

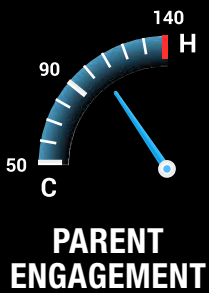
Pediatrics

NATIONWIDE

Advancing the Conversation
on Child Health

TEENS ON THE ROAD: HOW TECHNOLOGY, POLICY AND PARENTS INFLUENCE DRIVING SAFETY

DISTRACTED DRIVING



INSIDE THIS ISSUE

Learning in Real Time to Overcome COVID-19 and MIS-C

Microsurgery for Acute Flaccid Myelitis: Personalized Approach Leads to Remarkable Recoveries

How Patient-Derived Stem Cells are Changing the Trajectory of Congenital Heart Disease Research

Table of Contents

20 TEENS ON THE ROAD: HOW TECHNOLOGY, POLICY AND PARENTS INFLUENCE DRIVING SAFETY

Motor vehicle crashes are the leading cause of death for teens aged 16 to 19 in the United States. In 2019, nearly 2,400 teens died and more than 250,000 were treated in emergency departments as a result of motor vehicle crashes.

Risk factors for teen motor vehicle crashes can be lumped into four main categories: inexperience, risk-taking behaviors, distracted driving and substance use.

Gaining Experience

In most U.S. states, the process of getting your driver's license is one that involves many steps and different levels of licensure based on experience. As the teen gains experience, safety increases, but even when all the steps to full, unrestricted driver's license are taken, the fact remains that teens are vastly under experienced when it comes to driving.

Risk-taking Behaviors

Speeding, running "orange" lights and other risky behaviors are more dangerous for teens because of their inexperience. Additionally, risky behaviors such as substance use or cellphone use while driving can also prove deadly for teens.

Distracted Driving

Distracted driving is highly linked with cellphone usage. Cellphone use may involve manual distraction (hands off the steering wheel), visual distraction (eyes off the road), and cognitive distraction (mind off driving) and includes activities such as calling, texting, looking at apps and various other uses.

A 2019 national Youth Risk Behavior Survey revealed that 39% of high school students who drove texted and emailed while driving at least once in the month leading up to the survey.

Drinking, Drugs and Driving

Drinking any amount of alcohol before driving increases the risk of a crash among teen drivers. Given the same blood alcohol concentration (BAC), teens are more likely to crash than older drivers.

As marijuana use becomes more accepted through increased legalization and access to cannabis increases, the number of teens who drive under the influence of marijuana is also increasing. In fact, a 2020 study from *JAMA Network Open* reported that nearly 50% of teens that reported using marijuana also reported driving stoned.



INEXPERIENCE



RISK TAKING BEHAVIORS

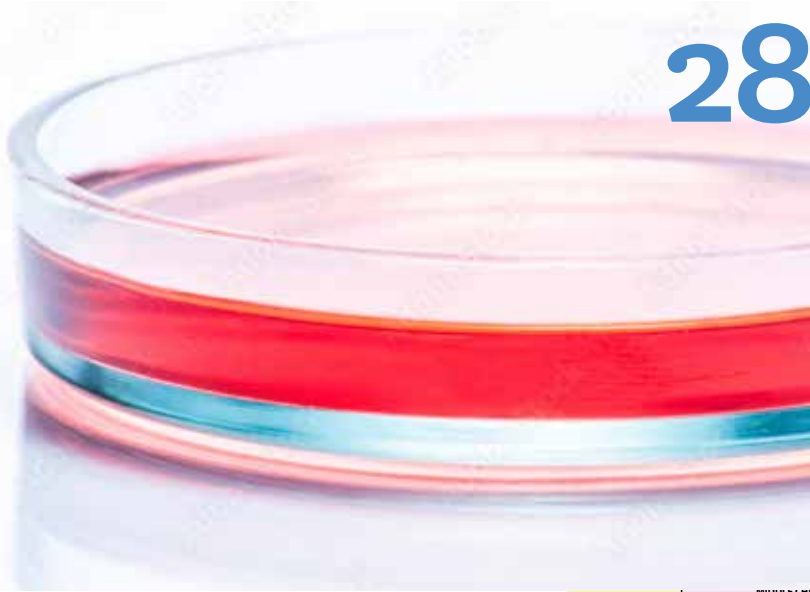


DISTRACTED DRIVING



DRIVING UNDER THE INFLUENCE

28



DEPARTMENTS

- 4 In Practice:** News From the Field
- 36 Second Opinions:** Building Momentum for School-Based Health Care
- 38 Connections:** Advancing the Conversation on Child Health

FEATURES

- 10** Learning in Real Time to Overcome COVID-19 and MIS-C
- 12** Reconsidering Screening in Primary Care
- 16** Microsurgery for Acute Flaccid Myelitis: Personalized Approach Leads to Remarkable Recoveries
- 20** Teens on the Road: How Technology, Policy and Parents Influence Driving Safety
- 28** How Patient-Derived Stem Cells are Changing the Trajectory of Congenital Heart Disease Research
- 34** Providing Education and PrEP for Teens at Risk for HIV

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12

“I feel guilty when I look at this list.... Including me, there are two full-time people in my office. How am I supposed to find the time to do all of this if there are six kids in my waiting room with ear infections?”

— Jill Neff, DO, the only independent pediatrician in rural Jackson County, Ohio

“iPSCs are excellent for studying CHD, because we can identify potential causative mutations using genome sequencing, then use the cardiomyocytes to look both at the disease and the defects that cause it—in a dish, using just cells, and without a biopsy.”

— Mingtao Zhao, DVM, PhD, principal investigator in the Center for Cardiovascular Research at Nationwide Children's Hospital

Is Tracheostomy Tube Placement in Premies Safe?

The procedure is safe and effective in newborns requiring high ventilator pressures.



Tracheostomy tube placement is a common procedure performed for premature infants requiring respiratory assistance. Compared to an endotracheal tube, placement of a tracheostomy tube is thought to allow the infant more opportunities for comfort, interaction, nutrition and growth.

However, rates of tracheostomy tube placement vary across centers. One reason is the assumption that newborns requiring high ventilator pressure will have higher complication rates during and after tracheostomy tube placement.

According to Edward Shepherd, MD, section chief of Neonatology at Nationwide Children's Hospital, this results in a Catch-22.

"The kids who really need the tracheostomies are the kids who require a lot of ventilator support, and the reason they need the tracheostomies is because they require a lot of ventilator support," he says.

The Comprehensive Center for Bronchopulmonary Dysplasia at Nationwide Children's is a standalone, referral-based unit devoted to the care of premature infants with respiratory difficulties and has extensive experience placing tracheostomy tubes in infants, even those requiring high ventilator settings.

In an effort to determine whether tracheostomy placement in infants requiring high ventilator pressure is safe and effective, Dr. Shepherd and colleagues recently

compared short-term outcomes of tube placement in infants with low versus high ventilator pressures.

The researchers analyzed the records of 50 infants under 1 year old who underwent tracheostomy tube placement at Nationwide Children's Newborn Intensive Care Unit between 2009 and 2018. They compared outcomes of patients requiring high ventilator pressures to those requiring low ventilator pressures over the seven days after tube placement.

"We were pleasantly surprised to see that there were no clinically significant differences between the two groups; everybody did just fine with the procedure," says Laura Banks, a student researcher in the departments of Otolaryngology and Neonatology and co-author of the study, which was published in *Otolaryngology Head & Neck Surgery*.

The analyses showed no intraoperative complications or deaths within the first seven days of tracheostomy tube placement in either group. Incidence of pneumonia and rate of mortality during admission were also similar in the two groups.

"These data provide evidence that placement of tracheostomy tubes in patients requiring high ventilator pressures is feasible and safe, with no additional short-term risks," says Banks.

Dr. Shepherd, who is also an associate professor of clinical pediatrics at The Ohio State University College of Medicine, says this study validates the practices at Nationwide Children's.

"We are known for our willingness to provide whatever support a baby might need, even if that means very high ventilator settings, much higher than most centers go," he says.

"Our hope is, through publishing a study like this, other centers will feel more comfortable in providing that level of support to these babies."

Banks L, Worobetz N, Hamersley E, Onwuka A, Shepherd E, Wiet G. Evaluation of short-term outcomes of tracheostomy procedures in a NICU population with high ventilator settings. *Otolaryngology Head and Neck Surgery*. 2021 Mar 9;194599821996226. [Epub ahead of print]

— Mary Bates, PhD



Kidney and Urinary Tract Protein Demonstrates Antimicrobial Activity

A little-studied peptide found in the urinary tract is a potential biomarker for urinary tract infection risk and could be developed into a novel therapeutic against drug-resistant bacteria

Researchers at Nationwide Children’s Hospital have demonstrated that an understudied protein expressed in the human kidney and bladder kills the bacteria that cause urinary tract infections (UTI). The findings were published in the *American Journal of Physiology-Renal Physiology*.

“The bacteria that cause UTIs are increasingly becoming resistant to antibiotics, driving the need to discover novel therapeutic approaches,” says co-first author and research associate Kristin Bender, of the Nephrology and Urology Research Affinity Group (NURAG) and the Abigail Wexner Research Institute (AWRI) at Nationwide Children’s.

“UTI doesn’t receive a lot of attention in the press, but it has a high prevalence and places a substantial burden on both patients and the health care system every year,” adds co-first author and research scientist Laura Schwartz, PhD, who is also a member of NURAG and AWRI.

Humans produce a large family of ribonuclease (RNase) A proteins, many of which have antimicrobial activity. For the study, the team sought to evaluate the antimicrobial function and tissue expression pattern of the least studied of this family, RNase 4.

In a series of *in vitro* experiments, they showed that RNase 4 has powerful antibacterial activity against uropathogenic *Escherichia coli* (UPEC) as well as multidrug-resistant UPEC, suggesting that it may be a promising candidate to develop as a novel therapeutic.

While the exact mechanism of action needs further study, senior study author John David Spencer, MD,

chief of the Division of Nephrology and Hypertension at Nationwide Children’s explains, “This antimicrobial protein has a series of positively charged amino acids that are attracted to the negatively charged proteins of the bacterium. It basically punches holes in the bacterial membrane, leading to cell death.”

Using human samples, the team found that RNase 4 is broadly expressed within the kidney cells that are targeted by the UTI-causing pathogens as well as within the bladder, and urinary RNase 4 concentrations were two-fold lower in samples from females with a history of UTI compared with those from females with no history of UTI, suggesting that RNase 4 could potentially be developed as a biomarker to identify individuals most at risk for the establishment or recurrence of UTI.

“This was the first time that urinary levels of RNase 4 in humans were found to contribute to the immune defenses against UTI, highlighting the multifaceted nature of the immune system,” says Bender.

Prospective studies are needed to determine if the relationship between RNase 4 levels and UTI risk is causal. “We are now studying RNase 4 levels in populations with higher risk of UTI, such as individuals with diabetes, patients requiring catheterization, and pregnant women,” says Dr. Schwartz.

The team’s long-term goal is to develop RNases as novel therapeutics to replace or augment traditional antibiotics.

Bender K, Schwartz LL, Cohen A, Vasquez CM, Murtha MJ, Eichler T, Thomas JP, Jackson A, Spencer JD. Expression and function of human ribonuclease 4 in the kidney and urinary tract. *American Journal of Physiology Renal Physiology*. 2021 May 1;320(5):F972-F983.

— Lauren Dembeck, PhD

Risk for Serious Complications From Vaccine-Preventable Infections After Hematopoietic Cell Transplant

Clinician-scientists reveal the burden of vaccine-preventable infections among children post-transplant, when immunity is low and risk is high.



When a hematopoietic cell transplant (HCT) recipient at Nationwide Children's Hospital was diagnosed with a vaccine-preventable infection (VPI), treating clinicians decided to evaluate the burden of VPI in HCT patients at Nationwide Children's and elsewhere. The team collected post-HCT VPI data on more than 9,500 children across the United States.

Their study, published in *Bone Marrow Transplantation*, revealed that 7.1% of children who underwent HCT were hospitalized for a VPI in the 5 years following their transplant, most frequently in the first 6-12 months after transplant.

The most common infections were influenza, varicella and invasive pneumococcal infections. Younger patients and those with primary immune deficiency or graft-vs-host disease were at greater risk for VPI-associated hospitalizations. Children with VPI also had longer hospital stays, a higher rate of intensive care unit admission and higher mortality in the early post-HCT period compared to children post-HCT without VPIs.

There are many reasons for VPI in this population. Some children may not have been vaccinated pre-HCT, while those who have been vaccinated can fall prey to VPIs

because of loss of vaccine-induced immunity or ongoing immunosuppression after transplant.

"If a VPI leads you to be hospitalized, that's a big deal," says Monica Ardura, DO, MSCS, an infectious disease specialist and medical director of the Host Defense Program at Nationwide Children's. "These data provide objective evidence that VPIs do indeed happen and can be associated with adverse outcomes in this population. The next question is what can we do better to protect our patients."

Dr. Ardura and her colleagues have begun examining the immune response to inactivated vaccines in HCT patients to better understand the ideal timing for post-transplant vaccination. The goal is to enable individualized recommendations for post-transplant vaccines and help clinicians know when they can safely recommend each vaccine for their patients.

Because of the heightened risk for VPIs in the first 6-12 months, the team at Nationwide Children's created a quality improvement initiative to provide inactivated vaccines beginning at 4-6 months post-HCT in eligible patients and optimize timely completion of age-appropriate vaccines. Depending on patient health and medications received, live-attenuated viral vaccines can be provided at two years post-transplant.

"These patients have gone through a lot. They have a complicated medical history, and after transplant there can be a lot of different complications — we don't want VPIs to be one of them," says Dr. Ardura. "Sometimes vaccines are an afterthought. We want to bring them more to the forefront as something clinicians should think about in every medical encounter."

Danino D, Stanek JR, Rangarajan H, Ardura MI. Hospitalizations for vaccine-preventable infections among pediatric hematopoietic cell transplantation recipients in the first 5 years after transplantation. *Bone Marrow Transplantation*. 2021 Jun 21. [Epub ahead of print]

— Katie Brind'Amour, PhD

Impulsivity, Not Inattention, Predicts Externalizing Disorders

Without early intervention, children with hyperactive-impulsive symptoms of attention-deficit/hyperactivity disorder may be vulnerable to developing other externalizing behavior disorders.

Contributing to a small but growing body of literature evaluating trait impulsivity theory, a team of researchers led by Mary A. Fristad, PhD, ABPP, director of Academic Affairs and Research Development in the Division of Child & Family Psychiatry and Big Lots Behavioral Health Services at Nationwide Children's Hospital, recently identified independent relationships between hyperactive-impulsive (HI) symptoms of attention-deficit/hyperactivity disorder (ADHD) and the later development of additional externalizing behavior disorders. Their analyses were published in the *Journal of the American Academy of Child and Adolescent Psychiatry*.

While externalizing disorders — which include ADHD, oppositional defiant disorder (ODD), conduct disorder (CD) and substance use disorders (SUDs) — have traditionally been treated as distinct by the Diagnostic and Statistical Manual of Mental Disorders (DSM), they are frequently comorbid. Many children who are diagnosed with one will be diagnosed with another sometime in their life, either simultaneously or sequentially.

A single, highly heritable trait, linked to the brain's dopamine response and expressed as impulsivity, is associated with these disorders. Trait impulsivity theory suggests that this trait, particularly when accompanied by environmental risks, predisposes some individuals to a specific pathway of externalizing disorder development, whereby HI symptoms of ADHD may precede ODD, ODD may precede CD and CD may precede SUDs.

To test this theory, Dr. Fristad and her colleagues analyzed data from the Longitudinal Assessment of Manic Symptoms (LAMS) Study, which recruited 458 boys and 227 girls, ages 6-12, from nine child outpatient mental health clinics in the Midwestern United States and followed them for up to eight years. Participants and their parents completed interviews and questionnaires every six months.

The team found participants' baseline levels of HI symptoms of ADHD when they joined the LAMS



study predicted their levels of ODD and CD symptoms eight years later. Diagnoses of ADHD-HI/C (ADHD with primarily HI symptoms or with a combination of both HI and inattentive symptoms) at 48 months predicted diagnosis of ODD at 96 months, diagnoses of ODD at 48 months predicted CD at 96 months and diagnoses of CD at 48 months predicted SUD at 96 months. ODD and SUDs did not predict later ADHD.

“In this large data set, we found strong evidence of symptom progression predicted by hyperactive-impulsive symptoms of ADHD,” says Dr. Fristad. “Inattentive ADHD symptoms did not predict this progression.”

Additionally, researchers also found participants in families who reported greater parental stress, more neighborhood violence and less parental monitoring of their child experienced accelerated progression through increasingly severe externalizing disorders.

“Our findings extend existing literature and point toward the importance of early diagnosis, treatment and family interventions for young children with ADHD-HI/C,” says Dr. Fristad. “Reversing established conduct problems is more difficult than preventing them among vulnerable children.”

Bell ZE, Fristad MA, Youngstrom EA, Arnold LE, Beauchaine TP; LAMS Consortium. Attention-deficit/hyperactivity disorder symptoms and externalizing progression in the LAMS Study: A test of trait impulsivity theory. *Journal of the American Academy of Child and Adolescent Psychiatry*. 2021 Jun 4:S0890-8567(21)00362-2. [Epub ahead of print.]

— Natalie Wilson

Distinct Transcriptional Regulatory Domain Identified in Ewing Sarcoma Fusion Protein

A better understanding of a newly defined region in the fusion protein that causes Ewing sarcoma may lead to novel approaches for therapeutic targeting.

Ewing sarcoma is an aggressive pediatric bone cancer defined by the presence of a single genetic abnormality: a chromosomal translocation. The translocation splits two genes and joins them abnormally, creating a fusion called EWS/FLI. The EWS/FLI protein broadly alters gene expression of the affected cell thereby initiating tumor growth.

Researchers at Nationwide Children's Hospital have discovered that a small part of the FLI half of the protein is required for EWS/FLI to fully alter gene expression and cause cancer. The findings were published in the journal *Oncogene*.

"We have known for a long time that EWS/FLI is the key to Ewing sarcoma," explains senior author Stephen Lessnick, MD, PhD, director of the Center for Childhood Cancer & Blood Diseases in the Abigail Wexner Research Institute at Nationwide Children's. "We have always believed that if we can understand how EWS/FLI works, then we can use that knowledge to block its function, stop cancerous growth and cure Ewing sarcoma."

The EWS portion of the protein is an intrinsically disordered transcriptional regulatory domain. "It does not form a consistent 3-dimensional structure. This shape-shifting ability makes it an unsuitable drug target," explains Dr. Lessnick. The FLI portion contains a DNA-binding domain flanked by two regions of unknown function.

"Because DNA binding domains of this type have conserved structures, no one studied the FLI portion carefully, and data on the flanking regions were conflicting," recounts Dr. Lessnick, who is also a

professor of pediatrics at The Ohio State University College of Medicine.

To dissect the functions of FLI portion, first author Megann Boone, PhD, who recently graduated from Dr. Lessnick's laboratory, removed endogenous EWS/FLI from a Ewing sarcoma cell line — rendering it non-cancerous — and then re-introduced a series of genetically-engineered EWS/FLI mutants with alterations in the FLI portion.

"A number of years ago, my team developed this method," explains Dr. Lessnick. "With it, we can ask a simple question: Which portions of EWS/FLI are required to make the cells cancerous again?"

The experiments revealed a previously unknown region, adjacent to the DNA binding domain, that is absolutely required for full transcriptional function, and thus, cancer development. This finding was completely unexpected.

"We always assumed that the only role of the FLI portion was to bind DNA. Only by shedding this assumption was Megann able to identify this new function that is critical for EWS/FLI-mediated sarcomagenesis," says Dr. Lessnick. "This study exemplifies why it is so important for people 'with fresh eyes' to come into labs and look at problems differently. Indeed, this is why we have a research institute next to the hospital: It drives innovative translational work that bridges science and pediatric medicine, and will ultimately revolutionize therapeutic approaches to devastating pediatric diseases."

Boone MA, Taslim C, Crow JC, Selich-Anderson J, Byrum AK, Showpnil IA, Sunkel BD, Wang M, Stanton BZ, Theisen ER, Lessnick SL. The FLI portion of EWS/FLI contributes a transcriptional regulatory function that is distinct and separable from its DNA-binding function in Ewing sarcoma. *Oncogene*. 2021 Jul;40(29):4759-4769.

— Lauren Dembeck, PhD

Lubiprostone Found to be Safe, as Effective as Placebo in Children With Constipation

The medication, FDA-approved for adults, may benefit older pediatric patients with less of a behavioral component to their constipation.

Pediatric functional constipation, though common, remains challenging to treat. Lubiprostone is a medication approved by the U.S. Food and Drug Administration (FDA) for the treatment of constipation and irritable bowel syndrome with constipation in adults.

In a new study mandated by the FDA, recently published in *Clinical Gastroenterology and Hepatology*, researchers at Nationwide Children's Hospital were among the international team evaluating the efficacy and safety of lubiprostone in children with constipation.

The researchers conducted a double-blind, randomized, placebo-controlled study and a long-term, open-label extension study in over 600 children 6-17 years of age with pediatric functional constipation.

“Much like every other large, double-blind study on pediatric constipation, we found lubiprostone was as effective as placebo in treating children with chronic constipation,” says Carlo Di Lorenzo, MD, chief of the Division of Pediatric Gastroenterology, Hepatology and Nutrition at Nationwide Children's and senior author of the study.

Dr. Di Lorenzo says he was not surprised that the medication did not show the same efficacy in children as in adults.

“Pediatric constipation is usually a behavioral issue, a completely different condition from constipation in adults,” he says.

Dr. Di Lorenzo points to a few factors affecting their results. The first part of the study was only 12 weeks in duration, often not enough time for children who withhold their stool because they are afraid it will hurt to overcome their fear. In addition, one of the outcome measures mandated by the FDA — frequency of bowel movements — may not be as relevant in children. While this measure is appropriate for adults with constipation, Dr. Di Lorenzo says that children with constipation complain more about hard stool or fecal incontinence than infrequent bowel movements.



The researchers did find that lubiprostone was well tolerated, with a safety profile similar to that in adults.

According to Dr. Di Lorenzo, the fact that lubiprostone was as effective as placebo does not mean it was ineffective.

“In the right patients, this medication worked well,” says Dr. Di Lorenzo, who is also professor of clinical pediatrics at The Ohio State University College of Medicine. “It was probably not beneficial in patients that withhold their stool. If a child is going to withhold their stool, there is no medication that will help until they overcome their fear.”

Dr. Di Lorenzo suggests that lubiprostone might be more appropriate for adolescent patients experiencing constipation with no behavioral issues.

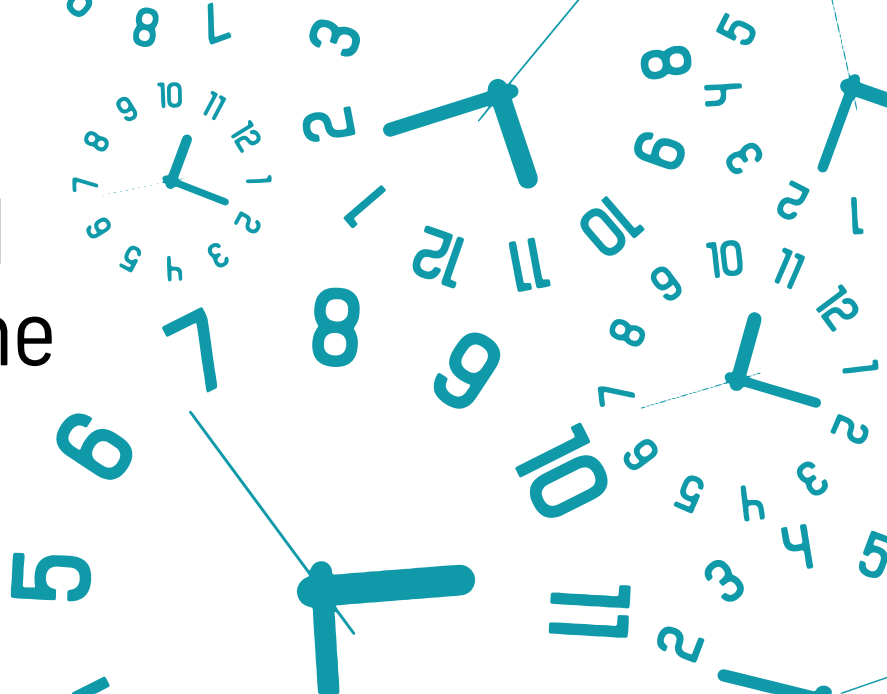
Based on these results, the FDA-approved labeling for lubiprostone has been updated to state that its safety and effectiveness have not been established in pediatric patients under 6 years of age, and that effectiveness has not been established in pediatric patients 6 years and older.

Benninga MA, Hussain SZ, Sood MR, Nurko S, Hyman P, Clifford RA, O’Gorman M, Losch-Beridon T, Mareya S, Lichtlen P, Di Lorenzo C. Lubiprostone for pediatric functional constipation: randomized, controlled, double-blind study with long-term extension. *Clinical Gastroenterology and Hepatology*. 2021 Apr 7;S1542-3565(21)00393-1.

— Mary Bates, PhD

Learning in Real Time to Overcome COVID-19 and MIS-C

Written by Natalie Wilson



When multisystem inflammatory syndrome in children (MIS-C) emerged in May 2020, the new condition made headlines. Although rare, MIS-C can appear in kids about a month after they’ve recovered from infections with SARS-CoV-2, the virus that causes COVID-19 — even if they haven’t felt sick at all.

“We don’t know why some children develop MIS-C,” says Mark W. Hall, MD, FCCM, chief and Development Board Endowed Chair of Critical Care Medicine at Nationwide Children’s Hospital. “The severity of a child’s initial COVID-19 disease does not appear to predict whether they will get MIS-C. In fact, some children who later develop MIS-C were asymptomatic and never knew they had COVID-19.”

Patients with MIS-C often develop fever, abdominal pain and lethargy. Most recover with treatment. For some, however, MIS-C is a serious and potentially deadly complication that causes the failure of blood vessels, the heart and other organs.

“MIS-C symptoms mimic the effects of an acute infection. After getting ‘turned on’ to protect the body during a COVID infection, the immune system becomes ‘confused’ and begins attacking blood vessels and the heart instead,” says Dr. Hall.

Now, new research from a network of more than 50 hospitals across the United States has begun uncovering evidence that will improve care for children with MIS-C and reduce its effects on their hearts.

TREATING AN EMERGENT ILLNESS

As a newly identified condition, MIS-C lacked clinical

guidelines regarding its treatment. But patients with MIS-C arrived at hospitals needing help — and quickly.

Jeffrey Burns, MD, MPH, chief of the Division of Critical Care Medicine at Boston Children’s Hospital, brought together pediatric critical care experts, including Dr. Hall, along with cardiologists, hematologists, rheumatologists and more, for weekly virtual meetings to discuss new observations in real time and determine how to tackle COVID-19 and MIS-C.

“We were able to learn and adapt through remarkably fast global collaboration,” says Dr. Hall.

Those initial grassroots efforts allowed Dr. Hall and other physicians and researchers to develop protocols for treating MIS-C. And once protocols were in place, clinical teams could observe the treatments working and share their insights with their peers. Protocols developed for Nationwide Children’s recommended the use of intravenous immune globulin (IVIG) first, followed by glucocorticoids, and appeared to be effective at treating the condition.

In order to build evidence for their approach — and to improve it — researchers needed to systematically collect and review larger amounts of data on patient outcomes.

RESEARCH WITH HEART

A research effort led by Adrienne Randolph, MD, MSc, a leader in Critical Care Medicine at Boston Children’s Hospital and founder of the Pediatric Acute Lung Injury and Sepsis Investigator’s (PALISI) network, allowed Dr. Hall and other researchers to do just that. Funded by the Centers for Disease Control and driven by PALISI

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site data, “Overcoming COVID-19” has headed up efforts to track and study cases of MIS-C in children across the United States.

In a study published in *The New England Journal of Medicine* in July, Overcoming COVID-19 examined the cases of 518 critically ill patients who were diagnosed with MIS-C while admitted to one of 58 U.S. hospitals, including Nationwide Children’s, between March 15 and October 31, 2020.

The study found that early treatment with a low dose of glucocorticoids — an even lower dose than what’s used to treat asthma, for example — in addition to IVIG was associated with a lower risk of new or persistent cardiovascular dysfunction in MIS-C patients than treatment with IVIG alone.

The group’s investigators focused on differences in cardiovascular dysfunction in patients on or after “day 2,” with day 0 being the first day the patients received any immunomodulatory treatment after hospital admission, and day 2 being the second calendar day after day 0.

Researchers used a propensity score-matched analysis and adjusted for baseline MIS-C severity and demographic characteristics in order to compare children who had the most similar levels of illness at the time of presentation and best isolate the influence their treatments may have had on their outcomes.

“If you compared all patients with MIS-C, you might find worse outcomes in the patients who were treated most aggressively, but that could be because they were

sicker to begin with, not because the treatments or doses they received were associated with worse outcomes,” says Dr. Hall, who is also the director of the Immune Surveillance Laboratory in the Center for Clinical and Translational Research in the Abigail Wexner Research Institute at Nationwide Children’s.

Even when accounting for other variables, the addition of glucocorticoids on day 0 was associated with better outcomes.

CONTINUING TO ADAPT

As a result of these findings, Dr. Hall says that he and others are modifying protocols for treating MIS-C to include the early use of real-time glucocorticoids.

“The symptoms of MIS-C look very much like what one sees in patients with overwhelming infection, or sepsis. We have historically limited the use of early, high-dose glucocorticoids in this patient population until we have ruled out the presence of sepsis, because high-dose glucocorticoids can worsen outcomes in septic children,” says Dr. Hall. “But we now believe that lower doses of glucocorticoids, which would likely be safer in septic children, can be an effective part of the early, empiric treatment of children suspected of having MIS-C.”

“This is great example of using existing networks, leveraging their infrastructure, gathering real-time data on responses to therapy in a national cohort of patients, and informing our practice,” he adds.

Son MBF, Murray N, Friedman K, ... et al.; Overcoming COVID-19 Investigators. Multisystem Inflammatory Syndrome in Children - Initial therapy and outcomes. *The New England Journal of Medicine*. 2021 Jul 1;385(1):23-34. Epub 2021 Jun 16.

“We now believe that lower doses of glucocorticoids ... can be an effective part of early, empiric treatment of children suspected of having MIS-C.”

– Mark W. Hall, MD, FCCM, chief and Development Board Endowed Chair of Critical Care Medicine at Nationwide Children’s Hospital



Recommendations for Preventive Pediatric Health Care
Bright Futures/American Academy of Pediatrics

Bright Futures
American Academy of Pediatrics

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Each child and family is unique. Therefore, these Recommendations for Preventive Pediatric Health Care are designed for the care of children who are receiving competent parenting. There are no recommendations of any separate health problems, and any growing and developing in a stable family fashion. Developmental, psychological, and chronic problems for children and adolescents may require frequent monitoring, and treatment visits separate from preventive care visits. Additional visits may become necessary if circumstances suggest variations from normal. These recommendations represent a consensus by the American Academy of Pediatrics (AAP) and Bright Futures. The AAP continues to emphasize the great importance of continuity of care in comprehensive health care and the need to avoid fragmentation of care.

Note to the specific guidance by age is listed in the Bright Futures Guidelines (Pages 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 13, 14, 15, 16, 17, 18, 19, 20, 21, 22, 23, 24, 25, 26, 27, 28, 29, 30, 31, 32, 33, 34, 35, 36, 37, 38, 39, 40, 41, 42, 43, 44, 45, 46, 47, 48, 49, 50, 51, 52, 53, 54, 55, 56, 57, 58, 59, 60, 61, 62, 63, 64, 65, 66, 67, 68, 69, 70, 71, 72, 73, 74, 75, 76, 77, 78, 79, 80, 81, 82, 83, 84, 85, 86, 87, 88, 89, 90, 91, 92, 93, 94, 95, 96, 97, 98, 99, 100, 101, 102, 103, 104, 105, 106, 107, 108, 109, 110, 111, 112, 113, 114, 115, 116, 117, 118, 119, 120, 121, 122, 123, 124, 125, 126, 127, 128, 129, 130, 131, 132, 133, 134, 135, 136, 137, 138, 139, 140, 141, 142, 143, 144, 145, 146, 147, 148, 149, 150, 151, 152, 153, 154, 155, 156, 157, 158, 159, 160, 161, 162, 163, 164, 165, 166, 167, 168, 169, 170, 171, 172, 173, 174, 175, 176, 177, 178, 179, 180, 181, 182, 183, 184, 185, 186, 187, 188, 189, 190, 191, 192, 193, 194, 195, 196, 197, 198, 199, 200, 201, 202, 203, 204, 205, 206, 207, 208, 209, 210, 211, 212, 213, 214, 215, 216, 217, 218, 219, 220, 221, 222, 223, 224, 225, 226, 227, 228, 229, 230, 231, 232, 233, 234, 235, 236, 237, 238, 239, 240, 241, 242, 243, 244, 245, 246, 247, 248, 249, 250, 251, 252, 253, 254, 255, 256, 257, 258, 259, 260, 261, 262, 263, 264, 265, 266, 267, 268, 269, 270, 271, 272, 273, 274, 275, 276, 277, 278, 279, 280, 281, 282, 283, 284, 285, 286, 287, 288, 289, 290, 291, 292, 293, 294, 295, 296, 297, 298, 299, 300, 301, 302, 303, 304, 305, 306, 307, 308, 309, 310, 311, 312, 313, 314, 315, 316, 317, 318, 319, 320, 321, 322, 323, 324, 325, 326, 327, 328, 329, 330, 331, 332, 333, 334, 335, 336, 337, 338, 339, 340, 341, 342, 343, 344, 345, 346, 347, 348, 349, 350, 351, 352, 353, 354, 355, 356, 357, 358, 359, 360, 361, 362, 363, 364, 365, 366, 367, 368, 369, 370, 371, 372, 373, 374, 375, 376, 377, 378, 379, 380, 381, 382, 383, 384, 385, 386, 387, 388, 389, 390, 391, 392, 393, 394, 395, 396, 397, 398, 399, 400, 401, 402, 403, 404, 405, 406, 407, 408, 409, 410, 411, 412, 413, 414, 415, 416, 417, 418, 419, 420, 421, 422, 423, 424, 425, 426, 427, 428, 429, 430, 431, 432, 433, 434, 435, 436, 437, 438, 439, 440, 441, 442, 443, 444, 445, 446, 447, 448, 449, 450, 451, 452, 453, 454, 455, 456, 457, 458, 459, 460, 461, 462, 463, 464, 465, 466, 467, 468, 469, 470, 471, 472, 473, 474, 475, 476, 477, 478, 479, 480, 481, 482, 483, 484, 485, 486, 487, 488, 489, 490, 491, 492, 493, 494, 495, 496, 497, 498, 499, 500, 501, 502, 503, 504, 505, 506, 507, 508, 509, 510, 511, 512, 513, 514, 515, 516, 517, 518, 519, 520, 521, 522, 523, 524, 525, 526, 527, 528, 529, 530, 531, 532, 533, 534, 535, 536, 537, 538, 539, 540, 541, 542, 543, 544, 545, 546, 547, 548, 549, 550, 551, 552, 553, 554, 555, 556, 557, 558, 559, 560, 561, 562, 563, 564, 565, 566, 567, 568, 569, 570, 571, 572, 573, 574, 575, 576, 577, 578, 579, 580, 581, 582, 583, 584, 585, 586, 587, 588, 589, 590, 591, 592, 593, 594, 595, 596, 597, 598, 599, 600, 601, 602, 603, 604, 605, 606, 607, 608, 609, 610, 611, 612, 613, 614, 615, 616, 617, 618, 619, 620, 621, 622, 623, 624, 625, 626, 627, 628, 629, 630, 631, 632, 633, 634, 635, 636, 637, 638, 639, 640, 641, 642, 643, 644, 645, 646, 647, 648, 649, 650, 651, 652, 653, 654, 655, 656, 657, 658, 659, 660, 661, 662, 663, 664, 665, 666, 667, 668, 669, 670, 671, 672, 673, 674, 675, 676, 677, 678, 679, 680, 681, 682, 683, 684, 685, 686, 687, 688, 689, 690, 691, 692, 693, 694, 695, 696, 697, 698, 699, 700, 701, 702, 703, 704, 705, 706, 707, 708, 709, 710, 711, 712, 713, 714, 715, 716, 717, 718, 719, 720, 721, 722, 723, 724, 725, 726, 727, 728, 729, 730, 731, 732, 733, 734, 735, 736, 737, 738, 739, 740, 741, 742, 743, 744, 745, 746, 747, 748, 749, 750, 751, 752, 753, 754, 755, 756, 757, 758, 759, 760, 761, 762, 763, 764, 765, 766, 767, 768, 769, 770, 771, 772, 773, 774, 775, 776, 777, 778, 779, 780, 781, 782, 783, 784, 785, 786, 787, 788, 789, 790, 791, 792, 793, 794, 795, 796, 797, 798, 799, 800, 801, 802, 803, 804, 805, 806, 807, 808, 809, 810, 811, 812, 813, 814, 815, 816, 817, 818, 819, 820, 821, 822, 823, 824, 825, 826, 827, 828, 829, 830, 831, 832, 833, 834, 835, 836, 837, 838, 839, 840, 841, 842, 843, 844, 845, 846, 847, 848, 849, 850, 851, 852, 853, 854, 855, 856, 857, 858, 859, 860, 861, 862, 863, 864, 865, 866, 867, 868, 869, 870, 871, 872, 873, 874, 875, 876, 877, 878, 879, 880, 881, 882, 883, 884, 885, 886, 887, 888, 889, 890, 891, 892, 893, 894, 895, 896, 897, 898, 899, 900, 901, 902, 903, 904, 905, 906, 907, 908, 909, 910, 911, 912, 913, 914, 915, 916, 917, 918, 919, 920, 921, 922, 923, 924, 925, 926, 927, 928, 929, 930, 931, 932, 933, 934, 935, 936, 937, 938, 939, 940, 941, 942, 943, 944, 945, 946, 947, 948, 949, 950, 951, 952, 953, 954, 955, 956, 957, 958, 959, 960, 961, 962, 963, 964, 965, 966, 967, 968, 969, 970, 971, 972, 973, 974, 975, 976, 977, 978, 979, 980, 981, 982, 983, 984, 985, 986, 987, 988, 989, 990, 991, 992, 993, 994, 995, 996, 997, 998, 999, 1000.

Reconsidering Screening in Primary Care

Screenings are an important part of preventive care, but the growing list of recommendations is daunting. How do we prioritize the limited time we have with patients and families?

Written by Jeb Phillips

There are 32 well-child primary care visits recommended by the American Academy of Pediatrics in its Bright Futures “Periodicity Schedule.” The first is prenatal, the last happens at 21 years old. During these brief visits, pediatricians need to address a family’s concerns, provide counseling, and, depending on the visit, screen for many different conditions, such as visual impairment, obesity, hypertension, elevated lipid levels, or depression.

The number of evidence-based screenings can be daunting to consider and feel impossible to complete.

“I feel guilty when I look at this list,” says Jill Neff, DO,

the only independent pediatrician in rural Jackson County, Ohio, and someone who is well known for her commitment to her patients. “I’m doing the best that I can, but I’m the nurse and the doctor. Including me, there are two full-time people in my office. How am I supposed to find the time to do all of this if there are six kids in my waiting room with ear infections?”

It’s a common concern among primary care providers, and it’s often paired with this one: “If a child does screen positive for a condition, how can I connect them to the services they need?”

There are no easy answers, but over the last several

years, a number of organizations and physicians have wrestled with these questions. Among the most recent efforts, this summer clinicians and researchers from Nationwide Children's Hospital helped lead the publication of a multiple-study supplement in *Pediatrics*, collectively called "Methods for Assessing the Impact of Screening in Childhood on Health Outcomes."

The supplement came from a meeting organized by the National Institutes of Health's Office of Disease Prevention to identify gaps in research needed to help clinicians prioritize the delivery of screening services to evaluate the long-term impact of screening on health and development.

Kelly Kelleher, MD, vice president of Community Health at Nationwide Children's, acknowledged the benefits of screening but called the study he was the senior author on "the most pessimistic one we've published" because it showed that inconsistent screening with inadequate follow up quickly takes away any benefit. (It was the first article in the publication because of the challenges it articulated.)

Alex Kemper, MD, division chief of Primary Care Pediatrics at Nationwide Children's and an author on several of the studies, said he continues to believe screening is a "core component of the preventive care we do for children."

Those sentiments aren't in conflict, they say. Screening is important, and it's also difficult — particularly when considering the time pressure in primary care and everything that must happen for a screening to be effective.

So how can we do better?

The Justification for Screening

If a condition is an important health problem; if it has a latent or early symptomatic stage that may not be obvious but can be identified; if there's a validated tool for identification; if patients who have the condition can be treated; if earlier treatment is better than waiting; if screening and early treatment do not lead to significant harm; and if there is not too great a cost. . . then screening is indicated.

Those are the basic principles laid down in a landmark 1968 international publication and they still hold, says Dr. Kemper. The best example of it working in practice is with newborns. The core newborn screening panel can help identify 35 conditions (or significantly more

in some states). Unlike the screening that happens in primary care, public health agencies have an active role in conducting the screening and providing follow-up care.

Other screenings are more complicated, in part because of knowledge gaps about how they can be effective and efficient in the primary care practice setting given the limited time of an appointment, says Dr. Kelleher.

Guidance like the kind in AAP's Bright Futures is the closest we have, says Joe Hagan, MD, the long-time co-editor of Bright Futures, clinical professor at the Larner College of Medicine at the University of Vermont and pediatric primary care provider. There are countless screening and preventive care recommendations from many sources, he says. Beginning in the mid-1990s, Bright Futures attempted to consolidate the best ones. Then in 2003, recognizing the research gap that existed for much of pediatric primary care, Bright Futures contributors started making a special effort to ensure the recommendations were evidence-informed.

Dr. Hagan has helped lead that effort. Dr. Kemper is an evidence consultant for Bright Futures and a past member of the United States Preventive Services Task Force, which issues opinions and statements on the evidence underlying preventive care.

The current periodicity schedule, last updated in March 2021, is the result of that work. Some of the assessments are nearly automatic parts of well child primary care visits and have been for decades, such as height and weight measurements. Those should then be used to screen for obesity using body mass index, starting at 2 years of age, according to Bright Futures.

Others, including depression screening in adolescence, are comparatively new. Insurance claims data and surveys from Partners For Kids®, Nationwide Children's accountable care organization, suggest that at best, 50% of adolescents who should be screened for depression are actually receiving that screen. And many teens with a positive depression screen do not receive high-quality follow-up care.

Certain screens that some health systems are now routinely conducting, such as those for social determinants of health and adverse childhood experiences, are not on the schedule at all. And even the strongest advocates of the schedule recognize it is not the be all, end all of pediatric primary care.



“Families may object to the screening because of the stigma associated with mental health issues. As children age, they may refuse to do them. On the provider side, someone needs to be educated on how to administer a screen, on how to interpret the results, on how to talk to the families about the results if there is a positive screen. There’s staff turnover. Billing for screening can be confusing. And there is always time pressure in the visits.”

– Heather Maciejewski, manager, Center for Clinical Excellence, Partners For Kids

“For a visit to be successful, you have to address the family’s and child’s agenda first, before the periodicity schedule,” says Dr. Hagan. “Bright Futures is not meant to be more important than the conversation with the family. But there are certain things that can be done and should be done for the best preventive care.”

The Screening Struggle

In Dr. Kelleher’s telling, the pediatric primary care system does an excellent job of doing what it was conceptualized for in the 1940s — episodic visits for acute conditions that can be resolved fairly quickly. It should be no surprise that providers struggle in managing the ongoing developmental concerns of children, though. Those providers have been asked to do ever more without an overall system of support.

“We don’t have good tracking mechanisms, good follow-up systems, good data collection and flow across platforms, good relationships with specialists,” he says. “Effective screening is complicated, because the actual “screen” itself is such a small part. There are so many steps, from the patient actually showing up to be screened through the treatment of the condition.”

Many of the recommended early childhood physical health screenings do get performed routinely in primary care. Blood pressure, height and weight, vision and hearing. The tools for those are widely available and understood, families expect those kinds of screens, and they may be required for school and other activities.

Screening can be more difficult as a child ages, or when the screening goes beyond physical and into developmental and behavioral health, says Heather Maciejewski, manager, Clinical Center of Excellence,

Partners For Kids. Among the quality improvement projects she leads are some directly tied to increasing screening rates in primary care.

“Families may object to the screening because of the stigma associated with mental health issues,” she says. “As children age, they may refuse to do them. On the provider side, someone needs to be educated on how to administer a screen, on how to interpret the results, on how to talk to the families about the results if there is a positive screen. There’s staff turnover. Billing for screening can be confusing. And there is always time pressure in the visits.”

Ultimately, what to do after a screen is positive may be the biggest problem, even for basic physical issues. More than 50% of Dr. Neff’s patients are covered by Medicaid, and she says she has difficulty finding an optometrist to take referrals of those patients in her area. Nationwide Children’s, 80 miles away, has the closest dental clinic for her Medicaid patients.

“Then you’re talking about time off work, transportation, a family’s anxiety about traveling to a city that they’re unfamiliar with, extra visits for complex issues. . .” she says. “There is only so much I can do, but there is also only so much that I can ask them to do.”

Looking For Solutions

Despite the problems, screening can improve health.

“Just because we don’t do a perfect job isn’t a reason we shouldn’t do it,” Dr. Kemper says. “It’s really a call for us to do it better.”

Solutions are possible through improved systems and processes, according to nearly everyone involved

— from the processes inside an individual pediatric practice to those at the health care system level. At the smallest scale, certain survey-based screenings can happen on a tablet in a waiting room, and the results can be scored before the actual appointment begins, alleviating some time pressure, says Dr. Kemper.

At Nationwide Children’s, the quality improvement projects spearheaded by Partners For Kids offer individualized solutions to the screening process, including setting up the steps for referral to specialized care if a screen is a positive, says Maciejewski. Part of the QI project involves training staff members on executing each part of the process. Having all of that in place before a screening even happens means there are fewer crises with a positive screen, she says.

Screening AND Surveillance

One of Dr. Kemper’s contributions to the *Pediatrics* supplement points out the differences between “screening” and “surveillance.” He suggests that focusing on surveillance, or the changes to a child’s health over time, reduces the pressure on screening, or a single threshold test during a single appointment. For example, if a child whose body mass index has been at the 50th percentile for their entire lives suddenly presents at the 70th percentile, that child still doesn’t screen as at risk for obesity. An observant provider will understand that surveillance is more important in that situation.

This, as it happens, is exactly Dr. Neff’s strategy in Jackson County.

“If I mention obesity, families get upset,” she says. “But if I notice a difference over time, I will say to the mom, ‘Has anything changed in your family in the last three months?’ and we work toward the issue that way.”

That’s what Dr. Kemper calls the “art of medicine.” It’s different from screening, but it’s in the service of the same goal. And there are other, larger-scale measures that can be considered upstream of screening, but that work hand-in-hand with screening to address health issues.

For instance, depression and anxiety are such population-level concerns in adolescence that screening one-by-one in a provider’s office should be considered only a part of well care. Prevention programs in schools reach a greater number of young people at once, and many themselves have a screening function. The Signs of Suicide® program trains school staff members to recognize and respond to young people at risk and includes many other prevention elements. The PAX Good Behavior Game® trains elementary school teachers in strategies to help children with self-regulation.

Nationwide Children’s administers both of the prevention programs in partnership with local districts, and both programs have good outcomes for children when delivered in schools. That, in the end, is the point of screening and preventive care, no matter how it is carried out.

“Medicine is a team sport,” Dr. Kemper says. “There is a lot we still need to do to make sure that screenings are as efficient and effective as possible. We need to be smarter. It’s all hard work, but if we do it, we can make a difference.”

Committee on Practice and Ambulatory Medicine, Bright Futures Periodicity Schedule Workgroup. 2021 recommendations for preventive pediatric health care. *Pediatrics*. 2021 Mar;147(3):e2020049776

Gardner W, Bevans K, Kelleher KJ. The potential for improving the population health effectiveness of screening: A simulation study. *Pediatrics*. 2021 Jul;148(Suppl 1):s3-s10.

Kemper AR, Lerostak T, Grossman DC. Incorporating longitudinal surveillance into the delivery of pediatric screening services. *Pediatrics*. 2021 Jul;148(Suppl 1):s33-s36

Wilson JM, Jungner YG. Principles and practice of screening for disease. Geneva: World Health Organization; 1968.



“Medicine is a team sport. There is a lot we still need to do to make sure that screenings are as efficient and effective as possible. We need to be smarter. It’s all hard work, but if we do it, we can make a difference.”

– Alex Kemper, MD, division chief of Primary Care Pediatrics at Nationwide Children’s Hospital

MICROSURGERY FOR ACUTE FLACCID MYELITIS: Personalized Approach Leads to Remarkable Recoveries

Children from around the world are coming to Nationwide Children's for specialized care for AFM with lower extremity involvement. Dr. Amy Moore invented many of the procedures that are leading to remarkable recoveries for these patients.

Written by Lauren Dembeck, PhD

After an ordinary cold, most people continue with life as usual; however, in some rare cases, a previously healthy child can go from running and playing one day to being unable to walk the next, experiencing rapid paralysis within days or sometimes hours of being sick. This uncommon, polio-like condition is termed acute flaccid myelitis (AFM). It predominantly affects children and is characterized by sudden muscle weakness in the arms and/or legs, which can sometimes turn into permanent paralysis.

Since 2014, cases of AFM have been increasing, with peaks occurring every two years. According to the Centers for Disease Control, 661 cases have been confirmed. In most cases, children with AFM had a cold or fever in the days prior to paralysis. Thus, researchers believe AFM may be caused by a common seasonal virus.

Children with AFM have what appears to be viral- or inflammation-induced damage to the nerves of the spinal cord, including those that control muscles in the arms and legs. While some of these children are able to recover by following activity-based rehabilitation programs, a small percentage have little recovery or see their progress plateau.

These patients and their families are finding hope in a specialized nerve transfer surgery developed by Amy Moore, MD, a plastic and reconstructive surgeon at

The Ohio State University Wexner Medical Center and Nationwide Children's Hospital.

In 2016, the first cohort of children with AFM were brought in for surgical treatment of the paralysis, recounts Dr. Moore.

"I work on adults and children to restore motion with nerve transfer, often following trauma or cancer," says Dr. Moore. "My colleagues who knew I was doing nerve transfers in the lower extremities asked if I would consider seeing these children who could not walk. It was a leap of faith for me and for the parents. When I was in the process of creating these nerve transfers, they trusted me to make this leap of innovation with their child."

NERVE TRANSFER

Nerve transfer techniques to restore function in the upper extremities were refined in the late 1990s and early 2000s. These often involve the brachial plexus, a group of nerves that originates in the spinal cord at the neck and controls the movement and feeling to the hand, wrist, elbow and shoulder. Dr. Moore recognized the potential to creatively adapt these techniques to the nerves in the trunk and lower extremities to restore function, including hip stability and leg movement.

During her tenure at Washington University School of Medicine in St. Louis, Missouri, between 2004 and



“I work on adults and children to restore motion with nerve transfer, often following trauma or cancer. My colleagues who knew I was doing nerve transfers in the lower extremities asked if I would consider seeing these children who could not walk. It was a leap of faith for me and for the parents. When I was in the process of creating these nerve transfers, they trusted me to make this leap of innovation with their child.”

– Amy Moore, MD, plastic and reconstructive surgeon at The Ohio State University Wexner Medical Center and Nationwide Children’s Hospital

2011, Dr. Moore pioneered a collection of microsurgical techniques for the lower extremities of children with AFM and recently published details of her approach in the journal of *Plastic and Reconstructive Surgery – Global Open*.

In 2018 Dr. Moore saw 78% of the estimated potential surgical candidates with AFM. She hopes that publication of the techniques will encourage more surgeons to offer this treatment to patients with AFM and to spread the word to parents that there may be options to further improve the muscle function of children’s paralyzed limbs.

“The lower extremities and the nerves that power them are no different than those in the upper extremities. A nerve is a nerve,” says Dr. Moore. “In nerve transfer, we are using a nerve that is working from a muscle of redundant function or one of less importance. We cut that nerve, move it, and rewire it to a nerve that powers a muscle of more important function.”

Dr. Moore suggests the nerve that allows us to wiggle our toes as an example. “We don’t need to wiggle our toes if we can’t stand.” The surgery works by bypassing the injury in the spinal cord and harnessing the ability of the peripheral nerves to regenerate and connect with the target muscle of greater importance, capitalizing on the brain’s plasticity and ability to relearn the neural pathway. In this example, rerouting the portion of the sciatic nerve that controls the toes to the nerve that controls the gluteal muscle, restoring hip stability.

Dr. Moore and colleagues uses a hierarchy for lower limb recovery goals with hip stabilization at the top of the list, followed by knee extension, then knee flexion. In addition to the restoration of gluteal nerve function using the sciatic nerve, the surgeries may also include

splicing of donor nerves that control the sartorius (a long muscle that connects the hip and knee), the obturator (a short muscle connecting the femur and pelvis), and the abdominal muscles to the nerves of the femur and/or hamstrings to restore leg movement and, possibly, the ability to walk again.

Together with physical medicine and rehabilitation specialists, the surgeons conduct a detailed physical examination to determine surgical candidacy — which nerves to reroute to where, depending on the availability of functional nerves. “It’s about being familiar with the anatomy and the topography of the nerves,” says Dr. Moore.

“The difficulty with AFM is that it is very asymmetric. The children do not present with a typical pattern of paralysis. Every child that we’ve seen has been different,” says Nationwide Children’s Physical Medicine and Rehabilitation physician Wilawan Nopkhun, MD, who works with the surgeons as well as with the social workers, physical therapists, and nursing team to plan and execute the children’s rehabilitation plan. “We have to see exactly how they are functioning — all their limbs and their whole body — to determine the donor nerves and the recipient muscles. It’s a combination of where can we take from in order to maximize and optimize their functional recovery.”

“We are seeing success in these kids. They are exposed to hours of therapy for incremental improvements in function,” adds Dr. Moore. “This is really an inspiring group of patients and parents that I feel so privileged to care for. They are the epitome of what hope should be.”

All the patients with AFM from the 2016 cohort have reported improved function after their nerve transfer



“To be able to help kids walk again, that’s really something incredible. Our collaboration has fostered the growth of this subspecialty at Nationwide Children’s, and these novel techniques complemented our existing repertoire of techniques and principles used for brachial plexus injuries and traumatic nerve injuries. Offering all of these techniques within one center is unusual, nationally and globally.”

– Kim Bjorklund, MD, director of the Brachial Plexus Program at Nationwide Children’s Hospital

surgeries. Among those who underwent the surgery for restoration of gluteal function, four of five patients transitioned from using a wheelchair to walking with assistive devices, while children who could walk with assistive devices prior to surgery now have increased endurance and can walk longer distances.

BUILDING AND BROADENING EXPERTISE

In 2019, Kim Bjorklund, MD, director of the Brachial Plexus Program at Nationwide Children’s, started learning the ins and outs of the nerve transfer techniques for the lower extremities from Dr. Moore. The two physicians now perform surgery side-by-side on the same patient, shortening patients’ time in surgery, improving safety, and promoting a uniform standard of care.

“To be able to help kids walk again, that’s really something incredible,” says Dr. Bjorklund, who is also a clinical assistant professor at The Ohio State University. “Our collaboration has fostered the growth of this subspecialty at Nationwide Children’s, and these novel techniques complemented our existing repertoire of techniques and principles used for brachial plexus injuries and traumatic nerve injuries. Offering all of these techniques within one center is unusual, nationally and globally.”

Nationwide Children’s is now developing a comprehensive care center for treating children with a variety of nerve conditions. “Peripheral nerve surgery in general is broad and has a lot of applications to improve function and quality of life for patients,” says Dr. Bjorklund.

In addition to brachial plexus injuries, AFM, and trauma-related injuries, the team is treating patients with a number of other nerve conditions, including those arising from other surgeries, following cancer

treatment, and after amputations. For example, the surgeons are able to treat phantom limb pain or ghost pain, a well-known phenomenon associated with amputation. “We perform a procedure called targeted muscle reinnervation, which not only helps with the pain but also improves patients’ function, when using a prosthetic,” explains Dr. Bjorklund.

As a comprehensive care center, multiple physicians in other disciplines, including neurosurgery, orthopedic surgery, internal medicine, general pediatrics, and physical medicine and rehabilitation, will care for patients during and after their nerve surgery.

“After now working with patients with nerve conditions for years, we see that they often have other health issues, such as spinal issues from their lack of muscles, leg length discrepancies, and gastrointestinal issues,” explains Dr. Moore.

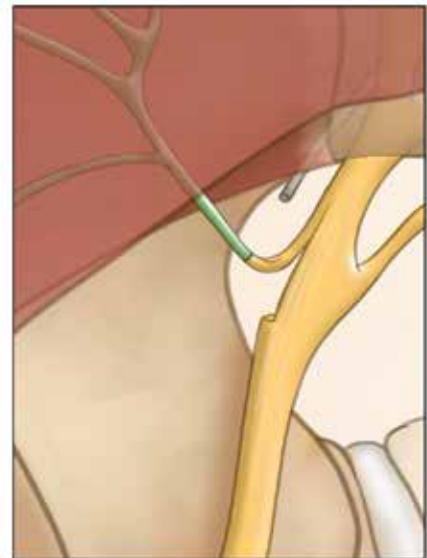
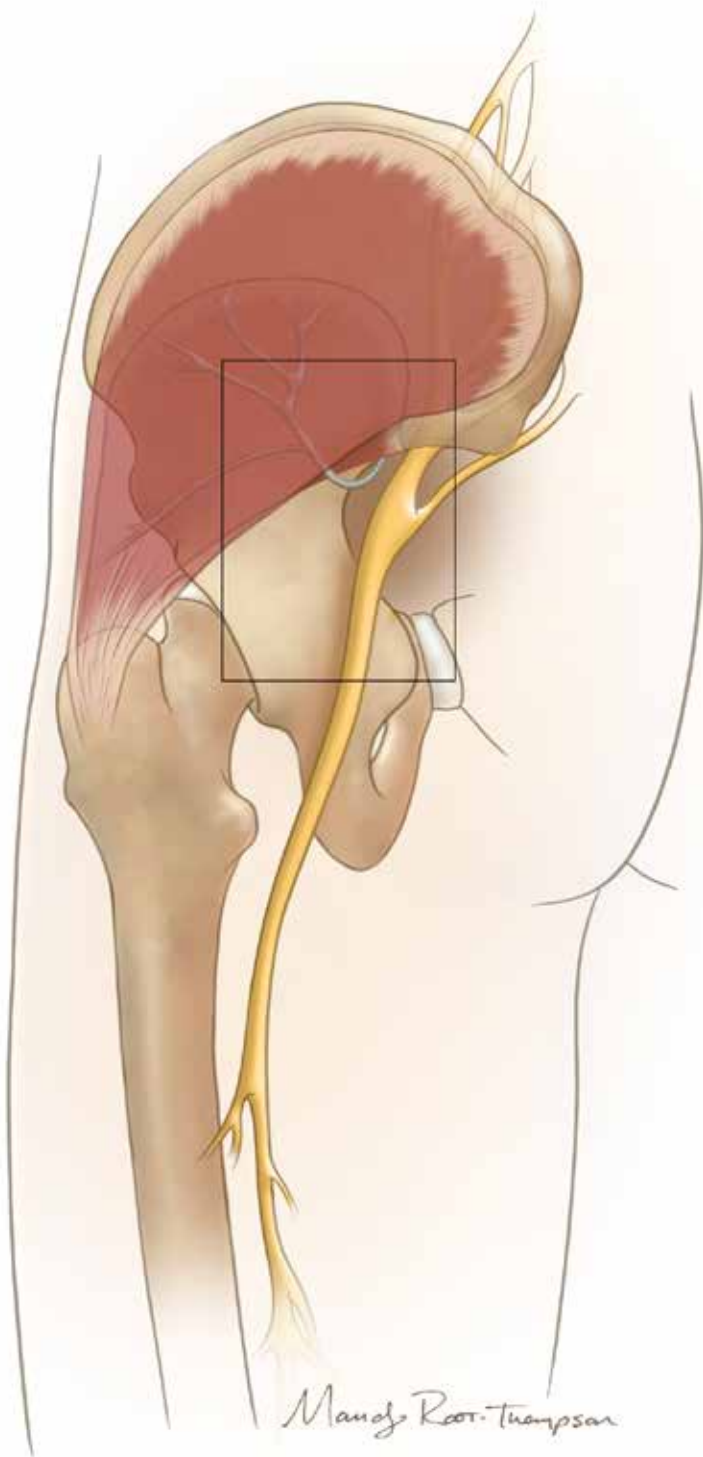
Additionally, an early referral is key, says Dr. Nopkhu, “Conducting a full assessment early is important because we typically have limited windows of time where we can potentially intervene for certain conditions and with an early referral we can potentially offer more treatment options.”

The center will also include both clinical and basic science research along with the clinical practice. “As the program grows, this is something that I think is going to benefit children all around,” says Dr. Bjorklund.

Centers for Disease Control and Prevention. Acute Flaccid Myelitis (AFM). Accessed July 20, 2021, at: <https://www.cdc.gov/acute-flaccid-myelitis/index.html>

Moore AM. Nerve transfers to restore upper extremity function: A paradigm shift. *Frontiers in Neurology*. 2014 Mar 31;5:40.

Moore AM, Bettlach CR, Tung TT, West JM, Russo SA. Lower extremity nerve transfers in acute flaccid myelitis patients: A case series. *Plastic and Reconstructive Surgery Global Open*. 2021 Jul 20;9(7):e3699.



End-to-End Nerve Transfer



Supercharge End-to-Side Nerve Transfer

Lower Extremity Nerve Transfer

Microsurgical nerve reconstruction techniques can address functional deficits in the lower extremities of patients with AFM or other nerve disorders. In this example, the patient's superior gluteal nerve is dysfunctional (indicated in gray). Hip stabilization and restoration of the ability to stand and shift weight can be achieved by transferring a redundant fascicle from the sciatic nerve to the superior gluteal nerve via an end-to-end nerve transfer (upper box) or supercharge end-to-side nerve transfer (lower box). Due to unpredictability in nerve injury patterns and the needs of each patient, a variety of donor and recipient nerves may be used in surgery.

TEENS ON THE ROAD: HOW TECHNOLOGY, POLICY AND PARENTS INFLUENCE DRIVING SAFETY

Traffic crashes are a leading cause of death in the United States. For teens, the stakes are especially high.

Written by Abbie Roth

Americans love cars. Some kids start saving for their first car before they get rid of their training wheels. And teens especially can't wait for that moment when they have the freedom to hit the open road, or at least drive to school. It's the subject of songs and movies, and it's deeply ingrained in popular culture: getting that driver's license is a ticket to freedom.

But each day in the United States, approximately seven teens die as a result of motor vehicle crashes, and an additional 685 are injured.

Among teens ages 16 to 19, automobile-related accidents are the leading cause of death. Distracted driving (primarily due to cellphones) and increased substance use have joined typical teen risk-taking and inexperience as major contributors to motor vehicle crashes. According to the Centers for Disease Control and Prevention (CDC), in 2019, nearly 2,400 teens died and more than 250,000 were treated in emergency departments as a result of motor vehicle crashes.

Even with the risks, driving is an important skill for



many teens to learn. In the United States, driving is a nearly unavoidable part of life in much of the country. For decades, researchers in the Center for Injury Research and Policy (CIRP) in the Abigail Wexner Research Institute at Nationwide Children's Hospital have been working with teens, parents, policymakers and pediatricians to understand teen driving behaviors and promote safe driving.

Some of that work, in combination with other efforts across the country, has changed the safety baseline for young drivers. From graduated driver licensing — going from learner's permit to restricted license to full license — and hands-free cellphone laws to apps that monitor driving and provide feedback to teens (and their parents), a variety of policies and tools have been developed that have the potential to increase safe driving among teens.

Supporting Parent-Teen Driver Relationships

Keeping the parent-teen relationship positive is a long-standing goal of safe driving researchers and advocates.

“The parent-child relationship is where safe driving starts,” says Dennis Durbin, MD, MSCE, chief scientific officer at the Abigail Wexner Research Institute at Nationwide Children's and injury prevention and policy researcher. “In both the learner permit phase and the restricted driver phase, parents establish the expected behaviors and enforce them with consequences.”

If you've ever been a teen learning to drive from your parent — or a parent teaching your teen to drive — you know that this can be a stressful process leading to fraught relationships.

“The parent-focused approach to safe teen driving relies on more than just setting rules and expectations — parents

need to be proactive in motivating their teens to engage in safe driving behaviors early on,” says Jingzhen (Ginger) Yang, PhD, MPH, principal investigator in CIRP. “And research shows that this can be a very effective approach.”

But after the learner permit phase of driving licensure, parents aren't always around to observe teen drivers and provide feedback. Can technology help parents be “in the car” when they aren't in the car?

Using Technology to Improve Driving Habits

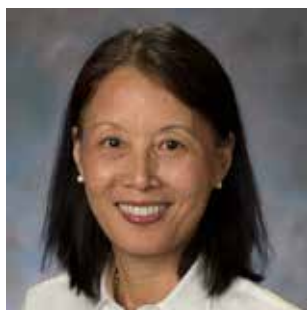
Dr. Yang and her team have three ongoing funded projects, two funded by National Institutes of Health and one funded by the CDC, focusing on high-risk, 16- to 17-year-old teen drivers who have a restricted driver license (starting to drive unsupervised) and received a traffic citation.

Existing studies show that motor vehicle collision risk is particularly high during the first six months of driving without supervision. Teen drivers who have committed a traffic violation are at even greater risk.

“Research shows that the parent role in teen driving safety is critical, so when we are looking at how to add technology into the mix, it is not to replace the parent, but to empower them,” Dr. Yang says. “Our projects use the technology to engage parents of the teens in the ways to strengthen their child's motivation to drive more safely.”

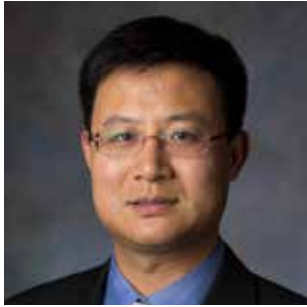
One of those technologies is a driving tracker.

Driving trackers can do more than save you money on car insurance. They can begin an important dialogue between parents and teen drivers. Dr. Yang and her team are using these devices in their ongoing studies to see how gathering driving data that are shared with



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— *Jingzhen (Ginger) Yang, PhD, MPH, principal investigator in the Center for Injury Research and Policy in the Abigail Wexner Research Institute at Nationwide Children's Hospital*



“While teens who are driving on a learner’s permit or in the restricted driving phase have less cellphone usage, teens and young adults ages 18 to 24 with full licenses have the highest of cellphone usage in all age groups. These are less experienced drivers, and distracted driving can be devastating.”

– *Motao (Matt) Zhu, MD, MS, PhD, is a principal investigator in the Center for Injury Research and Policy in the Abigail Wexner Research Institute at Nationwide Children’s Hospital*

teens and parents can increase parents’ involvement in their teen’s safe driving behaviors.

In Franklin County, Ohio, home to Nationwide Children’s, teens who have a traffic violation are required to appear in court with their parents. It’s here that they are introduced to Project DRIVE.

“When young drivers receive a traffic citation and are required to show up in court, this provides a very teachable moment, and an opportunity for them to join our program,” she says.

Her team teaches parents ways to increase their child’s motivation to drive more safely. The projects use an in-vehicle device that records teen driving behavior and sends summary reports to the teen and parent. With this tool, parents have objective data to use in conversations with their teens about their driving and safe driving behaviors.

“We tell parents, ‘Be sure to include praise in your

feedback and conversations with your teen drivers,’” says Dr. Yang. “Teens often say they only hear criticism or negative feedback on their driving. Having this report can highlight times that the teen did well — providing an opportunity for praise.”

So far, the feedback from parents and teens is positive, says Dr. Yang. “Parents are happy to have the support and training that we provide. The teens are happy to have proof of when they do a good job.”

Technology and Distracted Driving

Keeping your hands off your phone and on the wheel is a critical component of safe driving for everyone — especially teens. Using built-in or third-party apps that limit cellphone use during driving is growing in popularity. But do these apps really work? Are people using them?

Motao (Matt) Zhu, MD, MS, PhD, is a principal investigator in CIRP who wants to find out.

Top 6 Pieces of Advice Pediatricians Give to Support Safe Teen Driving

While parents are the most influential on teens who are learning to drive, pediatricians also have a role in supporting teens and parents as they navigate this important milestone.



1. Don’t drive after using marijuana, alcohol or other substances that impair reaction time and focus.



2. Put phones down. Use hands-free options or don’t use your phone at all.

He specializes in understanding how cellphone use influences teen driving behaviors — and how policy is the translational mechanism to change teen driving outcomes.

“Safe driving, especially for teenagers, is an important issue, and one where research can really make a difference,” he says. “Research and policy in support of safe driving can save lives.”

His most recent R01 grant from the NIH supports a randomized clinical trial to determine the effects of a cellphone app and a driving mode intervention in reducing cellphone use and high-risk driving events in drivers aged 18 to 24 years.

The study will follow 1200 young drivers using commercial apps or driving mode (both Apple and Android versions) to limit hands-on cellphone usage while driving. The active placebo group will have an app that isn't blocking anything but is tracking usage and driving.

“While teens who are driving on a learner's permit or in the restricted driving phase have less cellphone usage, teens and young adults ages 18 to 24 with full licenses have the highest of cellphone usage in all age groups,” says Dr. Zhu. “These are less experienced drivers, and distracted driving can be devastating.”

Earlier research has shown that reducing the amount of time or incidences where drivers are touching their phone can reduce crashes.

So, is hands-free cellphone use the answer? Not completely.

“Using hands free options while in the car is far safer than being hands on with your cellphone while driving,” Dr. Zhu says. “But even hands free sometimes can be a distraction. In driving simulations and epidemiological studies, researchers still found risk associated with hands-free cellphone usage. In naturalistic driving studies where cameras were mounted on the car, manual and visual distractions were associated with safety-critical events.”

Notably, Dr. Zhu points out, talking hands free, such as making or taking a call through the Bluetooth system, was not associated with safety-critical events in the naturalistic driving study.

Driving Simulation Studies

Dr. Yang's third NIH-funded project is supported by a \$3 million R01 grant focused on fitness to drive after concussion among young drivers assessed using a high-fidelity driving simulator.

Whether from sports, a car crash or other traumatic event, the CDC estimates 1.7 million to 3.8 million children 18 years or younger suffer from concussion, a type of traumatic brain injury (TBI), each year.

For Dr. Yang, who started her research career studying sports and concussions, learning how concussion recovery affects driving safety utilizes the experience and insights she's gained over her career.

“We have studies on how concussion impacts athletics and school ability, but none on how concussion



3. Keep a safety-first mindset. Driving is a privilege and should be taken seriously.



4. Communicate what the teen driver is doing well in addition to areas for improvement.



5. Set expectations for safe driving and enforce them with consequences.



6. Parents are their teen's first and best role model — they can practice this advice too, not just teach it. Teens are more likely to learn by example/if parents are following the same rules.



“The parent-child relationship is where safe driving starts. In both the learner permit phase and the restricted driver phase, parents establish the expected behaviors and enforce them with consequences.”

– *Dennis Durbin, MD, MSCE, chief scientific officer at the Abigail Wexner Research Institute at Nationwide Children's and injury prevention and policy researcher*

impacts their driving ability throughout recovery,” she says. “Often teens recovering from concussion have no restriction on driving. We want to know if that is safe — and we suspect that it isn’t.”

The study, which is a collaboration with The Ohio State University and the University of Alabama at Birmingham, aims to assess reaction time, decision making and risk taking under different levels of cognitive load over the course of recovery. Dr. Yang is leading an NIH-funded study to compare teen driving over time — tracking teens during their recovery from concussion and comparing them with matched controls.

“Our study will fill critical gaps by providing evidence on how acutely post-injury neurocognitive function — for example, delayed reaction time — may impact driving ability, identifying therapeutic targets to help teens return to drive after mTBI,” said Despina Stavrinos, PhD, principal investigator of the study from the University of Alabama, in a press release about the grant.

Using state-of-the-art driving simulation facilities at University of Alabama at Birmingham and The Ohio State University in this collaborative project will enable the researchers to have a large, diverse group of participants, they say.

The Future of Safe Driving Research

While many might have thought that driving flying cars would be on the scene in 2021, others suspected that automated driving would be prevalent by now. Though we’re still waiting for that fully self-driven auto, today’s cars do have automated options that influence the skills needed to be a safe driver.

For example, some cars are programmed to parallel park by themselves or to stay a set distance away from the car in front of them, accelerating and braking as needed, without cognitive input from the driver. As those automated features grow more prevalent, how does that change the skills needed to drive a car? How does driver’s education adapt to meet the new needs of drivers? And are there new skills that drivers will be required to learn as a result of automation?

“These types of questions fascinate me,” says Dr. Durbin. “When I shifted from research into administration, the role of automation on teen driving safety was one we were just starting to consider. Now, I think it is one of the biggest areas of driving research left to explore.”

Centers for Disease Control and Prevention. <https://webappa.cdc.gov/sasweb/ncipc/leadcause.html>. Accessed July 2021.

Li L, Hu G, Schwebel DC, Zhu M. Analysis of US teens driving after using marijuana, 2017. *JAMA Network Open*. 2020;3(12):e2030473.

How Policy Can Influence Distracted Driving

Written by Laura Dattner

To combat the risks of using a cellphone while driving, states have implemented a variety of laws. As of July 2021, 21 of 50 states have implemented comprehensive hands-free cellphone laws (i.e., comprehensive handheld cellphone bans), which prohibit almost all handheld cellphone use including texting, calling and using apps. In addition, three states and the District of Columbia (DC) banned calling and texting, 24 states banned texting, and two states had no prohibition on cellphone use for drivers of all ages.

A recent study led by researchers at the Center for Injury Research and Policy at Nationwide Children's Hospital looked at drivers, non-drivers (passengers, pedestrians, bicyclists, motorcyclists), and total deaths involved in passenger vehicle crashes from 1999 through 2016 in 50 U.S. states, along with the presence and characteristics of cellphone use laws.

The study, published in *Epidemiology*, found that comprehensive hands-free cellphone laws were associated with fewer driver deaths, but calling-only, texting-only, texting plus phone-manipulating and calling and texting bans were not. This could be due to greater compliance; hands-free cellphone laws clearly send the message that cellphones are not to be handled at all while driving. In addition, drivers may be more likely to believe that enforcement is possible when the laws govern cellphone use broadly.

"We're not suggesting states take people's phones away while driving or tell them not to use their phone while driving," says Motao (Matt) Zhu, MD, MS, PhD, lead author of the study and principal investigator in the Center for Injury Research and Policy at Nationwide Children's. "We're recommending that, if you need to use your phone while driving, you do so hands-free. Further, we recommend states implement comprehensive hands-free cellphone laws to encourage this behavior change."

Zhu continues, "Our research demonstrates that hands-free laws save lives and reduce the societal costs associated with distracted driving. We found that hands-free laws have prevented about 140 driver deaths and 13,900 driver injuries annually in the United States."

Distracted driving-related crashes are a major burden on emergency medical and trauma systems and result in significant medical expenditures for treatment and rehabilitation. In Ohio, the associated societal costs for distracted driving-related crashes are about \$1.2 billion every year, which is equal to \$2,300 every minute.

Data for this study were obtained from Fatality Analysis Reporting System by the National Highway Traffic Safety Administration, the Insurance Institute for Highway Safety and LexisNexis.

Zhu M, Shen S, Redelmeier DA, Li L, Wei L, Foss R. Bans on cellphone use while driving and traffic fatalities in the United States. *Epidemiology*. 2021 Sep 1;32(5):731-739.



Driving Simulation Lab



The Ohio State University is home to a state-of-the-art, high-fidelity driving simulator.



Thomas Kerwin, PhD, director of the OSU Driving Simulation Lab, and his team are collaborating on numerous experiments to measure how drivers respond to different stimuli while driving.



For Dr. Yang's TBI study, teens who are recovering from a mild TBI are matched with teens who are not. Both drive in the simulator and are instructed to complete specific tasks.





The simulator has a variety of environments, including rural, urban and suburban neighborhoods.

During a simulation, the driver's reaction time may be tested by a surprise event, such as a trash can rolling into the road.



Inside the control room, researchers provide instructions to the driver, manipulate the simulation, and record data.



How Patient-Derived Stem Cells are Changing the Trajectory of Congenital Heart Disease Research



Small blood samples — and the patient-specific, induced pluripotent stem cells (iPSCs) they enable — turn into valuable research material for understanding congenital cardiovascular disorders, especially when united with modern genome sequencing and editing, animal models and three dimensional tissue growth technologies.

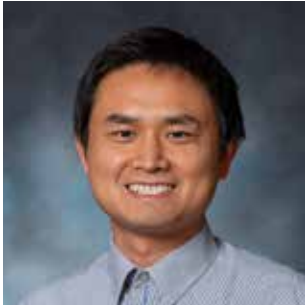
Written by Katie Brind'Amour, PhD

Patient-derived induced pluripotent stem cells (iPSCs) have a significant downside for studying most forms of adult heart disease: they resemble fetal heart cells in form and function. But this limitation, which keeps the cells from being easily applicable for the study of many adult conditions, is actually ideal for studying congenital heart problems.

Congenital heart defects or disease (CHD) affect about 1% of all live births in the United States and rank among

the leading causes of birth defect-related deaths. These defects can range from mild to very severe, and many require ongoing monitoring and multiple surgeries.

While operations and diagnostics have improved survival for many CHD patients — extending life into adulthood for many children who previously would have died in infancy or early childhood — much remains to be done to advance treatment options and maintenance therapeutics.



“iPSCs are excellent for studying CHD, because we can identify potential causative mutations using genome sequencing, then use the cardiomyocytes to look both at the disease and the defects that cause it — in a dish, using just cells, and without a biopsy.”

– *Mingtao Zhao, DVM, PhD, principal investigator in the Center for Cardiovascular Research in the Abigail Wexner Research Institute at Nationwide Children's Hospital*

Now that patient-derived iPSCs have entered the scene, however, researchers and clinicians are starting to use an exciting term when they discuss the trajectory of current CHD efforts: cure.

Making Cell Magic

Starting with about a teaspoon of blood, researchers separate out peripheral blood mononuclear cells, which they then reprogram into pluripotent stem cells using viral vectors. These are then subjected to a series of treatments to promote differentiation into the primary type of cells found in the heart — cardiomyocytes.

Once this is done properly and the cells ‘beat’ and signal like human heart cells, they can be reproduced so that there are enough to study in various ways: genetic profiling, genome editing, electrophysiological testing, organoid growth (3D tissue generation with multiple cell types), transplantation into animal models, drug screening and more.

“iPSCs are excellent for studying CHD, because we can identify potential causative mutations using genome sequencing, then use the cardiomyocytes to look both at the disease and the defects that cause it — in a dish, using just cells, and without a biopsy,” says Mingtao Zhao, DVM, PhD, principal investigator in the Center for Cardiovascular Research in the Abigail Wexner Research Institute at Nationwide Children’s Hospital. He recently published a protocol for cultivating human cardiomyocytes from routine blood samples; protocols are available for several other heart cell types as well.

Researchers often perform genome or exome screening to identify mutations that are worth studying in greater depth, then they edit the genome of human cardiomyocytes to see if the function of those cells changes.

“Once you know what gene causes what phenotype, you can establish a system to model this disease to

get more information,” says Dr. Zhao. “You can find similar mutations in mice or pigs to do further studies on orthologous variants in animals, or use genetic engineering to put the mutation into animals and see if heart defects develop.”

The next step in maximizing the potential of iPSCs for CHD, Dr. Zhao says, will be to correlate the data from iPSC, organoid and animal models to create a more comprehensive picture of the genetic basis of single ventricle heart defects, one of the most severe types of CHD, and — if the impact of the genetic mutation is confirmed — to seek out therapeutic options, such as gene therapy to stimulate the growth of an underdeveloped heart chamber.

Such a dramatic clinical translation of this technology would make a big difference for infants with single ventricle heart disease or an under-developed ventricular chamber, even if it only enlarges the defective heart enough to make surgical interventions more effective.

“With hypoplastic left heart syndrome and single ventricle syndromes, our options are palliative — we’re not curing it, and there are major limitations to mouse models for studying therapeutics,” says Vidu Garg, MD, PhD, director of the Center for Cardiovascular Research at Nationwide Children’s. Dr. Garg’s research primarily involves murine modeling of CHD and, now, use of iPSCs to help inform tactics taken in his lab.

That’s one of the reasons Dr. Garg recruited Dr. Zhao, who joined Nationwide Children’s in 2019 and has numerous iPSC-related projects now underway. During his time at Stanford University, Dr. Zhao collaborated with iPSC experts such as Joseph Wu, MD, PhD, director of the Stanford Cardiovascular Institute and professor of medicine and radiology at Stanford School of Medicine, who shares Dr. Zhao’s and Dr. Garg’s



“Patient-specific iPSCs are a game changer. The technology really allows you to understand the first step you need to know to make progress: disease pathology. Then with that you can understand the disease’s mechanism of action, which allows you to look for new drugs and find new therapies, and in turn improve patient care and outcomes.”

– Joseph Wu, MD, PhD, director of the Stanford Cardiovascular Institute and professor of medicine and radiology at Stanford School of Medicine

enthusiasm for the potential these cells hold for cardiovascular research.

“Patient-specific iPSCs are a game changer,” says Dr. Wu, whose lab focuses on iPSCs in cardiac applications, including adult congenital heart disease. “The technology really allows you to understand the first step you need to know to make progress: disease pathology. Then with that you can understand the disease’s mechanism of action, which allows you to look for new drugs and find new therapies, and in turn improve patient care and outcomes.”

Applying the Technology

Isabelle Deschênes, PhD, professor and chair of the Department of Physiology and Cell Biology at The Ohio State University, has studied a large family with congenital heart arrhythmias (congenital long QT syndrome, or LQTS) for more than two decades. When iPSCs came on the scene, she was able for the first time to investigate theories of variable genetic penetrance to determine what influences the severity of this potentially fatal — and highly unpredictable — congenital disease.

Her LQTS research showed that iPSCs derived from severely affected family members differed from mildly affected individuals physiologically. Then her team used whole exome sequencing to identify genetic variants present in these patients. Finally, they employed genome editing techniques (using CRISPR genetic engineering) to experiment with the removal or addition of these variants in iPSCs, confirming the roles of multiple genetic modifiers for congenital LQTS.

“Obviously, iPSC cardiomyocytes are a great advance in science, but that’s partly because of great progress in genetics and genomics,” says Dr. Deschênes. “Now, if

you suspect that a certain variant in a gene is worsening the phenotype of an individual, you can do CRISPR genome editing to correct it and test the patient-derived cardiomyocytes again. If you see the phenotype is then normal, that proves without a doubt this is why you have that phenotype in that individual.”

The identified protective and aggravating genetic variants were confirmed by the observed phenotypic differences in affected family members when Dr. Deschênes’ team screened the family for the genetic modifiers; the results were published in the *Journal of Clinical Investigation*.

Dr. Deschênes also collaborates with Dr. Zhao, Dr. Garg and others to advance cardiomyocyte iPSC protocols and applications via her expertise in electrophysiological testing, confirming that the cells function as true heart cells in terms of ion channel activity and electrophysiological signaling. This allows Drs. Zhao and Garg to use iPSC-derived cardiomyocytes to study the genetics and functional development of single ventricle heart diseases much as Dr. Deschênes did for LQTS patients: identifying potential genetic drivers of single ventricle disease, conducting genome editing, and seeing how the changes affect cell function.

“Making a genetically modified mouse to test some of the variants we can find through exome or genome screening of affected children is possible, but it takes a long time and is a very costly analysis,” says Dr. Garg. “That’s where iPSC technology has added value. Now, we’re taking human cells as opposed to mouse cells, and if we find an interesting genetic variant, we can fix it with genome editing and say, ‘Did it rescue that abnormality?’ There are exciting things we can potentially do with this tool.”



“So theoretically, we could have a molecular, probably fetal intervention to help a new ventricle grow better in children with single ventricle heart defects. iPSC cardiomyocytes open that door, and could offer a way to almost bypass the primary problem of a valve that isn’t growing.”

– Vidu Garg, MD, PhD, director of the Center for Cardiovascular Research in the Abigail Wexner Research Institute at Nationwide Children's Hospital

Putting iPSCs to Work for a CHD-Free Future

Because the fetal heart is fairly plastic and capable of some remodeling after surgery, Dr. Garg and others think iPSC-driven technology may hold particular promise for early CHD intervention — maybe even a cure.

“With CHD, we’re trying to look at whether iPSC-derived cardiomyocytes from children with single ventricle heart defects respond abnormally to biomechanical forces such as flow and stretch. If we are able to dissect out those mechanisms, it creates the possibility that we could molecularly direct growth or the right biomechanical forces to stimulate cardiomyocytes down their path to proliferate or differentiate,” says Dr. Garg. “So theoretically, we could have a molecular, probably fetal intervention to help a new ventricle grow better in children with single ventricle heart defects. iPSC cardiomyocytes open that door, and could offer a way to almost bypass the primary problem of a valve that isn’t growing.”

Drs. Zhao and Garg have two research endeavors underway applying iPSC technology to a single ventricle heart defect known as pulmonary atresia with intact ventricular septum (PA-IVS). The studies are funded by Additional Ventures, a nonprofit organization that provides significant grant money to advance the science and medicine around single ventricle heart disease.

In one project, they will examine maternal blood for possible cell-free biomarkers for PA-IVS by using patient-derived iPSCs and exosome profiling. The goal would be to predict fetal heart growth and health via a simple blood test for pregnant women.

In their other study, the team will examine patient-specific cardiomyocytes to understand the mechanisms involved in the development of PA-IVS, and whether those mechanisms offer insights for reversing defective heart growth.

“One of the fascinating things you can do is to model what a patient’s outcome was,” says Dr. Garg. “We’re going to have cells from PA-IVS patients, some of whom had bi-ventricle repairs, some of whom followed a single-ventricle pathway. In theory, if the outcomes and response to hemodynamic forces are a genetic phenomenon, we should be able to see differences in terms of ventricular growth by looking at their iPSCs.”

After learning the genetic architecture of single ventricle heart defects such as PA-IVS, investigators may be able to manipulate ventricle growth in animal and 3-D cell models, such as organoids that can form heart chamber-like structures, to help move these advances into formal preclinical therapeutic development. This could eventually lead to a fetal or postnatal intervention to change outcomes for children, from one ventricle to two.



“Now, if you suspect that a certain variant in a gene is worsening the phenotype of an individual, you can do CRISPR genome editing to correct it and test the patient-derived cardiomyocytes again. If you see the phenotype is then normal, that proves without a doubt this is why you have that phenotype in that individual.”

– Isabelle Deschênes, PhD, professor and chair of the Department of Physiology and Cell Biology at The Ohio State University

The idea may sound fantastic, but it is similar to work already being done on the left side of the heart, for children with hypoplastic left heart syndrome: the abnormal aortic valve is dilated with the hope that it will stimulate growth in the left ventricle by allowing for increased blood flow. iPSCs offer a new avenue to explore such therapeutic options in a host of other single ventricle defects.

The science will take time, though, and translation to the clinic will be complex.

“Cell culture models are not living animal models, and CHD involves multiple cells, so how do you know what you’re seeing in one cell type is truly what is happening in patients? That’s one issue,” says Dr. Garg. “There are weaknesses to the mouse model as well — it can’t serve as the CHD model when studying CHD-associated long-term morbidities. We need to create better models of disease if we’re going to come up with therapeutics or novel prevention strategies. That’s where cardiac organoid and 3-D tissue differentiation are going to improve things and offer a lot of advantages for bringing these findings to the clinic.”

Making Precision Medicine Possible

“We often joke that we’ve cured heart disease a million times over in mice, but it hasn’t always translated over to humans,” says Dr. Deschênes. “Working with human cells is a great advantage. iPSCs are not perfect, but they are one of the best options we have right now. The beauty is that they’re a patient’s real cells, not a model, so we can see what’s happening in that patient — what’s driving their disease and what are the potential targets we can hit to improve their health.”

Dr. Zhao, who recently published a paper describing the potential synergy across research modalities for CHD, believes that a combination of iPSC, genomic, animal, and organoid research methodologies could also carry other areas of medicine to new heights.

“Single cell genomics from iPSCs can give us very useful information regarding many other disease mechanisms that could allow personalized medicines and treatments, even beyond a gene therapy to grow a new heart chamber,” he says.

In that vein, Dr. Wu sees enormous potential for iPSCs to enable “clinical trials in a dish” — rapid screening for potential adverse effects or efficacy on a large number

of patients (through their cell lines) prior to making the investment in a true clinical trial. To aid in this and other research efforts, he has built the largest academic bank of iPSCs in the country, with more than 1500 patient samples.

Rather than using animal studies that typically involve clones — wherein testing on 1,000 mice is essentially testing just one mouse and 999 identical twins likely to be affected the same way — the iPSC bank could enable rapid screening for potential benefits or risks of a drug for 1,000 genetically different individuals. A 50-50 sex ratio and customizable ethnicity breakdown could allow valuable preclinical insight regarding who might be good responders, and thus who would be best to include in a clinical trial for that compound.

“Once you have the ‘clinical trial in a dish’ model, fast forward 10-20 years, and it should be possible to have true precision medicine,” says Dr. Wu, who has already demonstrated the potential for this approach with iPSCs and LMNA-related dilated cardiomyopathy, published in *Science Translational Medicine*. “For example, if you take a drug, how do you know if it will really work for you or not? In the future, we will use iPSCs and genetic screening to help understand who will improve and who won’t. In my opinion that’s the holy grail of precision medicine.”

The key to precision medicine and a CHD cure alike will be translation of the power of iPSCs and complementary technologies into the clinic.

“I often think some of these innovations are the answer we’ve been looking for — that we’re finally going to do it! But can we really move the knowledge we’ve gained into clinical practice?” asks Dr. Garg. “Time will tell. I think we can.”

Chai S, Wan X, Ramirez-Navarro A, Tesar PJ, Kaufman ES, Ficker E, George AL Jr, Deschênes I. Physiological genomics identifies genetic modifiers of long QT syndrome type 2 severity. *J Clin Invest*. 2018 Mar 1;128(3):1043-1056.

Lin H, McBride KL, Garg V, Zhao MT. Decoding genetics of congenital heart disease using patient-derived induced pluripotent stem cells (iPSCs). *Front Cell Dev Biol*. 2021 Jan 21;9:630069.

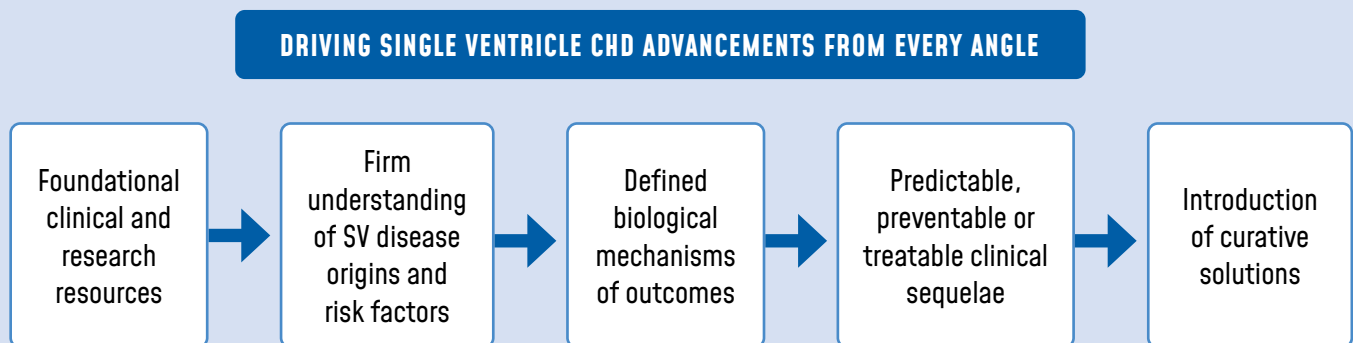
Sayed N, Liu C, Ameen M, Himmati F, Zhang JZ, Khanamiri S, Moonen JR, Wnorowski A, Cheng L, Rhee JW, Gaddam S, Wang KC, Sallam K, Boyd JH, Woo YJ, Rabinovitch M, Wu JC. Clinical trial in a dish using iPSCs shows lovastatin improves endothelial dysfunction and cellular cross-talk in LMNA cardiomyopathy. *Sci Transl Med*. 2020 Jul 29;12(554):eaax9276.

Ye S, Wan X, Su J, Patel A, Justis B, Deschênes I, Zhao MT. Generation and expansion of human cardiomyocytes from patient peripheral blood mononuclear cells. *J Vis Exp*. 2021 Feb 12;(168).

Additional Ventures: Investing in CHD Research to Advance Care

Additional Ventures is a purpose-driven nonprofit that has developed the Single Ventricle Research Fund (SVRF), an annual research award program dedicated to accelerating research and improving care for people with single ventricle heart defects. The fund supports investigators through multi-year, high-impact grants focused on different elements in their carefully structured research roadmap.

By funding investigators focused on key areas of the development and amelioration of SV CHD, Additional Ventures aims to make single ventricle defects better understood and more treatable.



In 2020, Nationwide Children's received a \$1 million Innovation Fund endowed by Additional Ventures, joining a handful of other research institutions in a large-scale coordinated effort to find new ways to functionally cure patients with SV CHD.

Nationwide Children's awarded portions of the Additional Ventures funding to three projects:

- **Elucidating Mechanisms of Ventricular Hypoplasia in PA-IVS Using Patient-Derived iPSCs**
 - Co-principal investigators Vidu Garg, MD, PhD, director of the Center for Cardiovascular Research at The Heart Center, and Mingtao Zhao, DVM, PhD, principal investigator in the Center for Cardiovascular Research
- **Development of a Protocol to Risk Stratify Individuals With Single Ventricle Congenital Heart Disease Using Deep Phenotyping and Genome Sequencing**
 - Co-principal investigators Kim McBride, MD, MS, division chief of Genetic and Genomic Medicine, and Peter White, PhD, senior director of Computational Genomics
- **Unlocking Our Regenerative Capacity: Elucidating the Role of LYST on Neotissue Formation in Tissue Engineered Constructs**
 - Co-principal investigators Christopher Breuer, MD, director of the Center for Regenerative Medicine, and Rick Wilson, PhD, executive director of the Institute for Genomic Medicine

More information on Additional Ventures and their funded SV CHD studies can be found at www.AdditionalVentures.org.



Providing Education and PrEP for Teens at Risk for HIV

In a recent PediaCast CME, Mike Patrick, MD, and Megan Brundrett, MD, share important information about offering PrEP and HIV-related education in your primary care practice.

Written by Abbie Roth

About 20% of new cases of HIV, the virus that causes Acquired Immunodeficiency Syndrome (AIDS), are occurring in youth aged 13 to 24. HIV/AIDS is a life-altering, life-long infection that, while treatments and survival rates have improved, can be deadly.

Improved treatment is also linked to improved prevention. Two drugs that are part of a successful three-drug treatment cocktail are also approved by the Food and Drug Administration (FDA) for prevention. Pre-exposure Prophylaxis (PrEP) for HIV is a once-daily pill consisting of emtricitabine and tenofovir alafenamide (Descovy) or emtricitabine and tenofovir disoproxil fumarate (Truvada). Both formulations are available for any individual weighing more than 35 kg (about 77 lbs).

When used as prescribed, PrEP reduces the risk of getting HIV from sex about 99%, according to the Centers for Disease Control and Prevention (CDC). For injection drug users, available data indicates that PrEP reduces the risk of getting HIV by at least 74%.

In a recent episode of PediaCast CME, Megan Brundrett, MD, medical director of the Family AIDS Clinic and Educational Services (FACES) program at Nationwide Children's Hospital, sat down with Dr. Mike Patrick to discuss what pediatricians need to know to begin offering PrEP to youth who are at risk for contracting HIV.

“While pediatricians can refer patients to clinics that specialize in care and prevention of HIV, such as the FACES clinic here at Nationwide Children's, not every

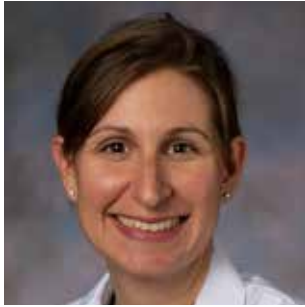
community has access to this type of clinic,” says Dr. Brundrett. “Pediatricians can easily equip themselves to offer the care and education needed to help teens at risk for HIV exposure.”

SCREENING FOR RISK

The first step in starting PrEP is screening for risk. By asking social risk questions during the one-on-one part of the well check, pediatricians can engage patients and ask questions that will help them ascertain their risk of HIV exposure.

Dr. Brundrett offers some suggestions for these conversations:

- Ask specific questions. Don't just ask if a teen is having sex, give them options about what types of sex they might be having. For example, “Are you having vagina, anal or oral sex?”
- Ask about needle-associated drug use and about needle sharing.
- Be aware that these conversations can be uncomfortable. Conversations about sexual activity and drug use early in the patient/physician relationship can normalize these topics and encourage patients to be more open and truthful in their responses.
- Explain why this information matters and about HIV risk.
- Be prepared to support the teen who may not want to share risk factors with parents in order to access PrEP.



“While pediatricians can refer patients to clinics that specializes in care and prevention of HIV, such as the FACES clinic here at Nationwide Children’s, not every community has access to this type clinic,” says Dr. Brundrett. “Pediatricians can easily equip themselves to offer the care and education needed to help teens at risk for HIV exposure.”

- Megan Brundrett, MD, medical director of the Family AIDS Clinic and Educational Services (FACES) program at Nationwide Children’s

GET APPROPRIATE LABS

If you’re risk screening and subsequent conversations with the patient and caregivers lead to the decision to start PrEP, certain labs must be obtained before starting the medication.

- Screen for HIV.
- Screen for hepatitis B and C.
- Screen for kidney function.

For HIV, a blood test should be obtained. If the patient shows signs of acute HIV infection, an HIV viral load test should also be performed. A swab for HIV is not recommended.

Labs for HIV, kidney function and hepatitis viruses B and C (HVB and HVC) should be negative within one week prior to starting PrEP.

Additionally, Dr. Brundrett recommends performing sexually transmitted infection testing for sexually active teens, specifically for chlamydia and gonorrhea, by swabbing any location where sex is occurring. A urine test alone can miss STIs in some cases. A blood test for syphilis is also recommended.

Once starting PrEP, patients should be counseled that it takes time to reach maximum protection. PrEP reaches maximum protection from HIV for receptive anal sex at

about 7 days of daily use. For receptive vaginal sex and injection drug use, it takes about 21 days of daily use. No data are currently available for insertive vaginal or anal sex.

FOLLOW UP WITH PATIENTS

Follow-up is dependent on the patient’s needs. Providers can only prescribe 90 days of PrEP at a time, and negative tests are required prior to each refill.

For adolescent patients, Dr. Brundrett recommend more frequent follow-ups. Adolescent adherence declines over time, she says. “For me, if they are 15 to 17, we meet monthly to check adherence and build relationship.”

Follow up to ensure adherence to the medication is essential because PrEP is much less effective when not taken as prescribed. For the patient to receive the full benefit of the medication, it must be taken consistently.

Dr. Brundrett also notes that PrEP is not necessarily a life-long medication. The need for PrEP ebbs and flows for many individuals depending on relationship status, drug use and other lifestyle factors. Building a relationship with patients so that they can come to you when they need PrEP or before they engage in higher risk behaviors can be a tremendous support for reducing new HIV infections.

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Building Momentum for School-Based Health Care

Written by Mary Kay Irwin, EdD, director of School Health, Nationwide Children's Hospital

Pediatric health care and the United States educational system share similar goals, even if they don't quite use the same words to describe them. Health care professionals often say they want optimal wellness for children, so they can thrive throughout their lives. Schools want optimal learning opportunities to prepare children to be successful, productive, happy adults.

The two systems have worked in parallel for children, but they haven't often worked together in the ways they could. But an expansion the last 20 years in how these systems define their missions has caused all of us to realize that we can do more good in partnership than we can in our own silos.

In health care, that expansion is a heightened focus on "social determinants of health." Those are factors outside of medical care, such as housing, workforce development and educational opportunity, that have a huge impact on a person's overall wellbeing. In schools, the expansion is the rise of the "whole child" model or framework. That's the idea that a child can best achieve their educational potential when the child is healthy, lives in a safe environment and has access to the resources they need.

Social determinants of health and the whole child framework are the same idea through different lenses. Good health helps a child succeed in school – it's hard to learn if you have to miss class for illness, or if you have difficulty concentrating because of a behavioral health concern. Educational achievement gives a child a better opportunity to become a healthy adult.

We've seen the health/education link clearer than ever during the COVID-19 pandemic. Countless children fell behind in school because of a worldwide health condition. Because so many children receive physicals, vaccines and other care as a condition of attending school in person, they fell behind in preventive care as well.

So pediatric providers and schools should work together

to help children, and for children without a medical home, one of the best ways to do that is through school-based health care. A primary care clinic located inside a school building can help provide services that some children simply are not receiving otherwise — prescriptions, screenings, vaccines, links to more specialized care.

Oregon, Washington and New York have robust, statewide school-based health efforts. At Nationwide Children's Hospital, where I lead the school-based health program, we operate 14 primary care clinics inside local schools, two mobile health clinics, vaccine clinics and a school-based wheelchair clinic. We have school-based asthma therapy in 254 schools across the 30 districts, wellness education programming with an annual reach of over 6,000 students, school nursing services, and we just launched our dentistry program this summer. In partnership with the hospital's Behavioral Health Services, we provide integrated care including prevention services, therapy and telepsychiatry. New this fall, we will launch our Diabetes and School Health program in partnership with the hospital's Division of Endocrinology.

We've seen dramatic decreases in emergency department visits for asthma, as well as other overall improvements in child health measurements. We also work hard to connect children we serve in schools to community providers, because we realize the need for young people to have a stable medical home.

It seems so obvious that health care and schools should work together, right? But as many who have tried the school-based health model can attest, it can be difficult. These are two distinct systems, with different ways of operating. They aren't used to inviting each other to the table, or to taking guidance and suggestions from one another.

Our years of experience at Nationwide Children's have shown us where the obstacles are, and how they can be overcome. This is what I tell school districts and systems who are starting down the road of school-based health:

- Get technical assistance from people who have successfully done this work before. They are naturally collaborative; they must be to create a school-based health model. They want to help.
- Realize this is not the same as outpatient medicine if you are the provider. It's not just another clinic, because you are co-locating in school. You are a guest. You have to engage and build trust with the school community. Talk to the teachers, go to the football games. You need to be a part of the school culture.
- Choose clinic staff members who are mission-driven and willing to do many kinds of tasks. School-based clinics are small, often just a converted classroom, so there's only room for a few staff members, which means staff in these clinics wear many hats.
- Conduct a collaborative, needs-based assessment of what the school and its students need. Can a school counselor, social worker or nurse be a part of the overall strategy? Who is in charge of the communications to students about health? School officials should be invited to clinic meetings; clinic staff should be invited to school staff meetings.
- Share data in an effort to build and maintain the school and clinic relationship. Is the school achieving results it wants, such as an increased attendance rate? Is the clinic achieving the results it wants, such as an increased vaccination rate? If not, what changes should be made?

I believe that as we slowly emerge from the COVID-19 pandemic, we have the opportunity to boost the momentum for school-based health. Federal, state and local governments are making funding more readily available. Schools and health systems see the benefit of collaboration. Nationwide Children's and others who have entered the school-based health space have seen encouraging results.

Beyond the opportunity, we have an obligation as well. If we want to improve life for children, we should be working together to make that happen.



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A Troubling Connection Between Justice System Involvement and Child Health

By Jeb Phillips

A first-of-its kind study, published in *JAMA*, finds that while only 2% of patients at a large children's hospital are identified with likely personal or family involvement in the justice system, they account for large proportions of some troubling diagnoses.

[PediatricsNationwide.org/troubling-connection-health-justice](https://www.pediatricsnationwide.org/troubling-connection-health-justice)



Unraveling the Role of Pioneer Factors in Childhood Cancer

By Abbie Roth

Transcription factors are proteins that read the DNA sequences and can direct the transcription of that sequence into mRNA for translation into a protein. Transcription can become deregulated in cancer. Pioneer factors are transcription factors that can read and manipulate “closed” or inaccessible chromatin. A new study from Ben Stanton, PhD, in the Center for Childhood Cancer and Blood Diseases, shows that the oncogenic transcription factor PAX3-FOXO1 is present and acting as a pioneer factor in the context of the rare childhood cancer rhabdomyosarcoma.

[PediatricsNationwide.org/role-of-pioneer-factors-in-childhood-cancer](https://www.pediatricsnationwide.org/role-of-pioneer-factors-in-childhood-cancer)



Alarming Upward Trend in Black Youth Suicide From 2003 to 2017

Written by Lauren Dembeck, PhD

For the first time, researchers have examined the trends and precipitating circumstances of suicide in Black youth only by age group and sex. The study, published in the *Journal of the American Academy of Child and Adolescent Psychiatrists*, identified specific risk factors and developmental mechanisms associated with Black youth suicide that could serve as targets in suicide prevention programming.

[PediatricsNationwide.org/Black-youth-suicide-influences](https://www.pediatricsnationwide.org/Black-youth-suicide-influences)

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The Collaboratory for Kids and Community Health: A hub for innovative ideas to improve the health of children and their neighborhoods

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