, focuses on interactive features and design choices.

In one study, 37 parent-toddler pairs read print books, basic electronic books, and enhanced electronic books that used hot spots to press and light with sound effects.

Children were much more likely to ask questions and engage with their parents when reading the print books — called serve and return interactions. With the enhanced books, kids would tap the hot spots and ignore the stories. Many times, parents stopped trying to read with their kids, and the toddlers would take the tablets and play alone, which reduced the pleasant exchanges between parents and children during reading.

In 2016, Radesky co-wrote American Academy of Pediatrics guidelines on technology that encouraged parents to co-view and play along with their young kids. This previous study helped researchers understand how challenging it can be to engage with a child when a device includes design features to capture a child's attention.

A second, larger study had similar findings, this time comparing a highly engaging nursery rhyme app, a lower-activity nursery rhyme app, and a book with the same rhymes and pictures. The results indicated that highly engaging apps don't support language development as well as analog interactions.

Unsurprisingly, taking away a tablet was also much more likely to prompt a toddler tantrum than taking away a print book.

A third study analyzed 124 of the most popular apps marketed as early childhood and educational. Overall, 58 percent of the apps did not meet previously published criteria for educational apps.

Policymakers around the world have taken note of this work, beginning efforts to shift design standards in the apps that kids use, including limiting advertising and manipulative design features.

The bottom line is that a little bit of tablet time won't harm kids. But the most popular design practices aren't always ethical, and there's work to do to help children's tech design become truly child-centered. M

How can Michigan innovations benefit researchers on a national scale?

When locally developed software is unique enough to gain national attention, it makes sense to package it up and share it across the country for the benefit of others. That's the thinking behind much of the work of pediatrician, researcher and informatician **David Hanauer, M.D., M.S.**

For more than 17 years, Hanauer has spearheaded the development, use and dissemination of a software tool called EMERSE, the Electronic Medical Record Search Engine. This powerful open-source program makes it possible for researchers to securely search information in free-text notes from electronic health records.

This is valuable information because an estimated 80 percent of all data collected during a clinical visit is stored in free text notes. Without EMERSE, this information would mostly be locked away and inaccessible.

With its powerful search functionalities, EMERSE can help researchers find cohorts and identify adverse events in clinical trials. For those studying rare diseases, EMERSE can retrieve rare references like mentions of genes, biomarkers and even disease names that would not otherwise be coded in the electronic health record.

EMERSE started at University of Michigan Health and is now used by academic medical centers from coast to coast. Recently, these centers have become interconnected in new ways: EMERSE now allows researchers to securely search another center's data while searching their own, as long as each center consents.

To date, nearly 500 peer-reviewed publications have used EMERSE, including numerous pediatric studies on topics ranging from congenital heart disease to children with special needs and many more.

Beyond EMERSE, Hanauer works to help data from University of Michigan Health mesh with other centers from around the world. This enables U-M to participate in large-scale, network-based research initiatives to seamlessly connect the hard work of Michigan scientists to researchers outside of the state. The idea is to standardize local pediatric information so it can be combined with similar data from other research centers. The combined efforts of many institutions enable far more powerful studies than any single institution could conduct on its own.

How can hospitals better treat somatic symptoms in kids?

Some children and adolescents with persistent, unexplained physical symptoms can struggle to find a cause. This leaves families bouncing around from primary care to specialists to the emergency room and back again without a clear explanation for their symptoms.

In some of these cases, the culprit is somatization, or when emotions or stress are expressed in physical symptoms. It's a challenging and costly problem that can affect everything from a child's sleeping and eating to academics, family life and socialization.

To help, pediatric psychologist **Kristin Kullgren, Ph.D.**, and multidisciplinary collaborators developed a new clinical pathway for children with somatic symptoms and are studying the clinical pathway's outcomes.

The goal is to try and find the right treatment plan for a physical problem that is most often explained by a combination of psychological and biological factors. It's more often a mind-body problem rather than just a body problem.

Now, when a child with persistent, unexplained physical symptoms arrives for care at Mott, specialists from psychology, psychiatry, social work, neurology, emergency medicine, physical medicine and rehabilitation, nursing and hospital medicine work hand in hand to find answers.

At Mott, the approach has yielded significant cost savings. In a study of nearly 400 patients aged 7 to 18, median costs per patient encounter dropped by almost $60,369. That's an estimated annual cost savings of $1.4 million.

The cost savings illustrate the impact of the clinical pathway because they indicate kids are getting out of the hospital and back to their lives faster. Other institutions have taken note and are using the research to develop their own clinical pathways for the care of somatic symptoms in children.

Next, Kullgren and her colleagues are investigating whether the stressors of the COVID-19 pandemic are causing increases in somatic symptoms in children and whether the same clinical pathway can help.

With the pandemic, Mott has seen an increase in the percentage of kids who are getting psychology or psychiatry consultations, and the team will study whether more kids are presenting with somatic symptoms and related disorders as a result.

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