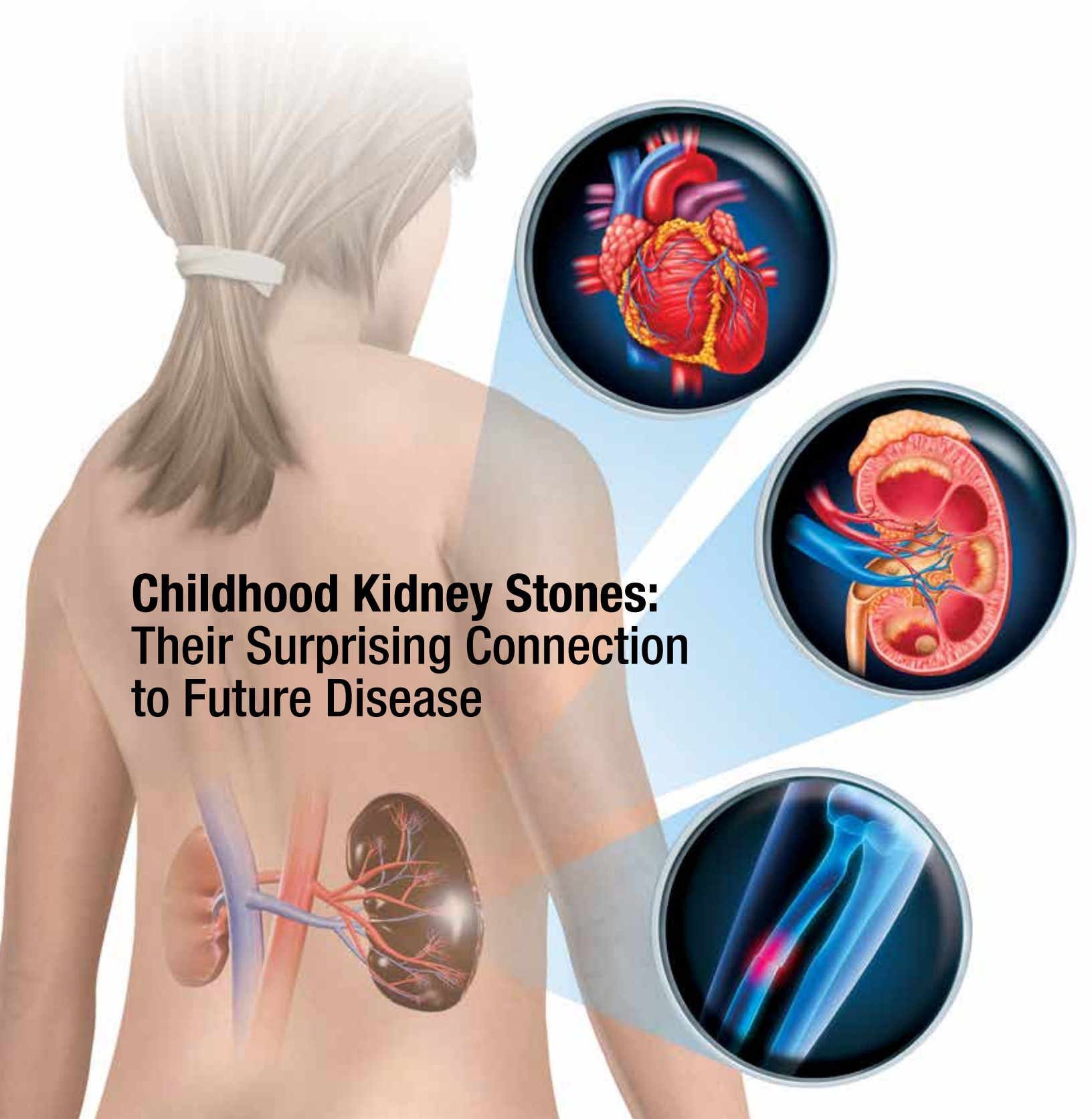
Fall/Winter 2016

Pediatrics NATIONWIDE

Advancing the Conversation on Child Health



Childhood Kidney Stones: Their Surprising Connection to Future Disease

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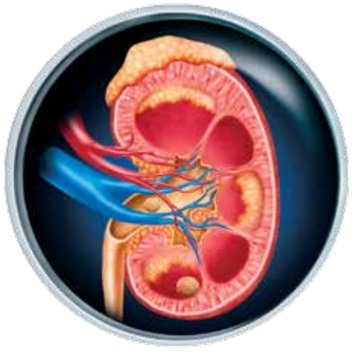
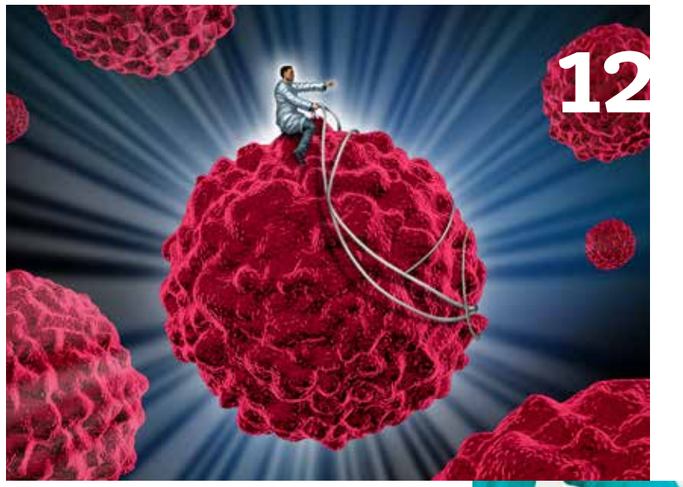
Once thought of as an adult problem, urinary stone disease is increasingly found in children. At the same time, researchers are discovering that stones are associated with cardiovascular issues, low bone density and chronic kidney disease. How can pediatric nephrologists confront this emerging concern?

HEART
Associations between kidney stones and atherosclerosis have long been known in adults but are recently recognized in children.



KIDNEY
Kidney stones are now known to be implicated in chronic kidney disease in children.

BONE
The association with low bone density is now so well recognized that some pediatric nephrologists automatically take a facture history in pediatric patients presenting with kidney stones.



FEATURES

DEPARTMENTS

"When I was talking to pediatricians, family practice doctors and emergency medicine physicians, I heard this over and over again; 'I was shocked to see this kid had a kidney stone. I didn't know kids could get kidney stones.'"

— David Sas, DO, MPH, pediatric nephrologist at the Mayo Clinic Children's Center (page 22)

"The immune system rejects cancer far more often than we give it credit for. Immunotherapy is focused on harnessing and manipulating that natural ability to fight cancers that gain footholds. The ultimate goal is to enable the body to defend itself."

— Dean Lee, MD, PhD, director of the Cellular Therapy and Cancer Immunotherapy Program in the Division of Hematology/Oncology/BMT and Center for Childhood Cancer and Blood Diseases at Nationwide Children's Hospital (page 13)

New Guidelines Better Diagnose Common GI Disorders

The new Rome IV criteria offer guidance to common but often misunderstood conditions.

Because there are no clear causes of functional gastrointestinal disorders (FGIDs), diagnosis and treatment can be difficult. Some physicians and parents may doubt the disorders exist at all, although pediatric gastroenterologists estimate they affect 30 to 40 percent of children. However, recently released best-practice guidelines should help primary care physicians and specialists alike.

The guidelines, collectively called the "Rome IV criteria," are the first revision of standards from the international, FGID-focused Rome Foundation in a decade. They cover all ages and a wide range of disorders, including functional nausea, functional constipation and irritable bowel syndrome.

"These criteria help people see these disorders as more legitimate," says Carlo Di Lorenzo, MD, chief of Gastroenterology, Hepatology and Nutrition at Nationwide Children's Hospital. "There has been an exponential growth in research. These conditions are very common and very costly. The criteria allow doctors to make a diagnosis more easily, and they allow patients to put a name to what they have."

Dr. Di Lorenzo chaired the six-person committee that developed the criteria for children and adolescents, and he is co-editor of the new book *Rome IV Pediatric Functional Gastrointestinal Disorders – Disorders of Gut-Brain Interaction*. Miguel Saps, MD, attending gastroenterologist and director of research for the Motility Center at Nationwide Children's, was also one of the international pediatric committee members.

Among the most important developments of the last decade is the growing ability to rely on symptoms alone to diagnose FGIDs, according to Dr. Di Lorenzo, who is also a professor of Clinical Pediatrics at The Ohio State University College of Medicine. Past criteria have included the advice to diagnose an FGID after "no evidence of an organic disease" is found, which some clinicians understood as a directive to order exclusionary tests.

Carlo Di Lorenzo, MD, chief of Gastroenterology, Hepatology and Nutrition at Nationwide Children's Hospital

"It's often not necessary to do dozens of tests to rule out every possible disease until you are left with a diagnosis of irritable bowel syndrome or dyspepsia, for example," Dr. Di Lorenzo says. "You can take a detailed medical history, perform a thorough physical examination and make a diagnosis in many cases."

As the subtitle of Dr. Di Lorenzo's book suggests, researchers have found strong links between stress, anxiety, depression, and other psychological issues and FGIDs – part of the so-called "brain-gut interaction." Medications can be effective for some disorders, but so can non-medical treatment options such as acupuncture, yoga, counseling and relaxation exercises.

"Patients, parents and clinicians may resist the idea that anxiety plays a role in generating symptoms, and they may also resist alternative treatment strategies," says Dr. Di Lorenzo. "Diagnosis and treatment can be driven by how willing patients are to accept them."

A set of criteria from experts that validates these concepts potentially allows patients with FGIDs to start feeling better sooner, which is beneficial for physicians and parents alike.

— Jeb Phillips

How Can You Optimize Care for Homeless Patients?

A recent policy statement from the AAP describes how pediatricians can help improve the health and well-being of homeless children in America.

As of 2014, the National Center on Family Homelessness reported that a staggering 2.5 million children are homeless each year in America, a historic high representing one in every 30 children in the country. These children experience a variety of challenges due to difficulty accessing health care, including chronic illnesses, hunger and malnutrition, education interruptions and significant psychosocial development issues.

"Housing and child health are closely intertwined," says Kelly Kelleher, MD, MPH, director of the Center for Innovation in Pediatric Practice at The Research Institute and a pediatrician at Nationwide Children's Hospital. "Policies and programs that aim to quickly place families in stable, permanent housing, rather than a continuum of emergency and temporary housing, is more cost-effective for the community and more stabilizing for families."

The American Academy of Pediatrics' Council on Community Pediatrics (COCP) policy statement outlines how pediatricians can optimize the health and well-being of children affected by homelessness, through practice change, partnership with community resources, awareness and advocacy.

The recommendations include promoting and facilitating Medicaid enrollment to eligible children and families and becoming familiar with best practices for care of this population. The COCP specifically advises that pediatricians become familiar with government and community-based services that assist families with unmet social and economic needs, as well as medical-legal partnerships and local departments of health.

Additionally, the COCP encourages providers to maximize acute care visits to provide comprehensive care, such as updating immunizations if a child is significantly behind. Relatively simple actions can be taken to acknowledge barriers associated with homelessness, such as determining patient access to phone and mail services, providing transportation vouchers, and offering more flexible office visit scheduling.

Healthy Homes, a cornerstone of an initiative at Nationwide Children's known as Healthy Neighborhoods Healthy Families (HNHF), is a nonprofit housing organization and collaboration with community partners that reduces substandard housing.

"Healthy Homes is unique in that it goes beyond the national recommendations of the AAP, changing the lives of families at a fundamental level above the provision of health care," says Dr. Kelleher, who is involved in strategy development for HNHF and is also vice president of Community Health and Services Research at Nationwide Children's. "Traditional health services themselves are not adequate to address all these problems; instead, community collaborations that engage multiple sectors such as education, housing, employment and health care simultaneously in our most difficult neighborhoods will be necessary to make a dent in child and young family outcomes."

— Tiasha Letostak, PhD

Novel Practice Pathway Addresses Problem Behaviors Among Patients With Autism

Pediatricians urged to investigate underlying causes.

Issues causing children with autism spectrum disorder to be irritable or belligerent can be difficult for parents, teachers and other care providers to uncover. And, wait times to see a specialist may leave a child frustrated, distressed or in physical pain for months.

Primary care physicians who see the patient and family regularly are in a unique position to help find what's beneath emotional outbursts and aggressive acts, and work with parents and schools to develop a treatment plan, researchers from across the United States say.

The researchers, assembled by the Autism Intervention Research Network on Physical Health and Autism Speaks Autism Treatment Network, published a practice pathway this year to guide pediatric primary care doctors in the *Journal of Pediatrics*.

They warn that irritability and aggressive behaviors interfere with a child's development and education, may result in isolation as family and classmates avoid them, or make them targets of bullying.

"One of the big points is to consider medical conditions as possible causes for these irritable and problem behaviors," says Daniel Coury, MD, chief of the Section of Developmental and Behavioral Pediatrics at Nationwide Children's Hospital and a leader of the research.

"Physicians are pretty good about asking about changes in caregivers or teachers or the environment that may be influencing the behavior,"Dr. Coury says. "But, they are less apt to consider an underlying medical problem."

In one case, when a child started reaching aggressively for their throats, a mother and father thought the child was trying to choke them. After medicines and behavior management made no improvement, a doctor asked if the parents noticed physical changes in their child when the reaching started. They recalled his breath sometimes smelled sour.

The boy had gastrointestinal reflux. He was trying to tell them his throat hurt, Dr. Coury explains.

"We know primary care pediatrics is a high-volume business – a typical visit is 8 minutes – but we emphasize taking a thorough history," Dr. Coury says. "It takes time and asking a lot of questions."

After considering medical problems, physicians are guided to assess and address other possibilities: the patient's lack of functional communication, psycho-social stressors, maladaptive behavioral patterns and co-occurring psychiatric conditions.

The pathway includes points at which the doctor may want to consider referrals to specialists. But for physicians willing, it provides steps to address the underlying problem with family, teachers and other caregivers.

"There are evidence-based treatments that can help these behaviors," says Dr. Coury who is also professor of Clinical Pediatrics and Psychiatry at The Ohio State University College of Medicine. "So the physician doesn't have to take a stab in the dark."

— Kevin Mayhood

One Dose Probiotic Biofilm Protects Against NEC

Probiotic biofilm enables the beneficial bacteria to withstand stomach acid, promote microbial activity and decrease intestinal inflammation.

A single dose of a probiotic biofilm grown on microspheres prevented or significantly reduced the severity of necrotizing enterocolitis (NEC) in animal models of the disease, researchers show.

This delivery method not only appears to protect against NEC but the fact that it is effective after administration of only a single dose may avoid the bacteremia and other morbidities resulting from the currently required administration of repeated, high doses of probiotics, according to an article published in June in the *Journal of Pediatric Surgery*.

Nearly 10 percent of infants born weighing less than 3.3 pounds develop NEC. The disease kills 20 to 30 percent of affected babies – a figure that's changed little in 50 years.

"In general, physicians think of biofilms as their enemy, because biofilms protect pathogenic bacteria from antibiotic therapy," says Gail E. Besner, MD, chief of Pediatric Surgery and a principal investigator in the Center for Perinatal Research in the Research Institute at Nationwide Children's.

Dr. Besner teamed with Steven Goodman, PhD, principal investigator in the Center for Microbial Pathogenesis at Nationwide Children's, who suggested they investigate whether a probiotic administered as a biofilm and introduced into the stomach could colonize long enough to do its job better, and to determine if that's enough to make a difference.

"If you could give a single dose of probiotic bacteria at a level that protects before NEC gets started, that's the holy grail," Dr. Goodman says.

The researchers chose their materials carefully.

First, they selected the probiotic *Lactobacillus reuteri* because its anti-inflammatory and antimicrobial activities may counter two harmful NEC activities. Then, they chose a surface for the biofilm to form: commercially-

made Sephadex microspheres. The spheres are made of material similar to the glycans *L. reuteri* normally synthesizes and binds to itself but is relatively inert to other bacteria, Dr. Goodman says.

In testing, 69 percent of untreated subjects developed NEC compared to only 14 percent of those treated with *L. reuteri* grown on the microspheres. Animals treated with this novel probiotic delivery system had substantially reduced intestinal permeability, indicating improved intestinal function.

The researchers are now closely characterizing the biofilm, microspheres and their interactions as well as experimenting with different cargos, to boost protection against NEC. They hope to begin clinical trials using an optimized version within three years.

"NEC attacks the youngest, smallest, and most vulnerable premature babies that we care for in the hospital," Dr. Besner says. "It may be that a single dose of something that's very safe delivered in this manner will give them a chance to live."

— Kevin Mayhood

Great Minds Aren't Thinking Alike About Asthma Care

A recent audit of the Pediatric Hospital Information System using template matching finds wide variation in care provided to pediatric asthma patients.

While asthma is a common and manageable disease, nine people still die from asthma each day. It is well known that asthma is the leading cause of pediatric hospitalization as well as the most prevalent chronic illness among children under sixteen.

Despite the prevalence of hospital admissions for asthma and the existence of well-established clinical treatment pathways, a new audit published in *JAMA Pediatrics* in September finds that practice styles in asthma treatment throughout pediatric hospitals are significantly varied. Of 37 institutions in the Pediatric Hospital Information System (PHIS), the average cost of a hospital stay varied by 87 percent, the length of stay varied by 47 percent and whether a patient was sent to the intensive care unit for treatment varied by 254 percent.

"We may have expected less variation in indicators of resource use if everyone was following the same protocol, but obviously they are not," says Jeffrey Silber, MD, PhD, director of the Center for Outcomes Research at the Children's Hospital of Philadelphia and lead author of the audit.

"This study demonstrates the striking need to address the variable care that a patient with asthma receives depending upon what part of the country they live in, or which hospital system they utilize for care," says David R. Stukus, MD, the director of the Complex Asthma Clinic at Nationwide Children's Hospital.

Some variation in care is normal, as not every patient admitted for asthma has the same symptoms or severity of the illness. However, the new method of comparison Dr. Silber and his colleagues used – template matching – accounts for this variation, reporting instead variation associated with hospital practice. This method creates templates of patients with similar asthma severity across hospitals and compares their care. This audit analyzed three years of data and compared nearly 49,000 patients' hospital stays in the PHIS.

"Template matching can be utilized to assess best practices by comparing hospitals', or groups of hospitals', performance on any specific outcome of interest. It is a fair test because it consists of similar patients. Hospitals that perform 'best practices' should have better outcomes," explains Dr. Silber, also professor of Pediatrics, Anesthesiology and Critical Care at the Perelman School of Medicine at the University of Pennsylvania. "If not, we may want to re-evaluate what are best practices."

"I am not surprised by their findings; I've witnessed extreme variability in the diagnosis and management of asthma among different providers and institutions, even though evidence-based asthma guidelines exist and have been shown to improve care when implemented," says Dr. Stukus. "Unfortunately, guideline adoption isn't universal and can lag years or even decades after publication."

Dr. Silber hopes that this audit encourages hospital leaders and quality improvement officers to improve and standardize practice styles. "Template matched analysis can be applied to other patient populations and will continue to provide direction for improvement in pediatric health care."

— Brianne Moore

How to Integrate Genomics into Clinical Practice

Recommendations from the Clinical Genetics Think Tank outline five key areas of focus for bringing genome and exome sequencing into the clinic.

Clinical genome and exome sequencing (CGES) as a diagnostic tool is altering practice for clinical geneticists, genetic counselors and other clinical specialists.

The Clinical Genetics Think Tank (CGTT) has identified five areas of focus for the integration of CGES in clinical practice: the pretest process, pretest education for patients and providers, phenotyping, sequence data interpretation and posttest patient care. These areas are the topic of a paper published online in May in *JAMA Pediatrics*.

"These key issues are all critical to the successful implementation of clinical genomics," says Gail Herman, MD, PhD, clinical geneticist at Nationwide Children's Hospital and a CGTT member. "Some institutions may be further along than others in each aspect, but these are challenges that we all need to address."

The pretest process addresses the challenge of determining which patients should have CGES, who should order the tests and how the costs should be covered. The CGTT algorithm presented in the recommendations offers a streamlined and consistent process for determining who is most likely to benefit from CGES.

Once a patient is determined to be a good candidate, educating the patient and family about the benefits and limitations of CGES are expected challenges. But pretest education and training is also important for providers and insurance and government stakeholders. Key areas of education for these groups are the validity and utility of CGES in the diagnosis and treatment of patients.

The need for a common language for phenotyping is a familiar challenge to genomics researchers around the world. With utilization of CGES, the importance of phenotyping ontology – consistent terminology for describing symptoms, physical features and diagnoses – enters the spotlight.

"A common ontology to describe phenotypes is essential to good data management, cohort building and ultimately patient care. It should be incorporated into the clinic and the electronic health record as soon as possible," says Dr. Herman. "This is an issue that needs to be addressed at all institutional levels and is critical to conducting genomics."

Once a patient has CGES, even the best analysis doesn't yield a definitive answer in every case. Yields are increasing, and methods are improving. However, the possibility remains that the variant causing a particular patient's symptoms simply hasn't been discovered or identified as pathogenic at the time of testing. So how often should the sequence data be reinterpreted?

"No one knows the answer to this right now," says Dr. Herman, who is also a principal investigator in the Center for Molecular and Human Genetics at The Research Institute at Nationwide Children's. "We don't have a lot of data to even look for patterns at this point. Moving forward, networks of sites working together will track the frequency of new variant discoveries and attempt to answer this question."

Once the tests have been completed and the results are in, the posttest patient care phase lasts a lifetime. In some cases, genetic diagnoses will be used to influence the care of a generation and beyond. This cycle of evaluation, education, testing, analysis and reanalysis, follow up and education lays the groundwork for a new era in medicine for generations to come.

— Abbie Roth

A New Use for Kangaroo Care

A parent's touch reduces agitation, allows infants and toddlers to remain extubated after heart surgery.

A small percentage of babies and young children who have undergone congenital cardiac surgery and early tracheal extubation are treated with a calming parent's touch at Nationwide Children's Hospital – a strategy that physicians have found works better in some cases than escalating analgesics.

The Cardiothoracic Intensive Care Unit (CTICU) employs kangaroo care, a staple of the neonatal ICU, when infants and toddlers show rising markers of agitation and probable delirium.

The protocol was begun after researchers discovered a troubling pattern among children younger than 1 year of age who had undergone bypass surgery and early extubation from 2010 to 2013.

Nationwide Children's pioneered the practice of early extubation and continues to study the impact of this technique on improving outcomes for these patients. The practice decreases exposure to medications, incidence of infection and pneumonia, length of hospital stay and provides other benefits for the great majority of infants.

Of 234 infants extubated in the operating room after surgery, however, 10 had rising markers of agitation and were treated with escalating analgesics. That led to respiratory depression, reintubation, associated morbidities and much longer hospital stays.

"One of the real difficulties in dealing with infants, because they can't communicate, is understanding what agitation is," says Peter Winch, MD, a cardiac anesthesiologist at Nationwide Children's and first author of the extubation study – published in July in *Pediatric Critical Care Medicine*. "Treating these young children for pain was perhaps missing a broader problem of disorientation, or delirium."

"The children awaken in a foreign environment with tubing and lines coming out of them and many different things going on at the same time," says Ayman Naguib, MD, director of cardiac anesthesia in The Heart Center and the Department of Anesthesiology and Pain Management at Nationwide Children's.

Staff in the CTICU have become experienced at telling the difference between pain and delirium, says Janet Simsic, MD, medical director of the CTICU in The Heart Center. Staff members use the pediatric analgesic emergence delirium scale and watch whether a child can focus on parents or medical staff. If narcotics increase agitation, that's a sign that delirium, not pain, is the issue.

For infants or toddlers suffering delirium, Tylenol and Toradol replace narcotics, Dr. Simsic says. "If the parents are calming and willing, we put the child in an adult bed and let the parent lie next to them. A nurse watches over them, making sure all the lines, tubes and wires remain in place."

The first time they tried kangaroo care, the baby calmed down and remained extubated, Dr. Winch says. It is now used on about two heart surgery patients per month.

"This," Dr. Naguib says, "is a very big step toward achieving our goals."

— Kevin Mayhood

Diagnosing GERD in Neonates? Be Cautious

Gastroesophageal reflux disease is likely over-diagnosed in neonates, leading to unnecessary and harmful treatment.

Approximately 10 percent of infants born preterm in the United States are diagnosed with gastro-esophageal reflux disease (GERD). But it's almost certain that not all of those babies actually have GERD, say neonatologists at Nationwide Children's Hospital.

The probable over diagnosis leads to unnecessary treatment, which may have unintended consequences, according to Sudarshan Jadcherla, MD, director of the Neonatal and Infant Feeding Disorders Program and the Neonatal Aerodigestive Pulmonary Program at Nationwide Children's.

During the last 20 years, Dr. Jadcherla and his teams have developed or standardized tests that measure reflux and aerodigestive reflexes in babies treated in neonatal intensive care units. These instrumental techniques have found that some babies who were presumed to have GERD did not have the disease.

"There is no consensus about how best to make the diagnosis of GERD in neonates," says Dr. Jadcherla, who is also a professor of Pediatrics at The Ohio State University College of Medicine "Most neonatologists, gastroenterologists and ear, nose and throat specialists make the diagnosis subjectively based on airway and digestive symptoms – breathing disturbances, cough, spit up, irritability, arching and feeding difficulties. It's true that GERD can cause those symptoms. Many other conditions can cause those symptoms as well, though."

A diagnosis of GERD may lead a clinician to change feeding strategies for a baby, like cutting down volumes, increasing caloric density, adding thickeners or even changing the type of feeds altogether. All of those strategies have problems potentially associated with them, including the risk of not providing proper overall nutrition.

Perhaps most importantly to Dr. Jadcherla and his colleagues, a GERD diagnosis may result in the prescription of acid suppressive medications for a neonate. Since 2006, several published studies have associated histamine-2 receptor antagonists and proton pump inhibitors with infections, necrotizing enterocolitis,

bone density changes, malabsorption of nutrients, as well as increased risk of death in babies born preterm.

Dr. Jadcherla was the senior author of a study published in July in *The Journal of Pediatrics* showing that 23.8 percent of babies treated in 43 children's hospital NICUs in the United States received these acid suppressive medications from January 2006 through March 2013.

The percentage has decreased in recent years as the negative associations have become better known. Still, a GERD diagnosis often leads to an acid suppressive therapy. Dr. Jadcherla notes that even if GERD is confirmed, stomach acid may not be the cause; stomach acid actually protects vulnerable neonates from some pathogenic organisms and is useful in other ways, so suppression can have negative effects.

Large-scale, well-controlled, long-term trials are needed to define true guidelines for diagnosing GERD, to learn how prevalent it is and to test multimodal therapies. For now, Dr. Jadcherla recommends 24-hour pH impedance and manometry studies, combined with observed symptoms, before making a diagnosis.

"Neonatologists should be cautious about diagnosing GERD without objective tests," he says. "Even if diagnosis and a decision to treat are made, the treatment should be a defined, short course based on improvement of symptoms."

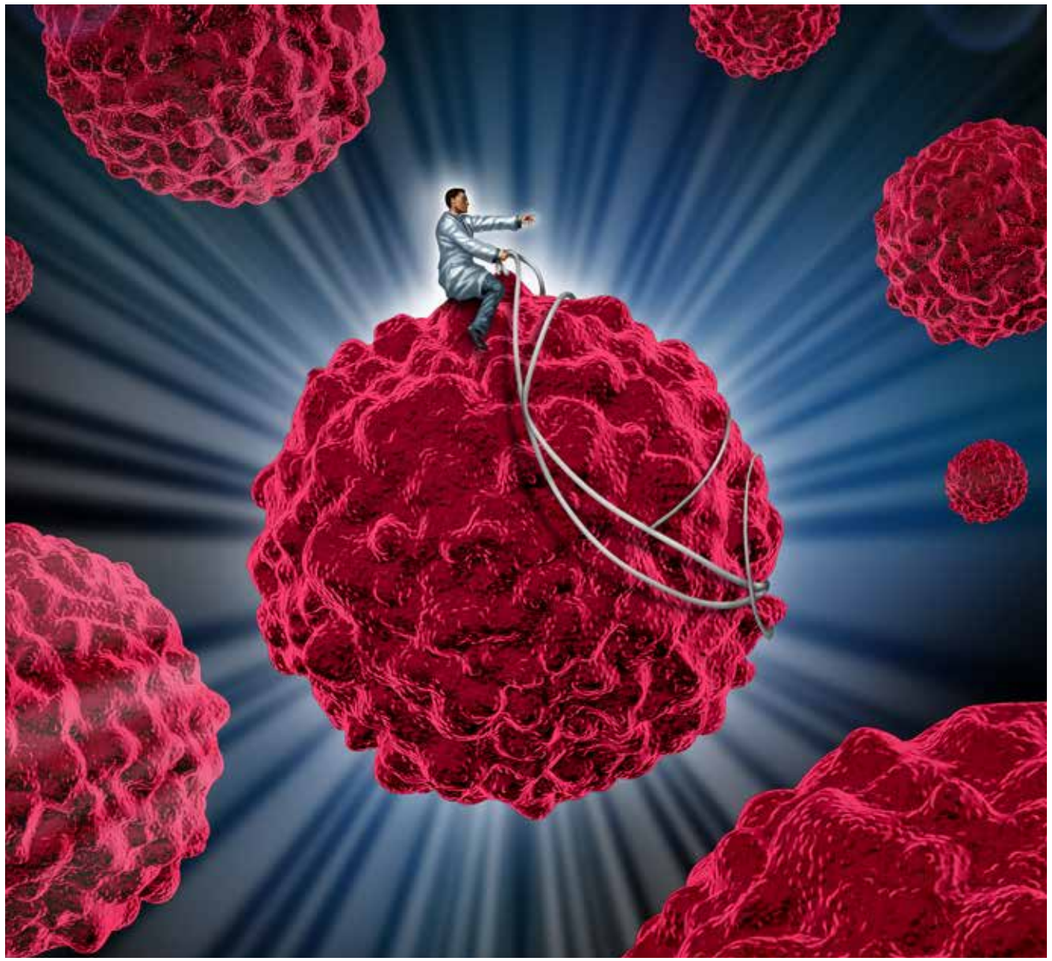
— Jeb Phillips

HARNESSING THE IMMUNE SYSTEM:

Has the Cure for Cancer Been Within Us All Along?

By learning to manipulate the immune system to target cancer cells, clinician-scientists are ushering in a new era in cancer treatments.

by Abbie Roth



The advances in cancer immunotherapy have been headline-making, and some clinical studies have produced stories of near-miraculous recoveries. From the immunotherapy drug credited with curing former president Jimmy Carter's cancer (pembrolizumab) to the promising results of CAR T cell clinical trials, advances in cancer immunotherapy have inspired politicians, investors and patients. With fewer, more manageable side effects, immunotherapy is demonstrating an advantage over other therapies in terms of quality of life and showing promising potential as a cancer treatment.

The concept is actually quite simple.

"The immune system rejects cancer far more often than we give it credit for," says Dean Lee, MD, PhD, director of the Cellular Therapy and Cancer Immunotherapy Program in the Division of Hematology/Oncology/BMT and Center for Childhood Cancer and Blood Diseases at Nationwide Children's Hospital. "Immunotherapy is focused on harnessing and manipulating that natural ability to fight cancers that gain footholds. The ultimate goal is to enable the body to defend itself."

Yes, it's a simple concept, with promising stories. But there have also been losses, unexpected adverse events, trials put on hold, and new questions to answer. And most of the immunotherapy research and trials have been focused on adult patients. Just as children are not miniature adults, childhood cancer is not the same as adult cancer. Childhood cancers originate from different tissues, are driven by different genetic abnormalities, and even when similar to cancer in an adult, they often respond to therapies differently.

Current investigations into immunotherapy for pediatric cancer range from monoclonal antibody and cytokine studies to cellular therapy and oncolytic virotherapy. As understanding of the immune system has developed, so has the ability to manipulate it. From creating small molecules to large proteins, advances in manipulating the cellular components of the immune system to develop targeted therapeutics has resulted in an arsenal of monoclonal antibodies and cytokines. Now, scientists are moving on to whole cell therapy and virotherapy to influence system-level immune responses.

"This is an exciting time in immunotherapy," says Jeffery Auletta, MD, director of Blood and Marrow Transplant and Host Defense Programs at Nationwide Children's Hospital. "Used in conjunction with current treatments such as hematopoietic cell transplant and conventional chemotherapy, cell-based immunotherapy can be the magic bullet to eliminate cancer and offer the best chance for complete remission and malignant disease cure."

"The immune system rejects cancer far more often than we give it credit for. Immunotherapy is focused on harnessing and manipulating that natural ability to fight cancers that gain footholds."

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BREAKING NEW GROUND WITH WHOLE CELLS

The implications and applications of cellular therapy are widespread. Cellular therapies are being used to avoid transplant regimen-related toxicity, augment hematopoietic cell engraftment, enhance immune reconstruction, and prevent and treat infection, graft versus host disease (GvHD) and malignant disease relapse by targeting and destroying cancer cells.

"With cellular therapy, the whole is greater than the sum of its parts," says Dr. Auletta, who is also an associate professor of Pediatrics at The Ohio State University College of Medicine and member of the Leukemia Research Program at The Ohio State University Comprehensive Cancer Center. "Engineered cells are responsive and prolific and, hopefully, will yield therapies that are less toxic than the current cytokine and monoclonal antibody therapies."

Some of the most promising approaches are focused on manipulating T cells and Natural Killer (NK) cells. Functionally, NK and T cells have similarities. They both have initial recognition mechanisms through major histocompatibility complex (MHC) signaling. They both exist to kill cells that pose a threat to the body. However, as part of the adaptive immune system, T cells are created and primed to recognize specific antigens. As part of the innate immune system, NK cells function on a broader "self versus nonself" standard. They see MHC as an inhibitory signal – a "safe" signal of being self. They look for cells expressing additional signals of being "stressed self" or "foreign." When the balance of self versus nonself is tipped toward nonself, the NK cells take action against the offending cell.

"T cells are the contract killers of the immune system," says Dr. Lee, who is also director of Cellular Therapy at The Ohio State University Comprehensive Cancer Center. "They'll ignore pretty much every other cell except their target. However, NK cells are more like the border patrol. They're looking at passports – MHC – and making judgments about what looks dangerous."

T CELLS: TO MODIFY OR NOT TO MODIFY

When it comes to T-cell treatments, there are two main approaches: genetically modify the T cells to target a specific antigen then infuse them into the body or select unmodified T cells that already recognize the antigen and infuse them.

CAR T cells are genetically modified to express a specific antigen receptor derived from a monoclonal antibody, instead of manufacturing and infusing the monoclonal antibody. They are the next chapter in the monoclonal antibody story.

T-cell therapy, in general, is like giving a hungry person a live chicken rather than a carton of eggs. The chicken (T cell) can lay more eggs, reproduce to make more chickens, and adapt to its environment. The carton of eggs (monoclonal antibodies) will help for a while, but eventually, the person will need more eggs.

So far, clinical trials of CAR T-cell therapy are reporting results that indicate it will be a "game changer" for B-cell leukemias and lymphomas.

"Immunotherapy holds a lot of promise," says Dr. Lee. "But we are also starting to get a deeper understanding of the responses and toxicities. We can't underestimate what the immune system can do."

At Children's National Health System, Conrad Russell Cruz, MD, PhD, and his colleagues are actively involved in trials studying T cells specific to leukemia antigens, which are enriched and added back to the immune system. Unlike CAR T cells, these are not genetically modified.

"While we hope to eventually replace chemotherapy with this protocol, our current protocols include chemotherapy," says Dr. Cruz, who is the director of Translational Research Laboratories in the Center for Emerging Technologies in Immune Cell Therapy at Children's National. "There is a synergistic effect. The chemotherapy primes the host for a better immune system response."

A SUPPORTIVE APPROACH

Across the country, institutions are investigating how T-cell therapy can support patients after blood and marrow transplants.

"After BMT, there is a window of time when the newly transplanted immune cells are growing and developing," Dr. Cruz explains. "During this time, the child is particularly vulnerable. The absence of the old immune system combined with the immature new immune system results in the child having no effective immune system."

"We give 'ready to kill' cells grown from the same source as the transplanted immune system," says Dr. Cruz. "The transplanted mature cells are specific to selected viruses as much as possible."

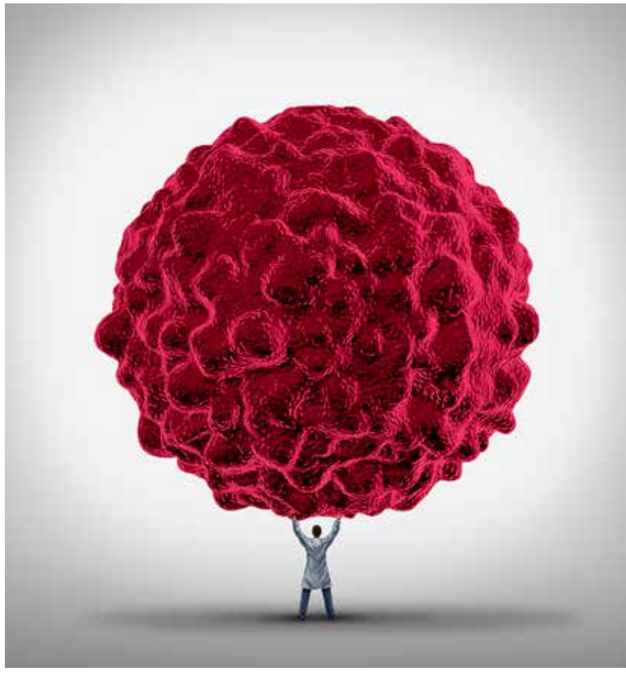
Similarly, at Baylor College of Medicine and Texas Children's Hospital, Helen Heslop, MD, DSc, and colleagues use T-cell therapy as a supportive treatment following blood and marrow transplant by giving infusions of T cells specific to viral infections after transplant.

"We typically use this if someone develops an infection," says Dr. Heslop, director of the Center for Cell and Gene Therapy at Baylor, Houston Methodist Hospital and Texas Children's. "Although, we can use it prophylactically if a patient is high risk for viral infection."

IDENTIFYING THE TARGET

T-cell therapies currently in clinical trials are highly specific. However, a clear target is not always available.

To identify an appropriate target, one needs to find a mutation in a gene coding for a protein that is expressed on the cell surface (antigen). The antigen



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IN THE LAST 40 YEARS THE OVERALL SURVIVAL RATE FOR CHILDREN'S CANCER HAS INCREASED FROM

10% TO NEARLY **90%** TODAY

BUT FOR MANY RARE CHILDHOOD CANCERS, THE SURVIVAL RATE IS MUCH LESS.

60%

OF CHILDREN WHO SURVIVE SUFFER DEVASTATING LATE EFFECTS SUCH AS SECONDARY CANCERS, MUSCULAR DIFFICULTIES AND INFERTILITY.

12%

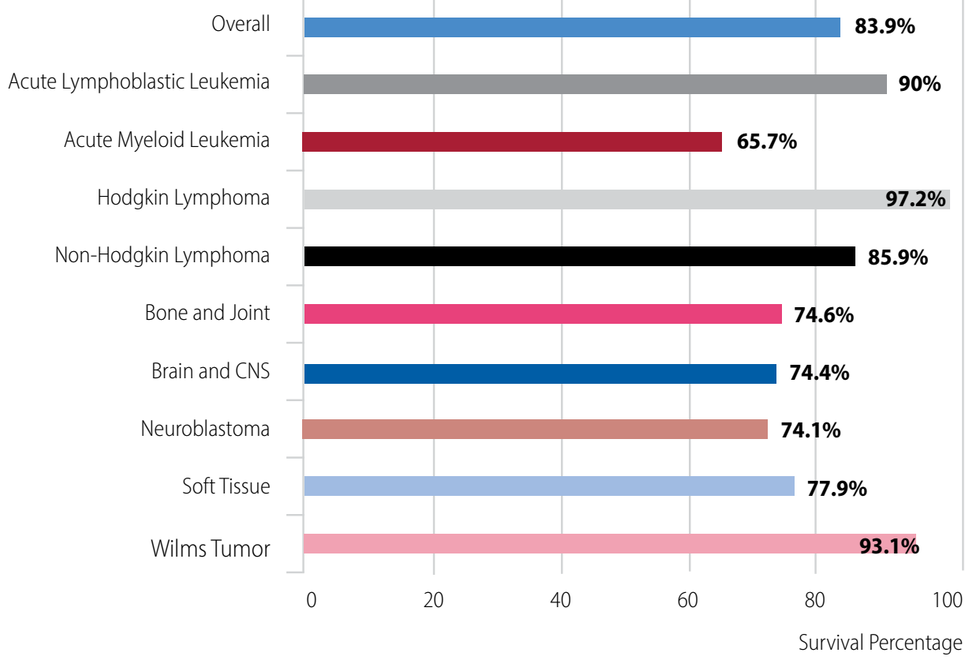
OF CHILDREN (1 OF 8) WHO ARE DIAGNOSED WITH CANCER DO NOT SURVIVE.

THERE ARE APPROXIMATELY

375,000

ADULT SURVIVORS OF CHILDREN'S CANCER IN THE UNITED STATES.

5 YEAR CANCER SURVIVAL RATE, AGE 0–19



Source: Surveillance, Epidemiology, and End Results (SEER) Program (seer.cancer.gov)
SEER 9 area. Based on follow-up of patients into 2012

"T-cell therapy for solid tumors has additional challenges. Not only is it harder to find target antigens that are expressed on tumor cells but not on normal cells, but solid tumors are much less accessible to T cells due to a denser solid mass and the fact that the tumors also possess more evasion mechanisms."

– Helen Heslop, MD, DSc, director of the Center for Cell and Gene Therapy at Baylor, Houston Methodist Hospital and Texas Children's and associate director of Clinical Research in the Dan L. Duncan Comprehensive Cancer Center at Baylor College of Medicine.

also needs to be specific only to the cell types that need to be eliminated.

In some cancers, such as melanoma, this is a straightforward task. Adult melanoma is understood as a very immunogenic cancer. It is one of the most mutated cancers, with at least 400 mutations in the average melanoma. It is very likely to find an antigen specific to melanoma for T cells to recognize.

Pediatric cancers, on the other hand, often have a low number of mutations. Sarcoma and brain cancers have as few as 20 mutations.

"There may be a low opportunity for success with these techniques for cancers that have few mutations," explains Dr. Lee. "If you can't rely on mutated proteins, what else can we use?"

A considerable challenge for future successes of T-cell therapy is to find a target on a solid tumor that isn't found in normal tissue.

"T-cell therapy for solid tumors has additional challenges," says Dr. Heslop, who is also associate director of Clinical Research in the Dan L. Duncan Comprehensive Cancer Center at Baylor College of Medicine. "Not only is it harder to find target antigens that are expressed on tumor cells but not on normal cells, but solid tumors are much less accessible to T cells due to a denser solid mass and the fact that the tumors also possess more evasion mechanisms."

NATURAL KILLER CELLS: AN INNATE ANSWER

Each person has an estimated 10,000 different kinds of NK cells. And while researchers have known about NK cells since the 1970s, it wasn't until the late 1990s that the first major receptors on NK cells were identified. NK cells have also been very difficult to grow in the lab. In 2012, Dr. Lee and colleagues published a method for culturing them that has become an important tool for NK cell research and for generating large numbers of these cells for clinical trials.

As with T cells, researchers are working on two broad applications of NK cells: supportive care following traditional therapies and treating the primary cancer.

Traditional cancer treatments – chemotherapy and radiation – are toxic to NK cells. One application of supportive NK therapy is to restore them in patients after chemotherapy and radiation treatments.

"It's important to remember that T-cell therapy and NK-cell therapy are not an either/or proposition. We may find that some cancers respond better to one than the other. And at some point, these will likely be combined to work synergistically."

– Conrad Russell Cruz, MD, PhD, director of Translational Research Laboratories in the Center for Emerging Technologies in Immune Cell Therapy at Children's National Health System

"We generate NK cells with a young phenotype and give them back to patients in high doses after their own NK cells have been wiped out," says Dr. Lee.

An upcoming clinical trial at Nationwide Children's will use NK cells in conjunction with dinutuximab. Dr. Lee, who joined Nationwide Children's in July 2016, is working to build cellular therapy trials that will be supported by a new good manufacturing practice (GMP) production facility in The Research Institute at Nationwide Children's, where the NK cells will be made for infusion.

NK cells are still bound by the rules of antigens and targets, though less specifically so than T cells. According to Dr. Cruz, this makes it possible to consider an NK cell approach to solid tumors. "We're developing protocols to investigate NK cells for neuroblastoma and pediatric brain tumors," he says. "NK cells are innate immune cells, meaning they are instrumental in protecting the body as a first-line defense as well as activating other immune responses. By harnessing this functionality, we could make a big impact on these difficult to treat tumors."

"It's important to remember that T-cell therapy and NK-cell therapy are not an either/or proposition. We may find that some cancers respond better to one than the other. And at some point, these will likely be combined to work synergistically," says Dr. Cruz.

Join the conversation. Have questions about T-cell or NK-cell therapies? Tweet them **@NCHforDocs** and our experts will respond.

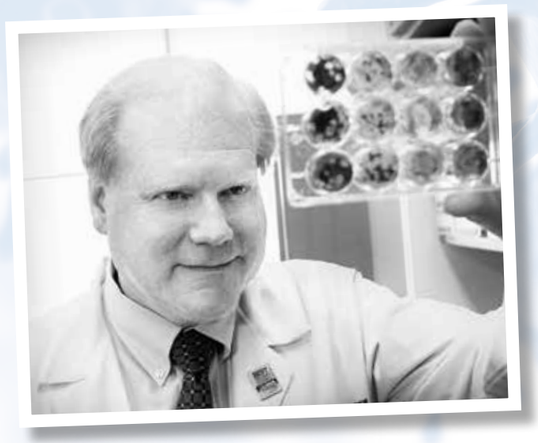
INFECTING CELLS TO MANIPULATE IMMUNITY: VIROTHERAPY

Immunotherapy is about more than injecting whole cells and antibodies. At its core, it's about manipulating and controlling the immune response to cancer.

Another way that researchers are manipulating the immune system to attack cancer is through oncolytic virotherapy.

The use of viruses to infect and kill tumor cells is a booming area of research, with the first FDA approval of a virus for the treatment of cancer last year. In developing oncolytic virotherapy, researchers are also learning more about how cancers evade the immune system.

If a cancer cell becomes infected with a virus, it sometimes begins to send out signals that call in T cells to dispatch the virus-infected cancer cell, explains Timothy Cripe, MD, PhD, division chief of Hematology/Oncology/BMT at Nationwide Children's. In this case, the virus didn't kill the cell, but the virus was instrumental in enabling the immune system to identify and kill it.



"In virotherapy, we're finding that, while we can use viruses to infect the cancer and potentially destroy it, the bigger impact is on immunity," says Dr. Cripe, who is also a principal investigator in the Center for Childhood Cancer and Blood Diseases in The Research Institute at Nationwide Children's. "Could virotherapy be combined with T cells to tag and kill tumor cells? That's a question we hope to answer."

In some cases, viruses interfere with the "shield" that the tumor puts up to protect itself from the immune system. The exact mechanisms for this activity are unknown. This effect of virotherapy is particularly intriguing for solid tumors, which create a microenvironment akin to a fortress to protect itself from the immune system. If the virus can infect the tumor cells, either by injection or another mode of infection, it could potentially dismantle the system from the inside.

In 2015, Amgen Tvec became the first FDA-approved oncolytic viral therapy in the United States. "We are excited to be part of the Amgen Tvec pediatric trial, as this drug shows potential not only for melanoma but for any solid tumor that can be injected with the drug," says Dr. Cripe, who is also professor of Pediatrics at The Ohio State University College of Medicine.

"In virotherapy, we're finding that, while we can use viruses to infect the cancer and potentially destroy it, the bigger impact is on immunity. Could virotherapy be combined with T cells to tag and kill tumor cells? That's a question we hope to answer."

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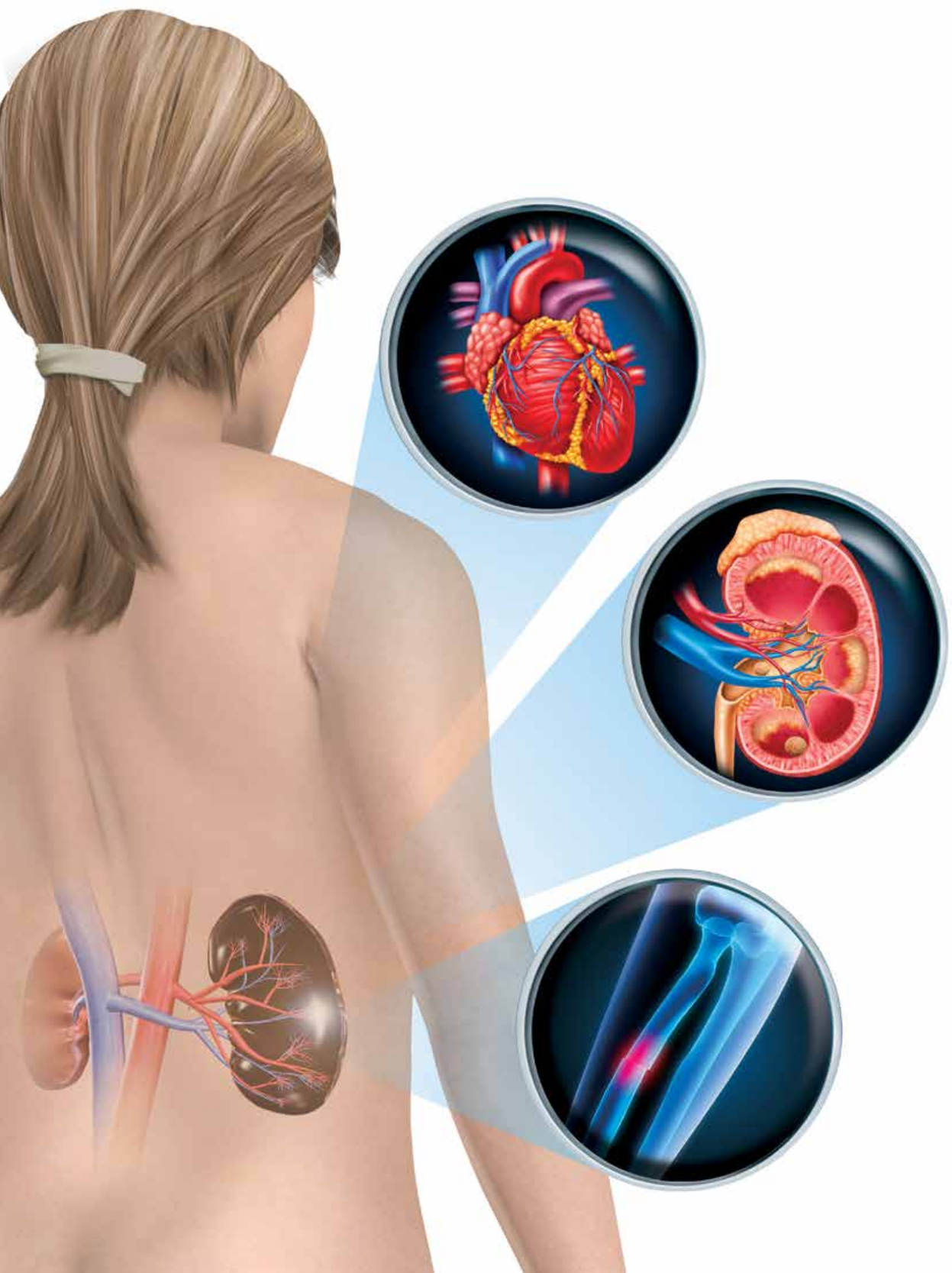

· CHILDHOOD ·

KIDNEY STONES

· THEIR SURPRISING CONNECTION · TO FUTURE DISEASE

by Jeb Phillips

Once thought to be an adult condition, urinary stone disease is increasingly found in children – and may be related to the development of cardiovascular disease, chronic kidney disease and low bone density.

By one well-regarded estimate, the risk of developing urinary stone disease in childhood doubled between 1997 and 2012.

That's worrying enough on in its own. But in the last decade or so, another issue has started to become clear as well. Experts once thought stones were problematic only when causing pain. Now they say:

"(Urinary stone disease) is more than just a symptomatic stone…the body of evidence today suggests not only a chronic metabolic condition punctuated by severely symptomatic acute events, but also a condition that heralds substantial future chronic morbidity and demands preventive efforts," in the words of a paper published this year from the National Institute of Diabetes and Digestive and Kidney Diseases (NIDDK), part of the National Institutes of Health (NIH).

Or, as Andrew L. Schwaderer, MD, research director in the Division of Nephrology at Nationwide Children's Hospital and co-author of the NIDDK paper puts it: "We are realizing how serious this is."

At the same time as the prevalence of stones is increasing, evidence is building of urinary stone disease's connection to cardiovascular issues, low bone density and chronic kidney disease. Taken together, those two ideas signal major implications for public health, says Ziya Kirkali, MD, senior scientific officer at the Division of Kidney, Urologic, and Hematologic Diseases at the NIDDK.

"This is a large issue in the pediatric population," according Dr. Kirkali, who was the lead author of the

recent paper from NIDDK detailing the seriousness of the disease. "It's going to affect a large number of people into the future."

Dr. Kirkali makes clear that his concern is for everyone, adults and children. All ages may be at risk for stones, and the connection to other conditions was established in adults first. Approximately 1 in 11 people will have a stone in their lifetimes.

But it's one thing for a 65-year-old to develop a stone, and another for a 13-year-old, who faces many decades of possible recurrences and sequelae.

Pediatric nephrology subspecialists and researchers know this relatively new information about urinary stone disease. Some primary care providers may not. While investigation into stone formation and prevention is accelerating, experts in the field say primary care physicians need to think right now about improving outcomes of their patients with stones.

THE INCREASING PREVALENCE

It's hard to know when urinary stone disease took hold in the pediatric population. It's possible, though, to put a date on the beginning of the national conversation about it, says Dr. Schwaderer, who is also a clinical professor of Pediatrics at The Ohio State University College of Medicine.

The New York Times carried a story on October 1, 2008 headlined "A Rise in Kidney Stones is Seen in U.S. Children." It didn't contain much in the way of hard data. It just quoted a number of specialists who all had the same experience: trained to believe that kidney stones were almost exclusively an adult problem, they were now regularly finding them in children.

This squared with what Dr. Schwaderer and many others were seeing. David Sas, DO, MPH, was a pediatric nephrologist practicing in South Carolina who had little knowledge about kidney stones initially. But he started seeing so many patients with them that he quickly became interested out of necessity.

"When I was talking to pediatricians, family practice doctors and emergency medicine physicians, I heard this over and over again; 'I was shocked to see this kid had a kidney stone. I didn't know kids could get kidney stones,'" says Dr. Sas, now at the Mayo Clinic Children's Center.

He became the lead author on one of the first population-based studies quantifying what *The New York Times* had identified. From 1996-2007, the incidence of pediatric kidney stones rose dramatically in South Carolina, the study found.

An expanded study that Dr. Sas co-authored this year revealed that the incidence of kidney stones increased 27 percent every five years in females ages 10-19. Risk of nephrolithiasis is increasing in this group faster than any other. Males 15-19 aren't far behind, though, with a 23 percent increase every five years.

Plenty of epidemiological work remains, but pediatric nephrologists broadly accept an increase in urinary stone disease – which has led to obvious questions with few good answers:

"What causes the stones? What is causing the increase?" asks Dr. Schwaderer. "We don't really understand the molecular basis for stone formation. We know stones have a genetic component, that approximately 70 percent of kids who have kidney stones have a first or second degree relative who also has kidney stones. That doesn't explain the increase, though. Why are adolescent females developing more stones than males? What role do diet and environment play?"

Specialists have some educated guesses. The large majority of stones are calcium based. An increase in dietary sodium, which leads the kidneys to excrete more calcium into the urine, may play a role, says Dr. Sas. So may a decrease in dietary calcium; calcium in food, as opposed to excreted calcium, can actually help prevent the formation of stones. (Obesity, while associated with stones in adults, doesn't seem to be implicated in children.)

A number of studies have noted that warmer temperatures have a correlation with increased incidence of urinary stone disease: dehydration can lead to concentrated levels of calcium oxalate and uric acid in the urine, which are factors in kidney stone formation. At least two recent studies have speculated that climate change might have some involvement in the rising incidence.

The growing incidence is worrying – and magnified by newly discovered relationships to other lifelong diseases.

A MULTI-SYSTEM CONDITION?

When a patient comes to Nationwide Children's with a kidney stone, Dr. Schwaderer tests for rare underlying issues that may have contributed to the stone, such as metabolic acidosis and hypercalcemia. He asks about hydration and diet. Those are the basics.

But in a move that may seem strange to children and their families at first, he also takes a fracture history. He wants to know about family experience with osteoporosis and bone complications. Depending on what the history reveals, he may recommend a bone density scan.

"Even though there are no standard recommendations about screening kidney stone patients for low bone density, we know there is a clear association between the two," Dr. Schwaderer says. "Osteoporosis may not be diagnosed in a patient until she is 70. If we can see it beginning in an adolescent because a kidney stone prompts us to look, we may be able to take some very early steps to help."

It's one thing to talk about the increase in kidney stones by themselves – how painful they are, or how they affect healthcare spending. It's another to talk of them as signals of conditions that the public takes more seriously such as low bone density, atherosclerosis or chronic kidney disease.

The connection of low bone density and kidney stones first emerged in adults in the 1970s, says Dr. Schwaderer. The association in adults between stones, cardiovascular conditions and chronic kidney disease has come more sharply into focus in the last decade. A 2010 study, for example, showed that adults with kidney stones have higher risks of carotid atherosclerosis and myocardial infarction.

And just in the last few years, evidence for associations in children has started to emerge as well. Dr. Schwaderer was the senior author of a 2015 study that found preliminary evidence of atherosclerosis in children with kidney stones. None of the study participants had been diagnosed with conditions known to cause atherosclerosis, so the authors suggested that damage to the arteries was related to the stones.

Evidence of association is not, of course, evidence of causality. It remains unclear if kidney stones cause these

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– Andrew L. Schwaderer, MD, research director in the Division of Nephrology at Nationwide Children's Hospital

other conditions, if these other conditions cause kidney stones or if some underlying issue contributes to all of them. Some researchers have suggested that calcium leaches from bones, leading to higher urine calcium and kidney stones. If that's true, it still doesn't tell the whole story, says Dr. Schwaderer.

The 2015 atherosclerosis study authors hypothesized that vascular and urinary calcifications have overlapping formation mechanisms, and that inflammation plays a role. Chronic kidney disease may be related to stone obstruction and other damage caused by stones.

A lot is left to learn. But the growing knowledge of future morbidities means early diagnosis, proper treatment and ongoing management of urinary stone disease have become crucial to overall childhood health.

DIAGNOSIS AND TREATMENT

According to pediatric nephrologists, this still happens all the time:

A child presents to a primary care doctor or a community Emergency Department with non-specific symptoms – vague back or abdominal pain. The child is diagnosed with a urinary tract infection or constipation, receives treatment but continues to hurt.

The pattern of pain, diagnosis, treatment and more pain continues, even after the child tries another provider. Maybe it goes on for months. Then the child ends up at Nationwide Children's or another large pediatric institution, where the correct diagnosis of kidney stones is finally made.

"There is still this idea, especially when children are initially treated at adult facilities, that kidney stones don't happen in pediatric patients," says Dr. Schwaderer. "Urinary stone disease is often not initially in the differential diagnosis, and so we see delays."

The urinary stone disease community should and will do more to educate physicians outside of the field, says Dr. Kirkali of the NIDDK. Dr. Sas, of Mayo, says that in conversations with primary care and emergency medicine physicians, he talks about the rising incidence of stones in children. But he also emphasizes the systemic nature of the disease, in part so other physicians will take the stones seriously.

"With adult kidney stones, a urologist may take care of the stone itself, and that's kind of it," Dr. Sas says. "That shouldn't be it for children. Every child who has a kidney stone warrants a comprehensive evaluation by experts."

And those should be pediatric experts, says Seth Alpert, MD, attending urologist at Nationwide Children's and a clinical associate professor of Urology at the OSU College of Medicine. Some children will have acute, symptomatic stones, and they need surgical intervention. Those interventions require small scopes and stents, along with special training and expertise, which adult urologists do not always have.

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"Along with the rise in stones overall, we seem to be seeing more kids, younger kids, who need surgery. A small child's anatomy can be challenging for an adult urologist."

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"Along with the rise in stones overall, we seem to be seeing more kids, younger kids, who need surgery," says Dr. Alpert. "A small child's anatomy can be challenging for an adult urologist."

Whether surgery is necessary or not, a pediatric multidisciplinary team can be useful in urinary stone disease management. Nephrologists, urologists, radiologists and dieticians all have roles. Medications to prevent stone formation may be necessary. So may a change in eating and drinking patterns.

Subspecialists are also keeping their eyes on new research about those connections to other conditions. Dr. Schwaderer has decided that best practice is to take a fracture history; so has Dr. Sas. Neither yet regularly screens for cardiovascular problems in patients with stones, though are open to it if future studies show them they should.

And with children's overall health so much at stake, that research into pediatric urinary stone disease is gaining momentum.

ACCELERATING RESEARCH

Last year, Dr. Kirkali and the NIDDK convened a national meeting called "Urinary Stone Disease: Research Challenges and Opportunities." Approximately 100 experts came together and laid out goals.

"With the epidemiological data we have, and our awareness that urinary stone disease poses a growing public health problem, we thought we really needed to do some focused research," says Dr. Kirkali. "We have held meetings before on the subject, but this was the first one that resulted in solid research priorities and funding opportunities. It's an exciting time in this field, and we're excited for what's coming."

Perhaps most importantly, the NIH has announced $20 million in funding over five years to establish the multicenter, multidisciplinary Urinary Stone Disease Research Network. The network will allow large-scale clinical studies of the kind that haven't been possible before, especially to determine the best strategies to prevent stones across the population, Dr. Kirkali says.

On the pediatric side, Dr. Sas has led the creation of a multicenter registry called Collaborative Research on Children With Kidney Stones. Dr. Sas' Mayo Clinic Children's Center was the first site for the registry, and Nationwide Children's and Children's Hospital of Philadelphia have joined the collaborative.

"I noticed in talking to other researchers in the field that we each had interesting findings, but none had enough numbers of patients to come to meaningful conclusions about what we had been seeing," he says. "If we're going to make headway, we need to go beyond single institution data sets."

"This is a large issue in the pediatric population. It's going to affect a large number of people into the future."

– Ziya Kirkali, MD, senior scientific officer at the Division of Kidney, Urologic, and Hematologic Diseases at the NIDDK.

This infrastructure allows for randomized controlled trials in children, says Dr. Schwaderer. Some studies to evaluate the effectiveness of drugs and diet have been published for adults, but almost none exist for the pediatric population. Until those are completed, many prevention and treatment strategies in pediatrics involve at least some degree of guesswork, he says.

Dr. Sas and Dr. Schwaderer are both investigating how the urinary system microbiome affects stone formation, and Dr. Sas is studying genes that may contribute to stones. Dr. Schwaderer recently collaborated with Daniel Cohen, MD, associate director of Emergency Medicine at Nationwide Children's, in research on the use of ultrasound versus computed tomography to detect stones in pediatric emergency centers. (International guidelines recommend ultrasound to limit radiation exposure.)

The adult disease has become one of childhood. The stones, once believed largely benign, now appear to be markers of other major conditions. And the healthcare field that used to worry about stones only when they became painful is working to keep pace with the new knowledge.

"Ten years ago, there was a paucity of pediatric research," Dr. Schwaderer says. "We were managing stones based on adult data. Now, we have more of an impetus to focus on children."

Join the conversation. Tweet your comments to **@NCHforDocs** using #kidneystones

HOW SHOULD **PRIMARY CARE AND EMERGENCY MEDICINE PHYSICIANS** HANDLE KIDNEY STONES?

The increase in urinary stone disease means that primary care and emergency department doctors either already see children with stones – or may start seeing them routinely in the near future. So increased knowledge of the disease among these physicians may be vital for improving outcomes.

DR. ANDREW SCHWADERER, RESEARCH DIRECTOR IN THE DIVISION OF NEPHROLOGY AT NATIONWIDE CHILDREN'S HOSPITAL, OFFERS THESE SUGGESTIONS FOR PRACTITIONERS:

- **Know when to include urinary stone disease in the differential diagnosis.**

A child with recurrent abdominal or flank pain, blood in the urine (hematuria) or voiding/obstructive symptoms may have stones. Those symptoms can overlap with urinary tract infections, and kidney stones are often initially misdiagnosed as a UTI. If urinalysis reveals white blood cells in the urine, but the culture is negative, stones are a possibility.

- **If ordering diagnostic imaging, use ultrasound instead of CT.**

Many physicians already follow the "imaging gently" credo in order to limit the radiation exposure to their patients. Because many children who have stones will eventually have recurrences, the judicious use of CT in this population is particularly important.

- **Refer every suspected kidney stone case to a pediatric nephrologist.**

Even if symptoms are mild or manageable in a primary care setting, pediatric nephrologists now believe that each case of urinary stone disease is serious enough to warrant evaluation by a subspecialist. A large pediatric institution has access to urologists, radiologists, dieticians and other experts who can contribute to treatment and ongoing management.

Best Practices for RESEARCH RECRUITMENT AND RETENTION

YOU CAN'T OBTAIN STUDY DATA WITHOUT PARTICIPANTS. FROM INITIAL DESIGN AND PROMOTION TO COMMUNICATION TACTICS AND PATIENT SATISFACTION, HERE ARE SOME STRATEGIES TO ENSURE SUCCESS.

by Tiasha Letostak, PhD

Advancing pediatric research depends on successful recruitment and retention of study participants. Unfortunately, 9 out of 10 trials end up having to double their original timelines in order to meet enrollment goals, while 48 percent of sites under-enroll study volunteers. Finding enough of the right participants – and keeping them – is often the most difficult and challenging aspect of conducting a study.

"Most people do have an altruistic nature, so they want to help with research," says Grace Wentzel, CCRP, director of Clinical Research Services at Nationwide Children's Hospital. "However, statistics show that we do a poor job of educating the public about why clinical research is important in the first place and of driving them to resources for finding those studies."

Data from the Center for Information and Study on Clinical Research Participation (CISCRP) prove Wentzel's points, revealing that 87 percent of the public are willing to participate in a study. Their reasons for doing so are to advance medicine (33%) or to help improve the lives of others (29%), rather than to improve their own condition (15%) or earn extra money (5%).

But a lack of general knowledge about research, combined with fears about side effects or risks to overall health, does keep individuals from enrolling. Twenty-six percent of the public doesn't even know where trials are conducted, and after a study ends, 88 percent of patients rarely or never talk with others about research.

"The value of a study coordinator cannot be overstated," says Rose Hallarn, director of the Participant Recruitment and Retention Program at The Ohio State University Center for Clinical and Translational Science. "When someone is not eligible for a study, it's really important that the coordinator selects the right words to explain to them why they're not eligible, thanks them for their interest in the study and connects them to other available or ongoing studies. If someone is found to be ineligible for a study and isn't redirected to another study or to other ways to find studies, almost 70 percent of them will never search for another one."

So, how do you garner interest in the first place?

"Recruitment strategies can range from just a flyer in the clinic or an online ad to a doctor directly talking to a patient," says Wentzel. "The key is to meet early with someone who will help you, preferably at least monthly, to dissect what's working and not working, because you have to be willing to change your strategy and to have that flexibility built into your study recruitment plan. The more upfront time you put into your plan, the more time you will save on the implementation side – for every hour of planning that you do, you will save 10 hours of actual work."

According to the CISCRP, the public is most likely to obtain clinical research information online (46%), through the media (39%) or via email (32%). Both directors advise research teams to be able to succinctly convey the significance of the study in one sentence for any print or online advertisement. This includes why the study is important and why people should want to participate. Research teams should design marketing materials in a way that the general public will understand and effectively demonstrate the significance of the study to potential participants and their families.

"Our experiences have shown that large deviations from the standard of care and exposure to many invasive procedures will negatively impact your recruitment efforts," says Wentzel. "Scientifically, the study may be rigorous – 14 blood draws or a number of invasive procedures – but it will be very difficult to recruit participants. If we can meet with a researcher early on, before the final study design is complete, we can assist in cutting down on the number of procedures or study visits to make it easier to participate, while ensuring that the study still meets scientific needs."

Hallarn echoes this sentiment. "The participant is the most important member of the study team, and if the participant burden is too high, then you have no study. Think about how your study design may change the number of people who would be willing and able to participate in your study."

Another aspect of study design involves identifying the best settings for recruitment, which may not always be a clinical setting when it comes to pediatric research.

"What is the standard of care for your study population, and where are they normally seen?" says Wentzel. "For example, if you were looking for healthy children under two years of age, you would find them in daycares. When studying a particular condition, you can look at what procedures you're doing that mirror what clinicians are doing elsewhere or where that patient population is already being seen, so you can try to take advantage of that existing standard of care."

Other recommendations for recruitment include tapping into advocacy groups, either in-person, online or through social media. This might include patient-family conferences or Facebook groups for specific rare diseases. And using a national volunteer registry, such as ResearchMatch, or a university-sponsored site, such as StudySearch, can also assist you in reaching your intended study population.

Grace Wentzel, CCRP, director of Clinical Research Services at Nationwide Children's Hospital and Rose Hallarn, program director for Recruitment and Retention Services at The Ohio State University Center for Clinical and Translational Science

"It cannot be a hassle; their research experience needs to be enjoyable. Because, unlike care, they don't have to be here."

– Grace Wentzel, CCRP, director of Clinical Research Services at Nationwide Children's

"Depending on your population, knowing how they communicate matters," says Wentzel. "If you're trying to recruit teenagers or young adults – who don't answer their phone or always check emails – using other methods such as texting, and getting approval to use that method, is crucial."

Making sure that you include all potential communication options in your IRB application, explains Hallarn, will save valuable time, so you don't have to go back and get these methods approved. "You may not think that you need all of these things, but get it approved. Then, if your initial recruitment strategies don't work out, you don't have to recreate your plan."

Both Wentzel and Hallarn agree that choosing the right participants in the first place is essential not only for recruitment but also for retention.

"If patients are no-shows or noncompliant with clinic visits, then they are highly likely to be no-shows or noncompliant with research visits," explains Wentzel. "These types of participants will likely adversely affect your research data and outcomes, unless it's a single-visit study. If you're expecting someone to be in your study for 6 months, 12 months, etc., then you will want to recruit someone who has a history of being compliant with their visits."

And what many investigators may not realize, says Hallarn, is that retention actually begins at the very first moment that a potential participant hears anything about your study or contacts you.

"If your response time is not within 24 hours, you lose about 67 percent of your potential participants," Hallarn emphasizes. "And they already begin to feel that this might not be a place that they can trust."

"I think what's important for both recruitment and retention is to really establish a rapport with these families," adds Wentzel. "Make sure they feel important, that we're responsive to them and their calls, that their visits are good experiences and that they don't have extensive wait times. It cannot be a hassle; their research experience needs to be enjoyable. Because, unlike care, they don't have to be here."

Efforts to retain participants by taking care of and anticipating their needs are akin to providing customer service, say Hallarn and Wentzel, because once a family has a good experience with research, chances are that the family will participate in other studies and recommend that others participate as well. The data reveals this trend, with the CISCRP demonstrating that 95 percent of participants would consider enrolling in another study.

Multiple factors can influence a research participant's decision to drop out of a study. Although some dropouts are inevitable and due to factors outside of the research team's control, many of these can be prevented.

Minimizing participant burden during protocol design, explaining the importance of their involvement, and clearly communicating expectations upfront during the informed consent form discussion, are all actions that can be taken early on during the recruitment stage. Retention can be augmented by promptly responding to inquiries, sending reminders for upcoming visits, showing appreciation and recognition, and accommodating participants' schedules as much as possible. Considering participants' needs in all aspects of the study will enhance the experience of participants and their families, increasing the likelihood of enrollment in future studies and the likelihood of recommending that others participate in research as well.

A Better Approach to Prescribing Medication

When doctors consider effectiveness, availability and costs, patients benefit.

by Jeb Phillips

A small change in the way a doctor prescribes a medication can make a big difference. Officials from the accountable care organization Partners For Kids use this example all the time:

Abilify, a behavioral health drug, is usually priced per pill, not by strength of dose. Two 5 mg pills cost nearly twice the amount of a single 10 mg pill. Abilify is long-acting, so the single 10 mg pill is just as effective as the two smaller doses taken at different times.

Physicians don't always know the drug's half-life or pricing. An analysis by Partners For Kids found that if all its patients on Abilify took just one dose per day, the potential savings would be more than $300,000 per year.

That kind of overall savings is important for insurers, for Medicaid and for the entire health care system, says Chet Kaczor, PharmD, MBA, director of Pharmacy Services for Nationwide Children's Hospital.

But if that's too abstract, think about how the example affects a single child and a single doctor, he says. A patient is more likely to take every dose of a medication if there is only one dose per day. An adherent patient is a healthier patient. A healthier patient needs fewer trips to a provider, freeing the provider to see patients who may need care more urgently.

"The overall idea of efficiency in prescription practices is taking the best possible care of the patient," says Cathy Kuhn, PharmD, a clinical pharmacist for Partners For Kids. "We are thinking about the patient's time, the doctor's time, ready access to medicine, cost and, ultimately, best outcomes."

Partners For Kids is one of the oldest and largest accountable care organizations in the United States. With Nationwide Children's as its hospital member, the organization works to keep children covered by Medicaid Managed Care Plans healthy in central and southeastern Ohio. Partners For Kids incentivizes its 1,000-plus member providers to focus on the quality and value of care instead of numbers of procedures or office visits.

Among its signature initiatives is its Pharmacy Program. And one of the Pharmacy Program's most important services is helping physicians understand best practices in prescribing medications. That includes giving guidance on insurance coverage, drug availability, drug costs and overall effectiveness of therapies for some very common conditions – asthma, allergies, ear infections, behavioral health issues, acne and others.

Some of the most recent guidance from the Partners For Kids Pharmacy Program is on the acid suppressive medication esomeprazole (Nexium). A prescription for a one-month supply of esomeprazole is $255. But if a provider writes a prescription instead for the over-the-counter Nexium 24HR – the same medication in every important way – the cost is $21 per month. Because of differing regulations on over-the-counter and prescription medications, a pharmacist can't make the substitution for the less expensive option; the provider must write the prescription the correct way.

"It's not always easy for a prescriber to figure out the right thing to do," says Hosain Aghamoosa, PharmD, a clinical pharmacist for Partners For Kids. "If you think about how much time a provider might have with a patient, there may not be an extra few minutes to figure out which medications an individual insurer covers or which might be more expensive for a patient who is paying out of pocket. Physicians want to provide the best possible care for their patients. But if a patient can't afford a medication or the insurance company doesn't cover it, then a physician may actually be delaying therapy."

Partners For Kids offers some information specifically tailored to its member providers. Prescribers don't have to be members, though, to begin thinking about prescription practices, or to incorporate Partners For Kids' attitudes into their work, its pharmacists say.

Partners For Kids makes some general medication guidelines publicly available on its website, **PartnersForKids.org**. Want to know if fluoxetine (Prozac) or sertraline (Zoloft) is the appropriate first-line medication for anxiety and depression? Or whether Ciprodex or Floxin Otic is the best initial step for the treatment of bacterial acute otitis externa?

You can find the answers in the "Resources" section of the website. (Spoiler alert: For anxiety and depression, the appropriate first medication is fluoxetine. For acute otitis externa, the answer is complicated, and a careful examination of the flow chart on the website will help.)

The guides are particularly useful for primary care doctors outside of metropolitan areas, Dr. Aghamoosa says.

"In a big city, a child may see a psychiatrist for a behavioral health condition," he says. "In a rural area, that same child has to rely on a primary care physician, who becomes a jack-of-all-trades. The guides help extend a pediatrician's comfort level to match the needs of the patients in their areas."

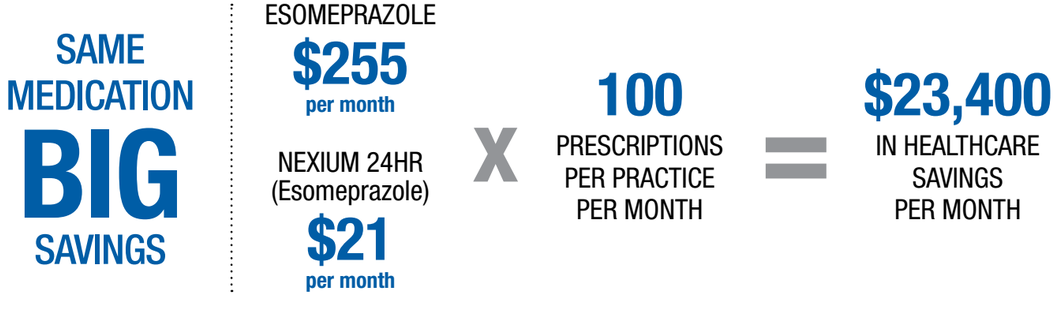
The website also includes a regularly updated document detailing many medication prices and coverages for Ohio's five Medicaid Managed Care Plans. These won't exactly match prices and coverages for every insurer or every state, but the document is a good guide for general trends, say Partners For Kids pharmacists.

Primary care physicians may also find medication management software and mobile applications, such as those produced by Micromedex Solutions and Epocrates, helpful, Dr. Kaczor says.

And the Partners For Kids Pharmacy Program has one more recommendation for prescribers: talk to your community pharmacists. Doctors are used to fielding calls from pharmacists who need a specific question answered about a prescription, or want to know if they can substitute one medication for another.

Doctors should remember the relationship works both ways, Dr. Kaczor says. Doctors can and should ask pharmacists about drug therapeutic information, costs, coverages and availability.

"Community pharmacists are the medication experts, and they're just a phone call away," Dr. Kaczor says.



Two Stage Surgery for Epilepsy

Surgery proves to be a viable option for patients with medically refractory epilepsy

Childhood onset epilepsy affects 1 percent of children worldwide. About 25 to 30 percent of these patients will have medically refractory epilepsy, continuing to have seizures despite using two or more antiseizure medications. Options for this group of patients include intercranial epilepsy surgery, Vagus nerve stimulator (VNS) insertion, Ketogenic diet and drug trials. It is increasingly recognized that epilepsy surgery may dramatically improve the quality of life for these children in some cases and is the only potentially curative option.

Phase I Monitoring

Phase 1 is an extensive presurgical workup that helps the neurologist localize the seizures and determine the patient's candidacy for epilepsy surgery. This involves multiple-day inpatient admission, prolonged video EEG and intended observation of at least three typical seizures.

The patient also undergoes imaging sequences including positron emission tomography (PET), single photon emission computed tomography (SPECT) and epilepsy protocol MRI, in addition to outpatient neuropsychology testing. Potential surgical candidates and all of their clinical and radiographic data are discussed thoroughly at the weekly Epilepsy Surgery Conference. Depending on the results from the Epilepsy Surgery Conference, single stage epilepsy surgery, two stage epilepsy surgery, or palliative surgical options (corpus callosotomy or VNS insertion) may be offered.

Single or Two Stage Epilepsy Surgery

Single stage surgery is performed if imaging and phase 1 data demonstrate concordant findings suggestions lesional epilepsy. It involves resection of the lesion and electrocorticography to ensure all abnormal tissue is removed. Alternatively, diffuse pathology affecting a cerebral hemisphere may warrant hemispherectomy/ hemispherotomy.

Two stage surgery is performed when phase 1 monitoring contains discordant data or inadequately localizes the epileptigenic zone. This approach allows identification of the epipleptigenic zone, potential adjacent areas of abnormal electrical activity and nearby eloquent functional areas of the brain. Eloquent areas of cortex are localized by cortical stimulation mapping.

Stage 1 Surgery

During stage 1 surgery, craniotomy and dural opening allow exposure of the cerebral cortex. Working in collaboration, the neurosurgery and neurology teams identify sites of coverage and access for subdrual grids, strips and/or depth electrodes. Intraoperative electrocorticography confirms adequate placement and signals of intracranial EEG electrodes. The electrodes are safely secured in place as the dura is subsequently closed.

EXPOSED CORTICAL SURFACE OF THE BRAIN

Sources: Jonathan A. Pindrik, MD, pediatric neurosurgeon, Nationwide Children's
Satyanarayana Gedela, MD, pediatric neurologist, Nationwide Children's
Graphic by: Christina Ullman, Ullman Design

Phase 2 Monitoring

During phase 2 monitoring, continuous, long-term intracranial EEG is monitored for approximately one week to identify abnormal electrical signals before and during seizures. Frequently, antiepileptic medications are weaned to help capture typical seizure activity (at least three events).

Near the conclusion of phase 2 monitoring, corticostimulation mapping may identify eloquent functional areas that will help surgical planning. Additional discussion during the Epilepsy Surgical Conference solidifies the surgical plan.

EEG technicians and epileptologists continuously monitor the prolonged video EEG in real time.

Stage 2 Surgery

Stage 2 surgery typically involves grid-based resection of the epileptigenic zone with careful preservation of adjacent eloquent functional areas. Intraoperative electrocorticography confirms the absence of any residual abnormal electrical activity or identifies additional sites requiring resection.

Post operative recovery Following surgery, patients are monitored closely in the pediatric intensive care unit. Once stable, they are transferred to the neurosurgery floor for further recovery. Often patients are discharged to home. However, if needed, transfer to Inpatient Rehabilitation allows for prolonged recovery.

SUBDURAL CONVEXITY GRID OVERLAYING CORTICAL SURFACE

EXTENSIVE GRID-BASED RESECTION OF EPILEPTIGENIC CORTEX

How Can We Increase the HPV Vaccination Rate?

By Michael T. Brady, MD

***Dr. Brady** is an infectious diseases specialist at Nationwide Children's Hospital and a past chair of the American Academy of Pediatrics' Committee on Infectious Diseases.*

Cancer is a terrifying diagnosis for a patient to receive or a doctor to give. So it would make sense that a vaccine proven to prevent cancer would be welcomed by everyone. The human papillomavirus (HPV) vaccine could prevent 28,500 HPV-related cancer cases – cervical, vaginal, vulvar, anal, rectal, penile and oropharyngeal – each year. The Centers of Disease Control and Prevention, along with the American Academy of Pediatrics, recommends the HPV vaccine series for every child at 11 or 12 years of age, though it can be started in 9-year-olds.

However, only 60% of eligible females and 42% of eligible males receive their first HPV vaccine dose; and only 40% of females and 21% of males complete the three-dose series. The annual incidence of HPV-related cancers has increased in the last decade. Why is a safe and effective cancer vaccine such a difficult to sell? What can we do to make it more acceptable?

We first have to understand why patients and families might struggle with the issue. The HPV vaccine can seem different from other vaccines. This is, after all, a cancer vaccine that also prevents a sexually transmitted disease. The three-dose series typically takes six months, and is intended for patients who often visit a pediatrician only for illnesses and sports physicals.

The public may be confused because the vaccine was initially licensed only for females. Traditional and social media have sometimes amplified misunderstandings and misinformation, including stories of adolescents who experience adverse events after the HPV vaccine (but were actually unrelated).

Then we have to address these concerns and misunderstandings thoughtfully. For parents worried that some adolescents may engage in sex sooner because they feel "protected," studies show the vaccine has led to no acceleration of sexual activity in recipients.

We can also take a more proactive approach as physicians. The HPV vaccine has been recommended as part of the "adolescent platform" of vaccines. It's possible to give the vaccines to children at 9 years of age, though, which may remove the immediate concerns about early sexual activity. And with a first dose at 9 years old, it's more likely the entire course will be completed by the time of sexual debut.

For families concerned about safety, it's important to point out that the three available versions of the HPV vaccine – HPV 2, HPV 4 and HPV 9 – only received approval from the U.S. Food and Drug Administration after large multinational studies. More than 80 million HPV vaccine doses were given through 2015, and no new safety concerns have been identified.

The most common adverse events are the same ones patients might experience with other shots: injection site discomfort and syncope. A 15-minute observation period after vaccination prevents significant syncope-related events. Reports to the federal Vaccine Adverse Event Reporting System have declined dramatically since 2008, and no serious adverse events have been reported in the last three years.

With more than 8 million doses given every year, it's inevitable that some recipients will experience issues that are temporally related to the vaccine but are not caused by it. Traditional and social media have made anecdotal connections between the HPV vaccine and Guillain-Barre Syndrome, seizures, stroke, venous thromboembolism, appendicitis, anaphylaxis, autoimmune conditions, ovaria failure, postural orthostatic tachycardia syndrome or death.

The CDC, however, has found no increase in these conditions and events due to the HPV vaccine.

Effectiveness might be the easiest argument to make. The vaccines reduced HPV-associated precancerous lesions by 100%. HPV 4 and HPV 9 vaccines reduced genital warts by 97% in females and 89% in males. Surveillance has shown a dramatic public health benefit even with low immunization rates, including a 56% reduction in prevalence of four HPV strains in adolescent girls eligible for the HPV vaccine in the United States.

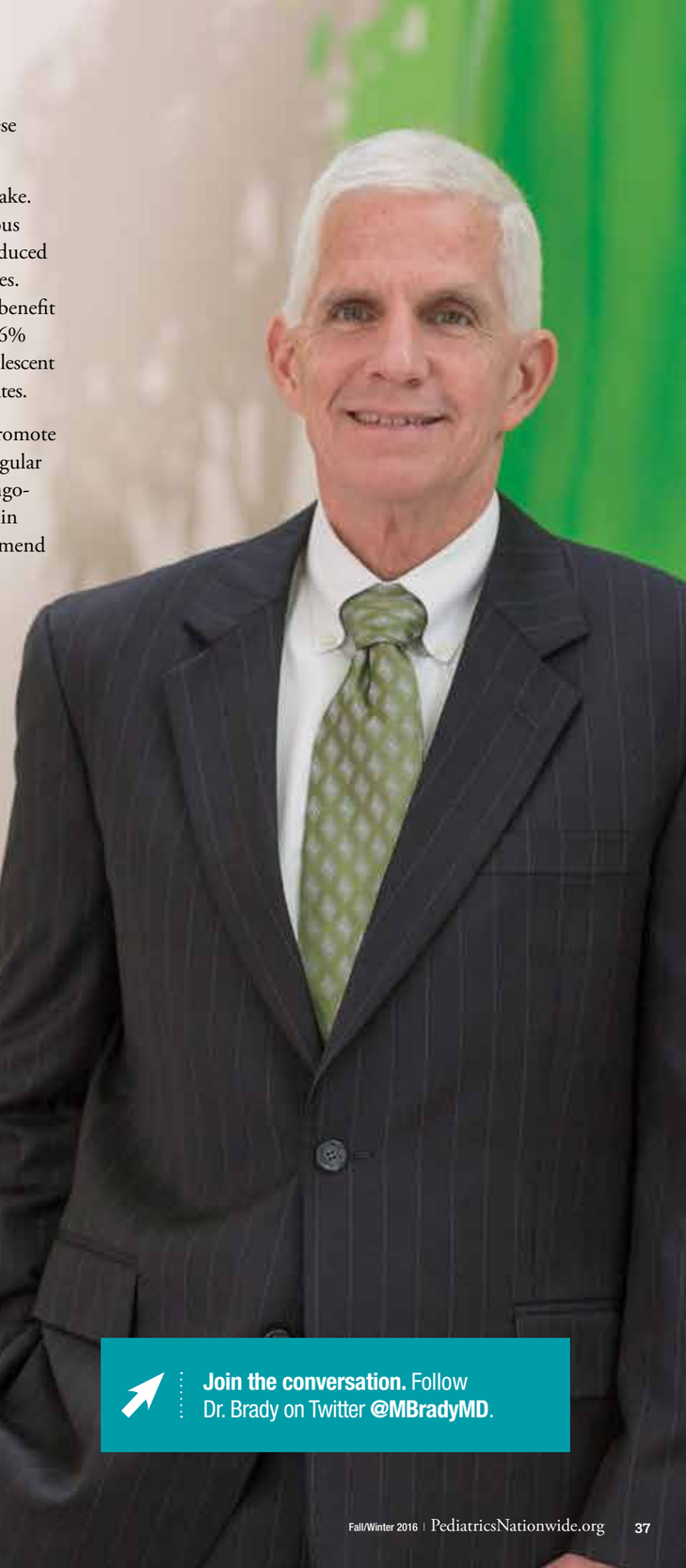
We also have to realize that we can do more to promote the HPV vaccine. There is evidence that at the regular 11-year-old visit, parents accept Tdap and meningococcal vaccines with minimal resistance, perhaps in part because of how confidently providers recommend them. Some providers are less comfortable with questions raised by the HPV vaccine and may be willing to delay the vaccine rather than have a potentially awkward conversation.

If we can prevent sexually transmitted infection and cancer, we need to prepare for those conversations. We should recommend the HPV vaccine as strongly as vaccines for Hib, measles, pneumococcal conjugate and other conditions. Sometimes it doesn't feel this way, but patients and their families respect their pediatrician's views on the value and necessity of vaccines. So there can be no equivocation from us.

Still, patients and parents may decline. We should use that opportunity to understand the factors that impact their decision. Asking questions may even allow pediatricians to counter their concerns. If nothing else, asking questions allows us to develop strategies for recommending the HPV vaccine to other patients.

So consider offering the vaccine to children at 9-years-old. Know the statistics about safety and efficacy. Ask questions of those who decline.

With the HPV vaccine, we have an easy way to help many children and families. We should take advantage of it.



Join the conversation. Follow Dr. Brady on Twitter **@MBradyMD**.

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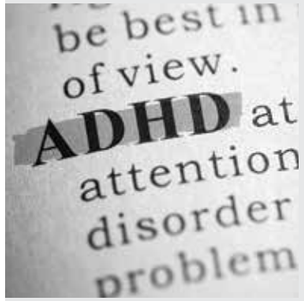


Pediatricians and Subspecialists May Need to Up Their ADHD Game

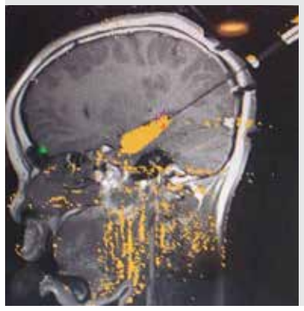
by Kevin Mayhood

Stimulants are the most effective medications used to treat ADHD but as diagnosis of the condition and prescriptions for the drugs has risen, so has evidence of diversion and misuse by adolescents seeking an edge in school or sports or to get high. Studies show pediatricians lack awareness of the trends and fail to follow recommended practices for diagnosing, monitoring and prescribing. Read more about the issues and impacts, and how physicians may safeguard patients at **PediatricsNationwide.org/ADHD-Medications**

Personal, Familial and Social Factors Surrounding Child Suicide

by Brianne Moore

In 2014, suicide was the 10th leading cause of death for children ages 5 to 11. This was the first time suicide had shown up in the top 10 leading causes of death for children in this age group. As suicide rates among children climb, researchers publish the first study exclusively focused on the precipitating circumstances of children and young adolescents, ages 5 to 14, who die by suicide. Read more about the trends the researchers uncovered at **PediatricsNationwide.org/Child-Suicide**



Minimally-Invasive Technology Proving Itself in Epilepsy Procedures

by Kevin Mayhood

MRI-guided stereostatic laser ablation (SLA) is proving comparable to open surgery in several types of epilepsy surgery. Importantly, it may even offer better outcomes in terms of shorter and easier recovery. Compared with open surgery, MRI-guided SLA boasts a smaller incision, no formal craniotomy, and decreased risk factors for infection. Read more about this new surgical approach at **PediatricsNationwide.org/SLA-Epilepsy**

> *"We cannot solve our problems with the same thinking we used when we created them."*
>
> *– Albert Einstein*

CITATIONS

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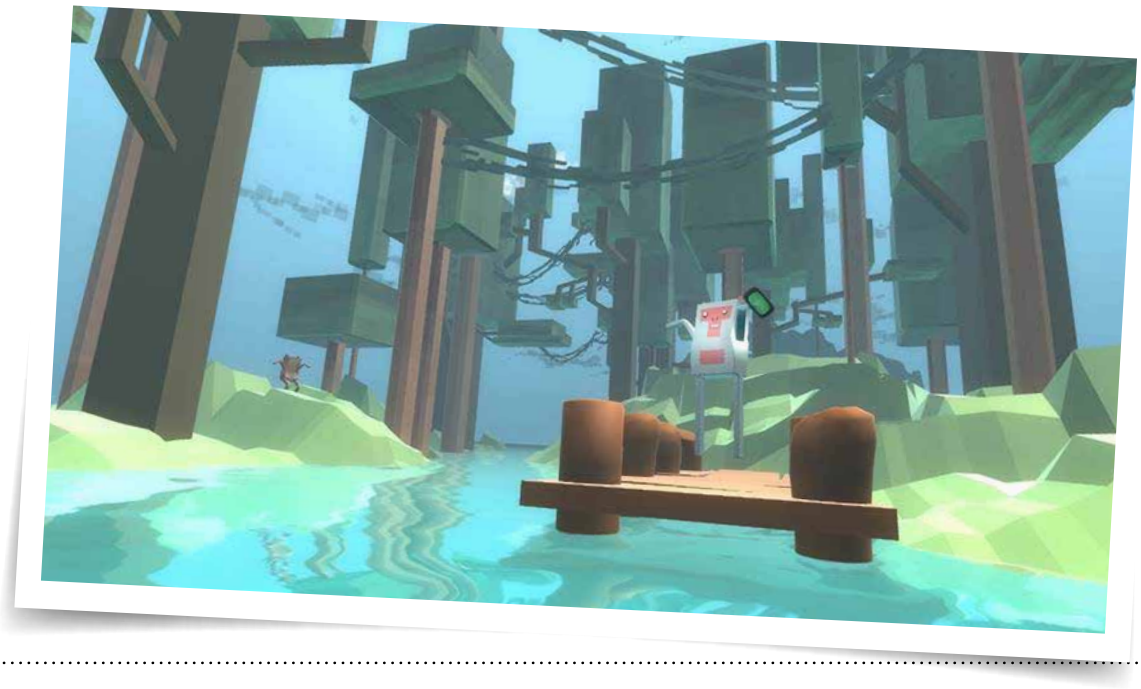

Changing the Game: Virtual Reality Distracts From Pain, Transforming the Patient Experience

A first-of-its-kind virtual reality experience from the hemophilia team and design experts at Nationwide Children's and The Ohio State University distracts patients with an immersive environment of penguins, pirates and hermit crabs during infusions and other procedures. A pilot study is testing the feasibility of integrating the virtual reality technology into the clinic setting. To learn more about how this virtual reality application is changing the patient experience in the hemophilia clinic, visit **PediatricsNationwide.org/Hemophilia-Virtual-Reality.**

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