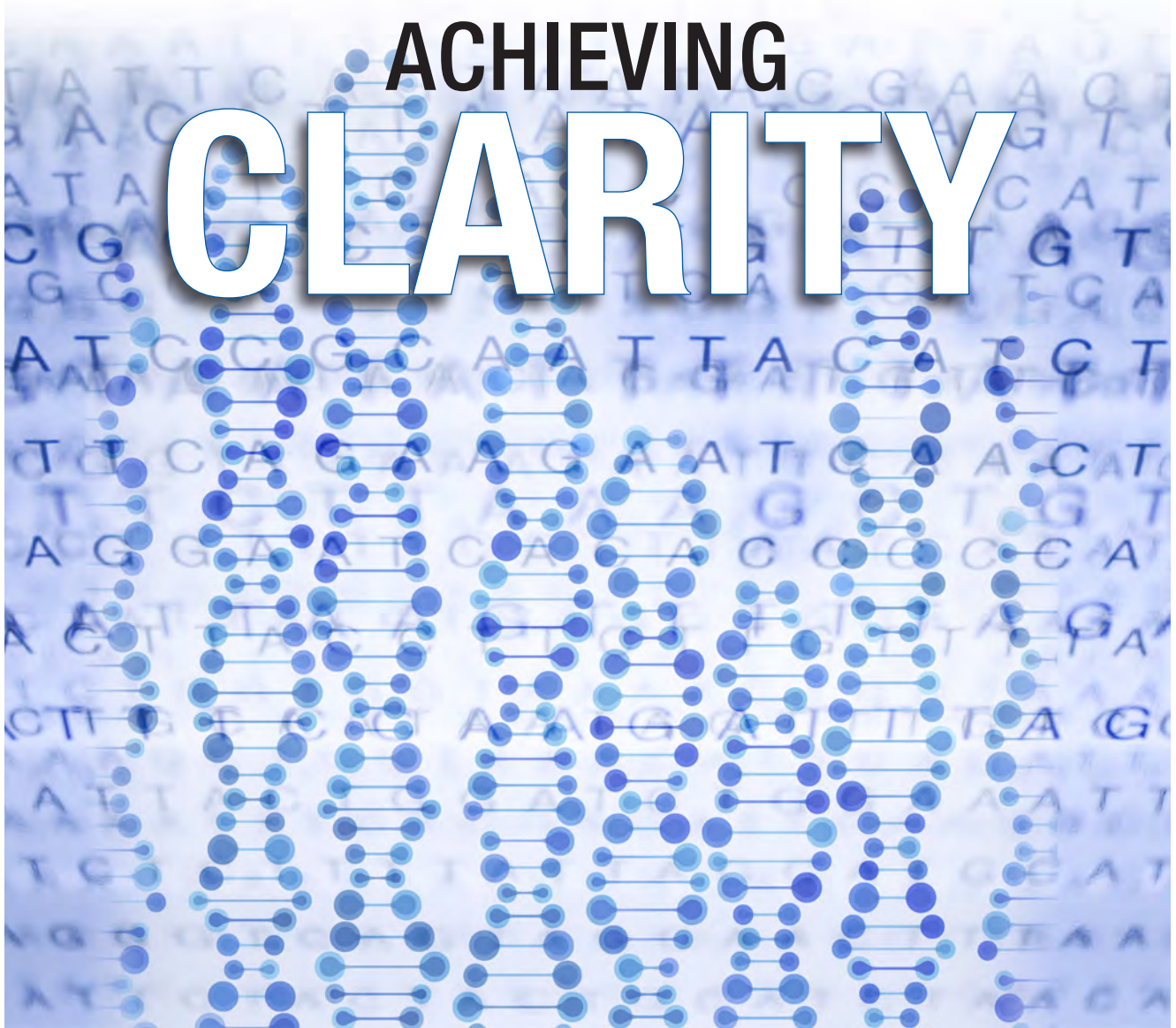


Spring/Summer 2016

Pediatrics

NATIONWIDE

Advancing the Conversation
on Child Health

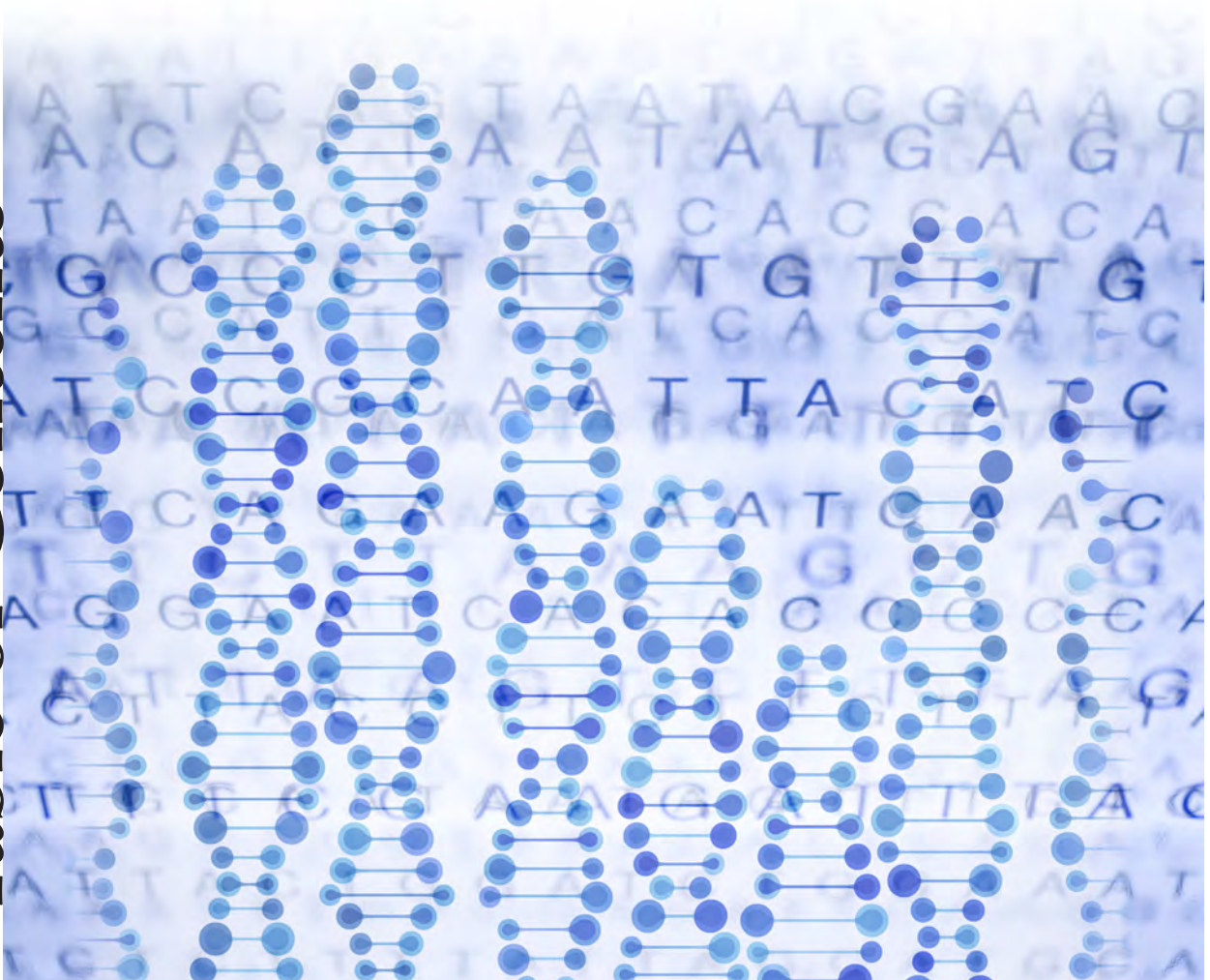


20

ACHIEVING CLARITY

The CLARITY Undiagnosed challenge focused on solving the undiagnosed diseases of five patient families. Using next-generation sequencing, advanced genomic analysis software and old-fashioned teamwork, a team of researchers from Nationwide Children's Hospital won the challenge.

Table of Contents



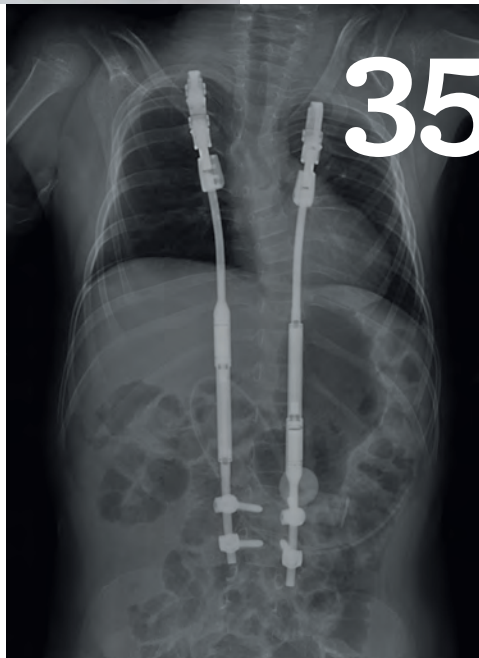


DEPARTMENTS

- 4** In Practice: News From the Field
- 34** In Sight: Remote Control Lengthening
- 36** Second Opinions: Using Social Media to Advance Care
- 38** Connections: Advancing the Conversation on Child Health

FEATURES

- 12** The Collapse of Biofilms?
- 18** The Journey to a Program Project Grant
- 20** Achieving CLARITY
- 28** Taking Aim at the Opioid Problem



“We wanted to put the power of genomics into action. The patients in the challenge were the toughest of the tough.”

— Alan Beggs, PhD, Director,
The Manton Center for
Orphan Disease Research,
Boston Children’s Hospital
(page 22)

“We’re trained to be negative and skeptical. We’re trained to ask question after question. But after a while, we just had to look at each other and say, ‘this keeps on working.’”

— Lauren Bakaletz, PhD, Director, Center for Microbial Pathogenesis, The Research Institute,
Nationwide Children’s Hospital (page 16)

Hearing Without Cochlear Nerves

Auditory brainstem implant devices may help young children with sensorineural hearing loss.

Sensorineural hearing loss (SNHL) is the most common type of hearing loss, accounting for about 90 percent of all hearing loss worldwide. SNHL involves damage to the inner ear (cochlea) or to the nerve pathways from the inner ear to the brain, and thus cannot be managed via hearing aids.

For more than 30 years, auditory brainstem implantation (ABI) has been used in adolescents and adults with SNHL due to neurofibromatosis 2 (NF2), with more than 1,000 ABIs performed worldwide.

However, Oliver F. Adunka, MD, FACS, director of the Hearing Program at Nationwide Children's Hospital, notes that, as of November 2015, the FDA has not approved ABIs for children under the age of 12 or for any patients without NF2.

“Since ABI remains unapproved by the FDA for children under age 12, our pediatric patients currently receive an off-label device, also known as a humanitarian use device,” says Dr. Adunka, who is also a professor and the division director of Otolaryngology, Neurotology and Cranial Base Surgery at The Ohio State University. “This is done only after careful analysis of the diagnostic protocol, as well as the potential risks and benefits.”

The first case of ABI at Nationwide Children's was performed on a 2-year-old boy named Colton who previously received a cochlear implant for bilateral profound hearing loss but had not benefitted due to the absence of the cochlear nerve. After activation of the new device, the patient initially responded to sound.

“Over the first few months of implant use, the parameters of the implant will be slightly modified,” explains Dr. Adunka, who is also director of Pediatric Otolaryngology at Nationwide Children's. “However, these changes are much more subtle when compared to the mapping changes typically employed with cochlear implants.”

Although scientific reports indicate that surgeons outside of the United States have been doing ABI surgeries in children for more than a decade, no formal



Colton is the first patient at Nationwide Children's to receive ABI as a humanitarian use device.

safety or feasibility studies under regulatory oversight have confirmed its benefits.

For this reason, the University of Southern California's Keck School of Medicine and several other institutions are conducting a three-year clinical trial of ABI for children under age 5. The trial, which began in March 2014, has led to successful implantation in four children.

According to reports, study participants are progressing at expected or better rates, offering hope for children who were formerly not considered surgical candidates for ABI, including those with congenital malformations and other causes of retrocochlear deafness.

— *Tiasha Letostak, PhD*

Signaling Pathway Changes May Flag CAVD, Offer Target for Therapies

Loss of Tgfb β 1 from the endothelium leads to a reduction in Sox9 expression and valve calcification.

A team of researchers has identified a molecular signaling pathway that, when altered, can contribute to calcific aortic valve disease (CAVD). The finding may provide a method for early diagnosis — many patients don't learn they have the disease until it's in the final stage — and a target for treatment therapies.

CAVD is the most prevalent valvular disorder in the United States, sending 55,000 patients to the hospital and causing 15,000 deaths annually. Long thought to be acquired during adulthood, there is increasing evidence to suggest the disease has its origins during embryonic development.

“The only effective therapy available now is surgical repair and replacement, which is very expensive and a very high risk burden to the patient,” says Joy Lincoln, PhD, a principal investigator in the Center for Cardiovascular Research at The Research Institute at Nationwide Children's Hospital and leader of the study.

“Surgical intervention costs the U.S. government around \$2 billion per year,” says Dr. Lincoln, who is also an associate professor of Pediatrics at The Ohio State University College of Medicine. “A less costly and less risky alternative would be beneficial to affected individuals.”

Building on her earlier work that found a reduction of the transcription factor Sox9 resulted in valve calcification in mice, Dr. Lincoln and her colleagues focused on identifying the signaling pathways that regulate this process.

“We and others have shown that calcification of the valve is similar to bone development,” she says.

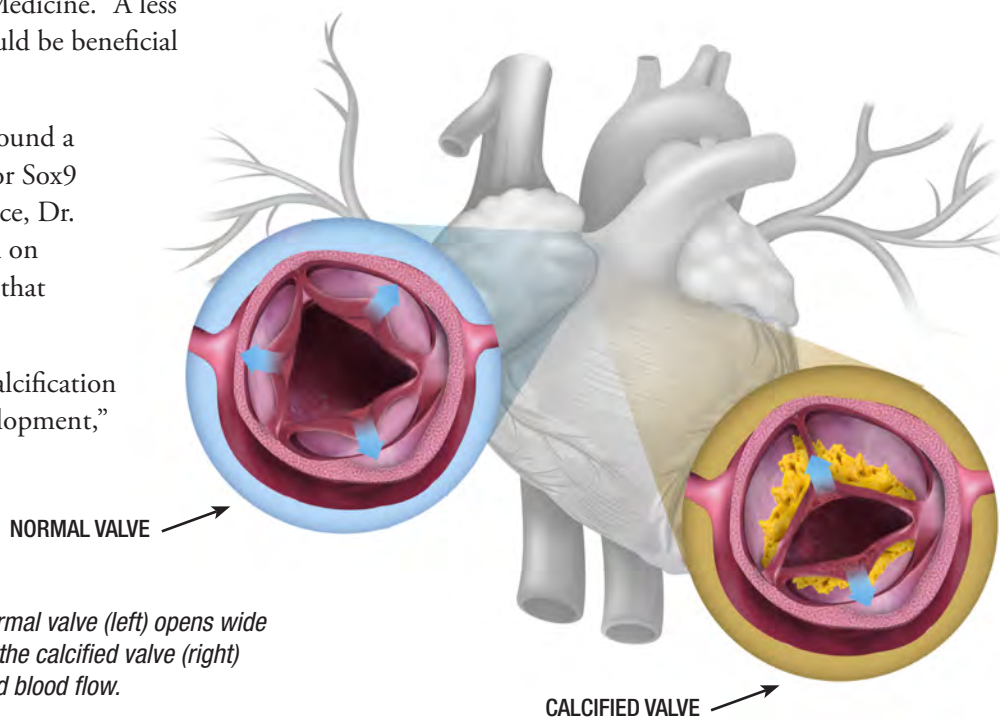
In mouse, porcine and human *in vitro* assays of isolated valve cells, they found that Tgfb β 1 is secreted by the layer of endothelial cells that overlie the aortic valve and molecularly communicate with underlying valve interstitial cells to regulate Sox9 expression. In mice, loss of Tgfb β 1 in the valve endothelium leads to a reduction in Sox9 expression in interstitial cells and subsequent CAVD.

“Tgfb β 1 promotes calcification in the bone,” Dr. Lincoln says. “But, in our system, it had the opposite effect, which was surprising to us.”

She believes that changes found in the signaling pathway could possibly be used to help identify molecular landmarks of CAVD, leading to earlier diagnoses.

The researchers are now investigating how genetic, environmental and biomechanical factors may trigger or influence the calcification process and whether they can manipulate signaling pathways or cell function to either reverse the disease or stop it from getting worse.

— Kevin Mayhood



Bicuspid aortic valve in diastole. The normal valve (left) opens wide to allow adequate blood flow; however, the calcified valve (right) limits cusp opening, leading to restricted blood flow.

Identifying Characteristics Associated With Timely Follow-Up Psychiatric Care

Nearly one in three youths with mood disorders receive no outpatient care within 30 days of psychiatric hospital discharge.



More than diagnoses and demographics influence whether youths receive critical outpatient care following psychiatric hospitalization. Individual attributes and aspects of the hospital where they receive treatment as well as the community they live in play roles, researchers from The Ohio State University and Nationwide Children's Hospital have found.

Outpatient care is essential to patients' success, due to short hospital stays, says Cynthia Fontanella, PhD assistant professor of psychiatry at Ohio State, who led the study. "In the 1990s, patients would be admitted and stay for months, but now it's three to five days. And that's not long enough to stabilize kids."

The highest risk period for relapse, readmission and suicide is the month following discharge. Yet nearly one in three youths fail to receive follow-up care in that time, the study shows.

"It's important to identify factors associated with timely follow-up in order to target the most vulnerable youth," says Jeffrey Bridge, PhD, director of the Center for

Suicide Prevention and Research at Nationwide Children's, and a study co-author. "We need to improve the transition from inpatient to outpatient care."

Hospitals and outpatient providers need to do more to coordinate care and tailor treatment strategies to individual patients, based on a variety of influences, the authors say.

The researchers reviewed Medicaid records of 7,826 youths ages 6 to 17, admitted to psychiatric hospitals with a primary diagnosis of mood disorders. Half failed to receive outpatient care within a week of discharge and 31 percent failed within 30 days.

The strongest predictor for receiving timely follow-up care is having had an outpatient visit prior to hospitalization.

"It's likely that having a relationship with an outpatient provider prior to discharge drives this finding," Dr. Fontanella says. "It suggests we need more bridging strategies connecting patients with outpatient providers while they're still receiving inpatient care."

Children in foster care, those who have a psychiatric comorbidity, youths who received their care in a teaching or psychiatric hospital and patients who live in counties with more child and adolescent psychiatrists are all more likely to receive outpatient care within 30 days.

The strongest predictor against timely follow-up treatment is substance abuse. Other negative predictors are older age and race — African Americans were least likely to receive outpatient care compared with other racial or ethnic groups.

Treatment in a hospital with higher concentrations of Medicaid patients was tied to longer waits, possibly due to the lack of outpatient providers in the system.

— Kevin Mayhoo

Predicting Risk for Chronic Renal Disease in Children

Studies using a new contrast agent have the potential to determine if infants born premature develop a full complement of nephrons.

A new magnetic resonance imaging contrast agent enables researchers to see the number and volume of blood-filtering nephrons in rodent kidneys and donated human adult kidneys, potentially offering a way to diagnose chronic renal disease far earlier than current methods.

The findings may be especially important for diagnosing and monitoring children born prematurely, says Jennifer Charlton, MD, a pediatric nephrologist involved in the research. Chronic renal disease results when a patient has too few nephrons to filter the blood and rid the body of extra water.

“You create all of your nephrons for all of your life by the time you’re born full-term, and most of those nephrons are formed in the last trimester of pregnancy,” says Dr. Charlton, who is also an assistant professor at the University of Virginia School of Medicine. “So if you’re born prematurely, do you complete this process normally? We don’t know.”

John David Spencer, MD, a nephrologist and principal investigator at the Center for Clinical and Translational Research at Nationwide Children’s Hospital, says, “This technique may be able to tell us how prematurity increases the risk for kidney disease, who will develop it and who won’t, and enables us to evaluate the development of kidney structure and function as patients grow up.”

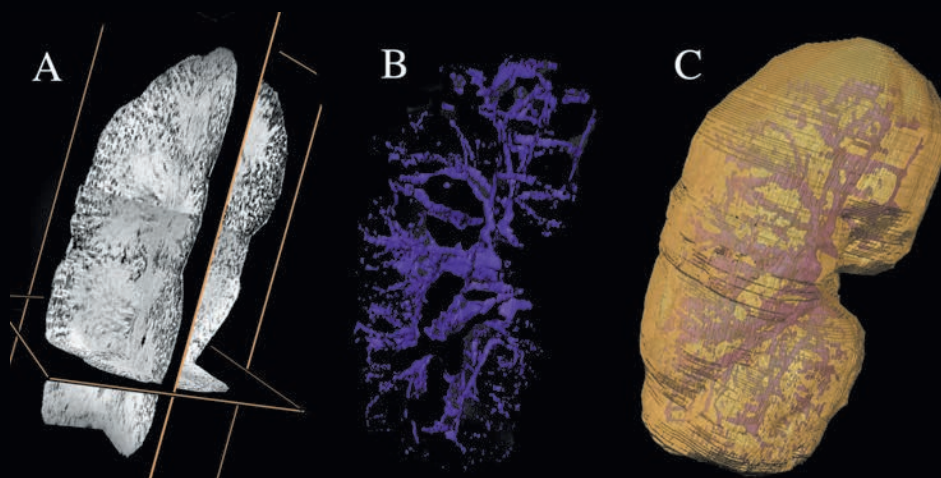
“Early identification of at-risk patients,” says Dr. Spencer, who is not involved in the research, “will potentially allow them access to care or treatments that can limit the progression and/or prevent side effects of kidney disease.”

The commonly used test for waste products in the bloodstream tells how kidneys are functioning, but patients may lose half of their nephrons before changes are evident. And a biopsy from one region of the kidney may not provide the full picture of the organ.

Dr. Charlton and her colleagues seek images of all the glomeruli, the capillary networks that filter blood in each nephron, in real time. Kevin Bennett, PhD, associate chair of the Biology Department at the University of Hawaii at Manoa, developed the agent, cationized ferritin (CF). Injected into the bloodstream of rodents and the renal artery of donated adult kidneys (from patients with varying levels of kidney and cardiovascular disease), CF particles bound to the glomeruli. Magnetic resonance images were used to determine nephron numbers, volume and distribution.

If the contrast agent proves unworkable in infants, Dr. Charlton says it may still be useful in testing the quality of donated kidneys prior to transplantation and monitoring the effects of toxic drugs on the kidneys. The agent could also show whether treatments increase or decrease nephron numbers or volume.

— Kevin Mayhood



(A) CF-labeled glomeruli in a neonatal kidney detected using GRE-MRI. (B) Major vasculature identified and visualized in relationship to the cortex of the kidney. (C) Overlay of the vascular and cortical structures.



On the Front Lines

Pediatricians can reverse health disparities among the LGBT population.

A recent position paper from the American College of Physicians (ACP) examines health disparities experienced by the lesbian, gay, bisexual and transgender (LGBT) population in the United States and includes recommendations for improving access to care.

The ACP found that some policies and accompanying social stigma of LGBT persons has led to significant health disparities compared to the heterosexual population, including fewer physician visits, lower rates of preventative care and higher rates of mental illness.

“Pediatricians see not only LGBT teens but also the children of LGBT parents, so the report is impactful,” says Gayathri Chelvakumar, MD, who is a physician in Adolescent Medicine and the THRIVE program at Nationwide Children’s Hospital. The THRIVE program specializes in differences in sex development, complex urological conditions and gender concerns. Dr. Chelvakumar says pediatricians may find these ACP recommendations most useful:

The ACP encourages . . . physicians’ offices and other medical facilities to adopt gender identity as part of their nondiscrimination and anti-harassment policies. Physicians and their staff should understand the difference between gender expression and gender identity. “Many people have never considered how gender can be defined. Education for all members of the health care team is important,” says Dr. Chelvakumar.

[The ACP] recommends that . . . health benefit plans include comprehensive transgender health care services . . . “Coverage of puberty suppressing hormones and transgender

surgeries has improved recently so it’s helpful to know what coverage is available to better advocate for patients,” Dr. Chelvakumar says.

The definition of “family” should be inclusive of those who maintain an ongoing emotional relationship with a person, regardless of their legal or biological relationship. Dr. Chelvakumar notes that it is very important not to assume anything, and ask patients to clarify relationships at the beginning of the visit.

Medical schools, residency programs and continuing medical education programs should incorporate LGBT health issues into their curricula . . . [and develop programs to] recruit LGBT persons into the practice of medicine. “Our understanding of LGBT medical needs is evolving rapidly,” says Dr. Chelvakumar. “If we don’t deliver accurate and relevant care – people will get it through illegal channels or not at all. Continuing to educate ourselves and our trainees on these topics is important to provide best level care.”

The ACP opposes the use of “conversion,” “reorientation” or “reparative” therapy. While there are still a few places across the nation that offer this type of service, the practice has been widely condemned by medical organizations.

Dr. Chelvakumar says the single most important step physicians can take is to create a safe, nonjudgmental environment for patients and families. This can be done in small ways with rainbow stickers, a visible nondiscrimination policy and posters that encourage respect for differences.

— Anne FitzSimons

A Novel Approach to Pediatric Fecal and Urinary Incontinence

A 9-year-old girl with caudal regression syndrome is the first child in the United States to be treated with pudendal nerve stimulation.

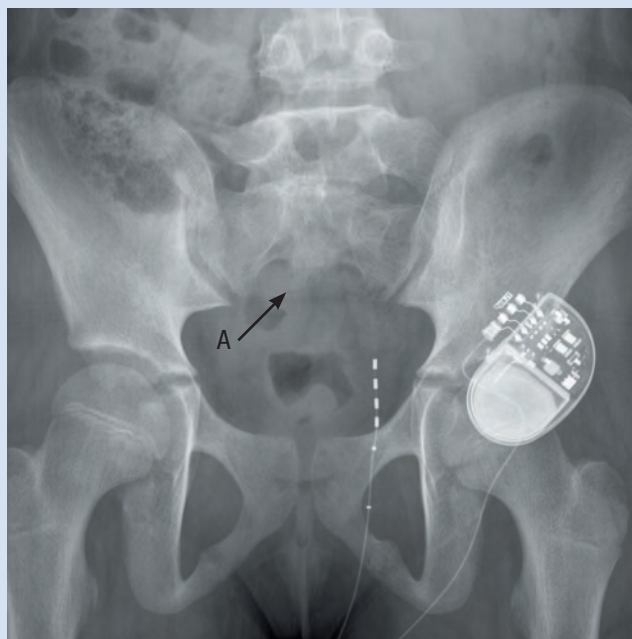
Neuromodulation of the sacral nerve, or sacral nerve stimulation, is rarely but increasingly used in children to help control fecal and urinary incontinence when standard medical management has failed. The treatment involves the implantation of a device that sends mild electrical impulses through a wire to sacral nerves which control bladder and anorectal function.

Patients with caudal regression syndrome may be missing all or part of the sacrum, however, making conventional sacral nerve stimulation impossible. That was the situation for a 9-year-old patient who had a history of refractory bowel/bladder dysfunction and came to Nationwide Children's Hospital seeking treatment in 2015. She had dysgenesis of the sacrum below the S2 vertebra, ruling her out as a sacral nerve stimulation candidate.

After further testing, however, she was found to have function in the pudendal nerve, which is also involved with bladder and bowel control. That gave Seth A. Alpert, MD, pediatric urologist and co-director of the Surgical Neuromodulation Center at Nationwide Children's, an idea. He knew of pudendal nerve stimulation treatments used elsewhere on adults with refractory bladder dysfunction and chronic pelvic pain. Could he adapt the procedure to help this 9-year-old?

"No one that we are aware of has done this in a pediatric-age patient in the United States," Dr. Alpert explains. "It uses the same technology as sacral nerve stimulation, but placement of the wire for the device is much more technically challenging in pudendal nerve stimulation. I felt that even someone with sacral nerve stimulation experience would need additional training in order to do it correctly."

So Dr. Alpert and three others from the Nationwide Children's neuromodulation team traveled to Michigan to observe Kenneth M. Peters, MD, perform pudendal nerve stimulator implantation procedures on several adults. Dr. Peters, chief of Urology at Beaumont Hospital in Royal Oak, pioneered the use of pudendal nerve treatment in the United States.



X-ray image showing the ischiorectal approach necessary in a pudendal nerve stimulator lead placement. Note the partial sacral agenesis seen in this patient (A).

Back at Nationwide Children's, Dr. Alpert and the team completed the two-phase procedure. The first surgery was placement of the subcutaneous wire with the assistance of real-time nerve electromyography monitoring and a trial of nerve stimulation with an external impulse generator. A few weeks later, the permanent implantable impulse generator was placed under the skin of the upper buttock.

The 9-year-old, who was having daily fecal accidents before the procedure, is now able to wear regular underwear and participate in sports, especially her favorite activity of basketball. Her fecal incontinence has essentially resolved.

"Although very few children will be candidates for this particular procedure, we are ideally positioned to offer unique therapies to patients with the most complicated bowel and bladder abnormalities in the Center for Colorectal and Pelvic Reconstruction," Dr. Alpert says.

—Jeb Phillips

Vaccine Fails to Reactivate Immunity to Hepatitis C Virus

T cells remain inactivated even after immunization in subjects with persistent, controlled infections.

Two papers recently published in *Hepatology* uncovered evidence of permanent immune system damage after hepatitis C virus (HCV) infection. The studies used a vaccine currently in clinical trials to attempt to restore immunity against HCV in animal models and humans with chronic HCV infection.

“In chronic HCV, CD8+ T cells are present, but they are not functioning,” explains Christopher Walker, PhD, director of the Center for Vaccines and Immunity at The Research Institute at Nationwide Children’s Hospital and lead author of the animal model study. “We wanted to see if the vaccine would illicit an immune response that would reactivate the CD8+ T cells against the virus.”

After vaccination, Dr. Walker’s team detected an increase in the T cells against the viral epitopes in the vaccine, but it could not restore the immune function of the T cells against circulating HCV.

“Our results suggest that HCV permanently damages the immune system,” says Dr. Walker, who is also a professor in the Departments of Pediatrics and Molecular Virology, Immunology, and Medical Genetics at The Ohio State University. “But we don’t know why.”

Similar results were observed by a team led by Ellie Barnes, PhD, professor of Hepatology and Experimental Medicine at Oxford University, in the first study of a potent HCV vaccine for chronically infected patients.

“Overall, the magnitude of HCV-specific T-cell responses following vaccination was markedly reduced compared to that in healthy volunteers,” says Dr. Barnes. “A potent T-cell vaccine alone is unlikely to restore T-cell immunity in chronically infected patients.”

The number of people infected with HCV has been steadily increasing over the past few years, according to the Centers for Disease Control and Prevention. In the pediatric setting, infants are acquiring this silent infection through maternal transmission, while



adolescents are developing it through IV drug use. Unless individuals are tested due to risk factors, they might be unaware of the infection until years, sometimes decades, later when symptoms arise.

“If left untreated, the liver can produce 10 trillion new viruses a day,” Dr. Walker says. “The good news is that medications to treat HCV are very good, and more and more, a cure is possible. Unfortunately, even after a cure, many patients reacquire HCV after stopping treatment.”

Increasing infection and reinfection rates underscore the importance of an HCV vaccine.

“Although the vaccine is not being used as a therapy for HCV, there remains a real need for a preventative HCV vaccine,” Dr. Barnes says.

— Abbie Roth

Helping the Sickest Children Navigate the Health Care System

Care coordination focuses on better outcomes for children with medical complexity.

Consider a child with cerebral palsy who needs a feeding tube to eat. She has special equipment for a basic life function. She requires regular visits with a primary care physician and specialists in neurology, orthopedics and gastroenterology. She has frequent acute infections that lead to emergency department visits.

“Just surviving day-to-day is intense for this child and her family,” says Sean Gleeson, MD, president of Partners For Kids. “It is very easy for these children to receive sub-optimal care, just because they have so many different points of contact with the health care system. Even when providers are doing their best for the patients, the coordination among services can be overwhelming for the family to manage.”

The group that Dr. Gleeson leads is working to change that with its care coordination program called Care Navigation. Partners For Kids is one of the oldest and largest pediatric accountable care organizations in the United States. It brings together Nationwide Children’s Hospital and more than 1,000 specialists and primary care doctors, and it is responsible for the health care of approximately 320,000 children in central and south-eastern Ohio covered under Ohio’s Medicaid Managed Care Plans.

Partners For Kids focuses on keeping children healthy with regular wellness visits. But fragile newborns and some children with chronic diseases and behavioral health conditions need more than that. So in 2013, the organization began its care coordination program.

Care coordinators — social workers, nurses and quality outreach coordinators — individually work with families to help them navigate the health care system. They visit patients at home to gain insight into a family’s particular challenges. They can help schedule several physician appointments on one day, reducing the number of trips families must make.

Care coordinators may also attend physician appointments with patients; ensure patients get screenings and interventions they need for their individual conditions;

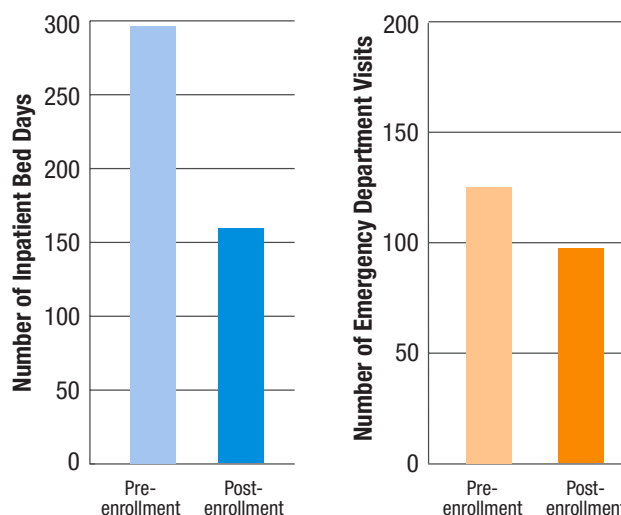
help connect patients with useful community resources; and help patients learn self-management as they grow, so they can transition successfully to adult health care.

Data from 2014 show that patients enrolled in care coordination for at least 120 days saw hospital inpatient admissions and emergency department visits decrease. Partners For Kids is working to expand the program to build on its success. The organization now has approximately 45 care coordinators. That number will more than double by 2017.

“Children with medical complexity spend the most time in the hospital, have some of the worst health outcomes, and their families have difficulty managing all that must be done,” says Kimberly Conkol, RN, Partners For Kids’ director of Care Navigation. “Care coordination helps change this reality for these patients. Our team works with the family to help them achieve their goals for the child.”

— *Jeb Phillips*

Pre- and Post-enrollment Utilization Characteristics of Selected Patients Enrolled in Care Navigation 2014



THE COLLAPSE OF BIOFILMS?

Scientists are working to eliminate the causes of countless chronic and recurrent human infections.

..... by Jeb Phillips

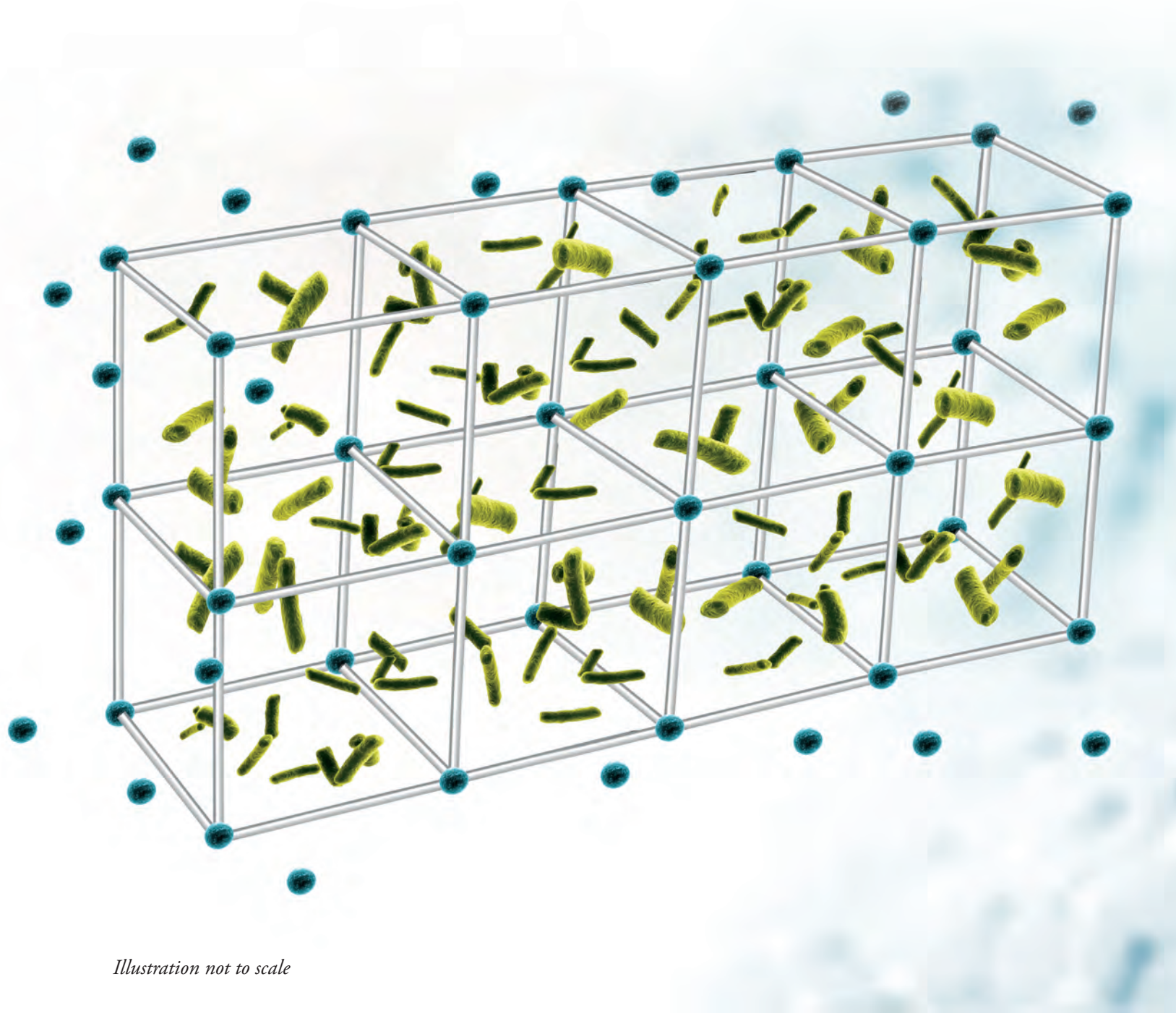


Illustration not to scale

Before the discoveries that could lead to biofilm eradication, before the idea that he was even working on treatments for the bacterial communities that are crucial to most human infections, Steven Goodman, PhD, had a mystery on his hands. For nearly 15 years.

Dr. Goodman, then a biochemist at the University of Southern California's Herman Ostrow School of Dentistry, found a certain group of proteins outside the cells of the *Streptococcus mutans* bacterium in 1994. He didn't expect that. *S. mutans* is one of the primary causative agents of tooth decay. He was studying the DNABII proteins inside the bacteria — the proteins help create the architecture of the cell's DNA.

But he had found the proteins outside, too. What could they be doing there?

"It was driving me nuts," he says.

Over time, other researchers discovered that DNA was also outside of bacterial cells. So there was extracellular DNA (eDNA), and there were extracellular DNABII proteins that could help bend the eDNA. Still, no theory that Dr. Goodman had could tie them together.

Then came Dec. 4, 2008. Dr. Goodman attended a presentation by Lauren Bakaletz, PhD, director of the Center for Microbial Pathogenesis in The Research Institute at Nationwide Children's Hospital. A vaccine she had developed targeted middle ear infections.

Organizers had asked Dr. Goodman to be a discussant — essentially, to pose questions about Dr. Bakaletz's work after she spoke.

But he didn't ask a single question. He was stunned into silence. Because as part of her presentation, Dr. Bakaletz showed a slide to illustrate the focus of the vaccine. In the background, just for context, was a large eDNA structure stained blue. It looked like a lattice. Dr. Bakaletz actually remembers saying as she showed the slide: "Ignore the blue, though I am interested in why the DNA is this perfect basketweave."

And just like that, Dr. Goodman thought he had the solution to his mystery from 1994. That blue-stained structure was the extracellular matrix of a biofilm. He believed the slide was showing a huge mass of eDNA shaped into a basketweave by the same kind of extracellular proteins he had found so long before.

"I almost fell off of my chair," he remembers. "If you are lucky, you get two or three "aha!" moments in your career. This was one."

Dr. Bakaletz, who is also a professor of Pediatrics and Otolaryngology at The Ohio State University College of Medicine, wanted to push the idea once he explained it to her. If they could prove how the extracellular matrix was put together, maybe they could collapse it. And if they could collapse a biofilm, a host of chronic microbial infections that are caused by bacterial biofilms — urinary tract infections, cystic fibrosis-

"[THE DNA AND THESE PROTEINS ARE] AKIN TO STEEL GIRDERS IN A BUILDING. THE BUILDING CAN HAVE ROOMS MADE OF WOOD OR OF PLASTER OR WHATEVER ELSE, BUT THE STEEL GIRDERS ARE THE SAME. THE PROTEINS ARE THE ESPERANTO OF STRUCTURAL MATERIAL. IT'S THE LANGUAGE EVERY BACTERIUM SPEAKS."

— Steven Goodman, PhD, principal investigator in the Center for Microbial Pathogenesis in The Research Institute at Nationwide Children's



associated infections, endocarditis, middle ear infections and many, many others — might be treatable in a way they aren't now.

“If all of this worked out, I thought it was going to be the coolest thing I had ever seen,” Dr. Bakaletz says.

A FORTRESS FOR BACTERIA

Biofilms are highly-organized communities of cells that are attached to a surface and encased in an extracellular polymeric substance or matrix. About 80 percent of bacteria live in biofilms instead of in a free-floating state, and the matrix protects the bacteria from harsh environmental elements such as the host's immune system, antibiotics and shear force.

Biofilms form on human and animal tissue, but they can form on almost any other type of surface. They can be on catheters, implanted artificial joints, medical equipment and kitchen cutting boards, says Dr. Bakaletz. They foul water and oil pipes. They create drag on ship hulls and airplane wings.

Human and animal infections can be extraordinarily difficult to treat because of the protective matrix. In fact, the most effective treatment is mechanical removal of the biofilms. That's possible with teeth and airplane wings. Not in a child's middle ear or a cystic fibrosis patient's lungs.

Beyond the protective matrix, there are other issues to consider, Dr. Bakaletz says. Bacteria in biofilms have slowed metabolisms and are no longer dividing, so antibiotics that work only on dividing cells are ineffective. And biofilms are rarely homogenous; a single biofilm is most often a consortium of different bacteria interacting with each other. The various etiologies make it difficult to knock out all of the bacteria with a single treatment.

What does appear to be consistent among many different biofilms, however, is the structure of the extracellular matrix and the way DNABII proteins work to hold the eDNA together for that matrix. The extracellular proteins that Dr. Goodman found in 1994 with *S. mutans* bacteria — the contributor to tooth decay — were the same kind of proteins that Drs. Bakaletz and Goodman found nearly 15 years later with nontypeable *Haemophilus influenzae*, a common cause of middle ear infection.

“If all of these bacteria are going to interact with one another under the same shield, then that shield needs to have the same structure,” Dr. Goodman says. “What is the biological material they all have in common? We argue it's DNA and these proteins. It's akin to steel girders in a building. The building can have rooms made of wood or of plaster or whatever else, but the steel girders are the same. The proteins are the Esperanto of structural material. It's the language every bacterium speaks.”

The proteins stabilize the biofilm matrix. Take away the proteins, and the biofilm could collapse.

COLLAPSING THE MATRIX

Before that important day in 2008, Dr. Goodman had developed an antibody to the DNABII proteins from the bacteria *E. coli*. The antibody recognized the proteins; Dr. Bakaletz used it in 2009 to show the proteins were at the vertices of the *H. influenzae* biofilm matrix. The researchers hypothesized that if they introduced the antibody while a biofilm was forming, the antibody would soak up the proteins and prevent the formation.

Dr. Bakaletz tried an even more robust experiment — she added the antibodies to an established biofilm. It should not have worked, Dr. Goodman points out. Conventional wisdom is that antibodies cannot penetrate a biofilm. So they should have no effect on an established biofilm. But they did.

“It was amazing,” Dr. Bakaletz says. “Biofilms were collapsing left and right. They were collapsing *in vitro* and *in vivo*. When a biofilm collapses in a body site and the bacteria are cleared, it means the disease is cured. We said to ourselves, ‘we have to run with this.’”

Dr. Goodman eventually joined Dr. Bakaletz at Nationwide Children's as a principal investigator in the Center for Microbial Pathogenesis. The pair has since shown that while the antibodies do not pull proteins out of biofilms, they do titrate off the proteins that occasionally detach. Those proteins cannot rejoin the extracellular matrix. When enough proteins have detached and are unable to reattach, the matrix crumbles.

That has proven to be true in every biofilm that the researchers have tested, but Drs. Bakaletz and Goodman are now working on a study about a kind of exception they have found. Proteins from the bacterium *Porphyromonas gingivalis*, which causes gum disease, are recognized by a different antibody. That

“BIOFILMS WERE COLLAPSING LEFT AND RIGHT. THEY WERE COLLAPSING IN VITRO AND IN VIVO. WHEN A BIOFILM COLLAPSES IN A BODY SITE AND THE BACTERIA ARE CLEARED, IT MEANS THE DISEASE IS CURED. WE SAID TO OURSELVES, ‘WE HAVE TO RUN WITH THIS.’”

— Lauren Bakaletz, PhD, director of the Center for Microbial Pathogenesis in The Research Institute at Nationwide Children’s



antibody is selective for the *P. gingivalis* protein and can disperse *P. gingivalis* biofilms, but it does not affect other bacterial biofilms. This suggests that it is possible to target harmful biofilms while leaving helpful ones intact.

“There are good bacteria and biofilms in our body... the gut has biofilms that are healthy for most of us,” Dr. Bakaletz says. “You don’t want to disrupt those. You do want to eradicate the most pathogenic ones if you can.”

OTHER DIRECTIONS

Scientists all over the world are working on the issue of biofilm infections. Preventing their formation with anti-adhesive surfaces and attacking young biofilms with antibiotic combinations are some of the strategies seen as having the greatest potential.

Established biofilms, like the ones Drs. Bakaletz and Goodman work on, can be more resistant to treatment. Some of the most promising recent research on eradicating established biofilms has come from the lab of Robert W. Huigens III, PhD, an assistant professor in the College of Pharmacy at the University of Florida. Dr. Huigens’ research team designs, chemically synthesizes and evaluates novel small molecules against biofilms, with the goal of bringing a biofilm-eradicating agent to the clinic for therapeutic use.

Dr. Huigens has found that a group of compounds called halogenated phenazines (HP), which are inspired by a marine antibiotic, can eradicate methicillin-resistant *Staphylococcus aureus* (MRSA) and other biofilms.

“The mechanism by which these compounds kill biofilm cells is not entirely clear,” Dr. Huigens says. “But as an alternative to antibodies and proteins, these HP small molecules infiltrate biofilms and kill the persistent bacteria inside.”

Unlike some other biofilm-eradicating agents, HPs do not “punch holes” in cellular membranes. HP small molecules show selectivity toward bacterial cells over healthy human cell types, such as red blood cells. Dr. Huigens, like Dr. Goodman, says that one of the most vexing issues with biofilm eradication is killing the bad while leaving the good. Previously discovered compounds have not made the distinction, but Dr. Huigens says that the HP compounds do.

“We have made an important first step in discovering and developing potent biofilm-killing agents,” Dr. Huigens says. “From here, it’s important to figure out exactly what is happening with these HP compounds. This will allow many different scientists with different expertise to work on this major problem too. This discovery has the potential to change people’s lives, as it is estimated that 17 million Americans are affected by biofilm infections each year.”

LONG-TERM IMPACT

That is ultimately what excites Drs. Bakaletz and Goodman at Nationwide Children's as well: the huge impact this biofilm research could have on so many aspects of human life.

"We hope to eradicate biofilm infections, but there are other applications," Dr. Goodman says. "It can be hard to find a biofilm infection in a person. Well, the antibodies can recognize biofilms, so they can be used as a diagnostic. They could recognize biofilms on food preparation surfaces and medical equipment and determine if they have been properly cleaned."

Many questions remain, Dr. Bakaletz says. Do these antibodies work on every organism? What are the

restrictions and parameters? How do we best deliver treatment? How often? Every day or just once?

All of those questions await more research. When Drs. Bakaletz and Dr. Goodman start to talk about it, though, they lean forward and their words come fast. In some ways, they seem as excited as they were on that day in 2008, when Dr. Goodman saw a blue-stained matrix and almost fell off his chair.

"We're trained to be negative and skeptical," Dr. Bakaletz says. "We're trained to ask question after question. But after a while, we just had to look at each other and say, 'this keeps on working.'"



"We are very excited about the impact that this technology could have in the treatment of chronic infections and ProclaRx is an ideal partner driving the technology forward on this front."

– Matt McFarland, RPh, PhD, director of the Office of Technology Commercialization

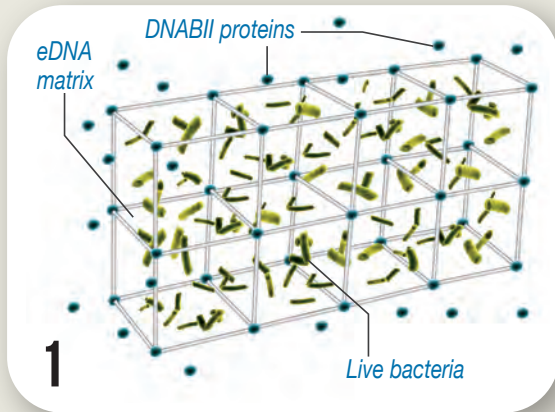
The biofilm discoveries from Drs. Bakaletz and Goodman have spawned a biotechnology company, ProclaRx. Initially called Lattice Biotech when it was formed in 2014, ProclaRx wants to bring the biofilm matrix collapse work done at Nationwide Children's to the marketplace.

Drs. Bakaletz and Goodman are co-founders, co-chairs and scientific advisors to ProclaRx. The executive leadership is comprised of other scientists with long histories in the biotech field, and Nationwide Children's Office of Technology Commercialization has facilitated the company's creation.

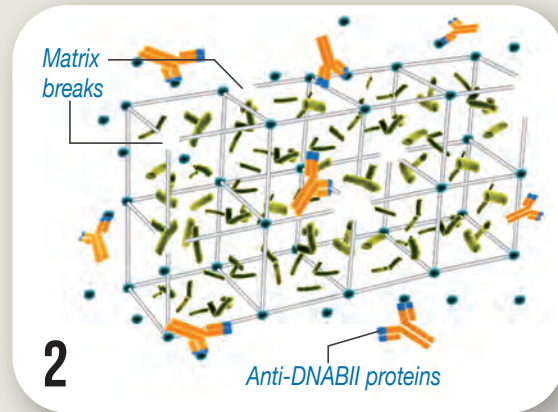
"We are very excited about the impact that this technology could have in the treatment of chronic infections and ProclaRx is an ideal partner driving the technology forward on this front," says Matt McFarland, RPh, PhD, director of the Office of Technology Commercialization. "We also recognize that this is a platform technology and may have significant implications in industries far beyond health care."

By early 2016, ProclaRx had secured \$5.5 million in investments. The company would like to begin initial clinical trials by the end of this year, according to Dr. Bakaletz.

HOW BIOFILMS COLLAPSE



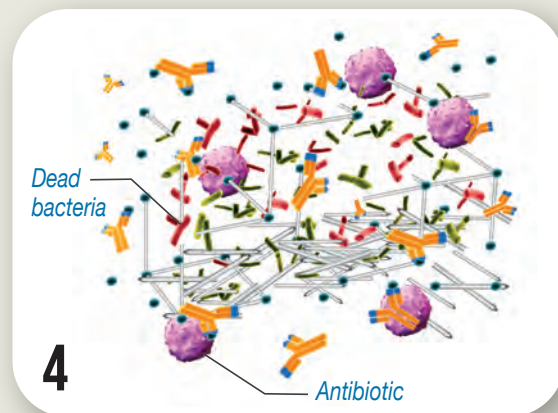
Biofilm is established. DNABII proteins provide structural integrity, protecting bacteria.



Anti-DNABII antibodies capture and titrate DNABII proteins as they dissociate from the eDNA matrix.



As equilibrium shifts, the loss of DNABII proteins induces biofilm dissociation.



The newly released bacteria are rendered susceptible to killing by antibiotics, antibodies and other therapeutics.



Join the conversation. Dr. Goodman shared one of his “aha! moments; let’s hear yours! Tweet them to @NCHforDocs using #AhaMoments.

THE JOURNEY TO A PROGRAM PROJECT GRANT

Recommendations from a multi-institutional research team who persevered to obtain a P01 to develop a vaccine for RSV.

..... by *Tiasha Letostak, PhD*

In 2015, the National Institute of Allergy and Infectious Diseases (NIAID) awarded a \$6.75 million program project grant to Mark Peeples, PhD, Octavio Ramilo, MD, and M. Asuncion Mejias, MD, PhD, all principal investigators in the Center for Vaccines and Immunity at The Research Institute at Nationwide Children's Hospital.

Unbeknownst to the public, however, the acquisition of this funding was a multifaceted endeavor that involved connecting with research experts from multiple institutions and persevering through three consecutive years of grant submissions.

“For investigators looking to collaborate on multi-project research, a program project grant, or P01, offers multi-disciplinary, long-term funding,” says Dr. Peeples, who is also a professor of Pediatrics at The Ohio State University. “Unlike an individual basic research (R01) grant, however, a P01 is far more complex in terms of its research scope and budget.”

According to Dr. Peeples and colleagues, successful P01 submissions have a number of critical, shared characteristics.

“In addition to innovatively tackling a clinically significant topic, our team's broad spectrum of expertise was a strong contributor to success,” explains Dr. Ramilo, who is also chief of Infectious Diseases at Nationwide Children's and a professor of Pediatrics at Ohio State. “After

working together on a variety of projects throughout the years, we developed a history of collaboration and were able to get all the right people together in the same location to meet periodically.”

The precipitating event was a 2010 meeting of investigators from the Center for Vaccines and Immunity who were interested in respiratory syncytial virus (RSV).

“Dr. Ramilo was understandably frustrated with the lack of a vaccine for the overwhelming number of RSV patients at our hospital,” says Dr. Peeples. “But he was unaware of the obstacles in terms of what it takes to develop a protective immune response, so I shared my personal insights.”

By the end of that initial meeting, Drs. Ramilo and Peeples had identified five problems, potential solutions for each and rough outlines of projects to reach these solutions. Dr. Mejias was also on board and convinced that it was the way to proceed, but the three-person team needed additional collaborators to fill the gaps of their expertise.

Their search for colleagues led them to include Jianrong Li, DVM, PhD, and Stefan Niewiesk, DVM, PhD, both from Ohio State's School of Veterinary Medicine, as well as Michael Teng, PhD, from the University of South Florida. Two decades earlier, Dr. Teng had been an NIAID postdoc in the same lab where Dr. Peeples was on sabbatical.

“Our expanded team began meeting every two months, Skyping in Dr. Teng, to discuss how to demonstrate feasibility for all our projects,” explains Dr. Peeples. “And by sharing progress toward those goals, we built momentum with each meeting.”

In early 2013, they began discussions with their Program Officer at NIAID. By the summer of 2013, they submitted an extensive Letter of Intent which needed to be, and was, approved by NIAID. Ten weeks later, they submitted their first P01 grant application.

Although the first submission received a respectable score, it was not sufficient for funding.

The team continued to troubleshoot how to improve their impact scores, from leveraging commonalities in their research projects to generating additional data to boost the strength of their resubmissions. As a backup, Dr. Teng also submitted his project as an R01 at the same time as the P01 submissions.

“Our second submission a year later was greatly improved and received an excellent score,” says Dr. Ramilo. “As our team was preparing for a third and final submission in the fall of 2015, we were unexpectedly awarded the grant from funds remaining at the end of the fiscal year.”

“We were very happy to accept the award, even though it was for less than we had hoped,” says Dr. Niewiesk, who is a professor in the Department of Veterinary Biosciences at Ohio State. “We’re now working to partner with big pharma, because we need help to move as fast as possible into animal model studies and clinical trials.”

“Our goal is to develop a live, attenuated virus for RSV that can be given as nose drops to infants,” adds Dr. Mejias, who is also an infectious diseases specialist and an associate professor of Pediatrics at Ohio State. “We also hope to improve production efficiency of the



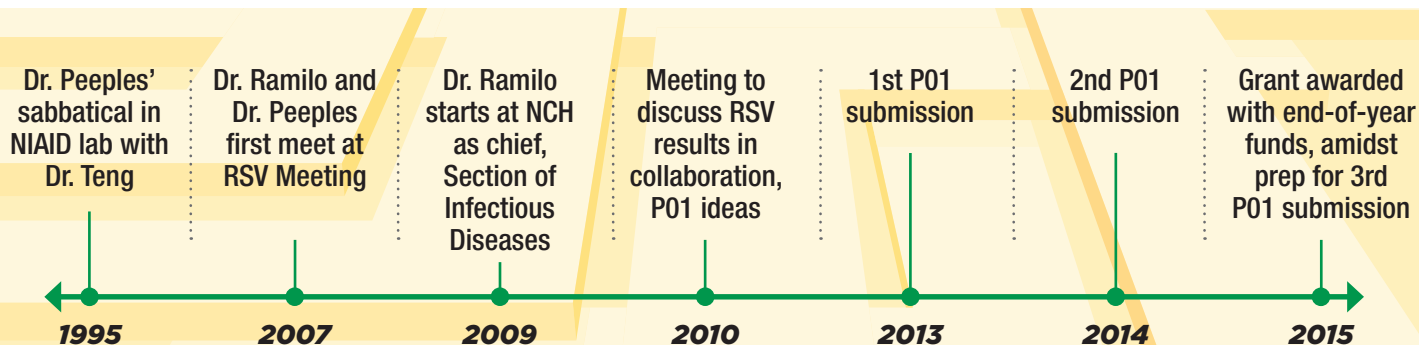
Mark Peeples, PhD, M. Asuncion Mejias, MD, PhD, and Octavio Ramilo, MD, principal investigators in the Center for Vaccines and Immunity.

vaccine and develop new methods to evaluate its safety and effectiveness.”

GUIDANCE FOR PREPARING A MULTIPROJECT RESEARCH APPLICATION

According to the National Institutes of Health, a program project grant or P01 features the following five features:

1. At least two interrelated research projects related to a theme, with each capable of standing on its own scientific merit but complementing one another.
2. Collaboration and interaction among projects and investigators to achieve a common goal.
3. Synergy among projects.
4. One grantee institution that will be legally and financially responsible for the use of funds.
5. Support as needed for shared resources — core resources or facilities — that provide services or resources to at least two research projects.





ACHIEVING CLARITY

Multidisciplinary Team from Nationwide Children's wins International Genomics Competition

..... by *Abbie Roth*

Accurate, patient-centered, comprehensive. That's how the judges and leaders of the CLARITY Undiagnosed Challenge described the work of a team from Nationwide Children's Hospital. Those same words could be used to describe the highly motivated and diverse team who surprised themselves by winning the challenge.

"When we entered the challenge, we knew we would learn a lot. We believed we could help the families involved in the cases in their search for answers. But

we didn't know we would win," says Peter White, PhD, team leader and director of the Biomedical Genomics Core in The Research Institute at Nationwide Children's.

In 2015, Dr. White and his team of clinical practitioners and research scientists entered the CLARITY Undiagnosed Challenge with 25 other teams from around the world.

The CLARITY challenges are led by Boston Children's Hospital as a way to bring together the best teams in the world to address genomic research and clinical

challenges. The first challenge, launched in 2012, focused on interpreting genomics data.

In 2015, the program coordinators met Katia Moritz, a psychologist and documentary filmmaker. She is also a patient with an undiagnosed illness. This meeting inspired the course of the next challenge and brought the undiagnosed illnesses of five families into focus for a worldwide crowdsourcing effort.

KATIA'S STORY

Katia Moritz, PhD, ABPP is clinical director of the NeuroBehavioral Institute and a board certified cognitive and behavioral therapist specializing in children and families affected by anxiety disorders, autism and obsessive compulsive disorders. Upon waking from a routine endoscopy in 2010, she began suffering from flu-like symptoms, severe pain in her upper right quadrant, difficulty swallowing, headaches, low grade fevers, pain behind her eyes, muscle fatigue and cramping, hair loss, blood-flow difficulties in her extremities and other struggles. Her muscle problems are getting worse and, at times, she has trouble breathing.

Extensive testing and visits to countless specialists failed to diagnose the cause of Dr. Moritz's symptoms, and she joined the ranks of the millions of people around the world suffering from an undiagnosed disease.

In her journey to find an answer for her own illness, Dr. Moritz began meeting other undiagnosed patients. Even though their symptoms were different, they were

connected by the loss, abandonment and frustration they felt with a medical system that does not have a way to care for them.

"Undiagnosed patients are looking for a community, a sense of identity and a medical home where they can receive treatment," she explains. "We truly are medical refugees looking for asylum."

It was this, and her strong desire to help others, that led to the documentary film UNDIAGNOSED: Medical Refugees. For the past several years, Dr. Moritz and her production team have been traveling around the country documenting the stories of undiagnosed patients.

"My life is about helping people with severe and debilitating anxiety disorders," says Dr. Moritz. "Because I am healthier than many of the undiagnosed patients, I am also able to help the undiagnosed community by being an advocate to the patients and their families who are fighting to get proper care and support in order to survive."

In interviewing the leaders at the Undiagnosed Diseases Network (UDN), a project of the National Institutes of Health (NIH), Dr. Moritz was introduced to CLARITY co-organizers, Isaac Kohane, MD, PhD, chairman of the Department of Biomedical Informatics at Harvard Medical School, and Alan Beggs, PhD, director of The Manton Center for Orphan Disease Research at Boston

.....

“ The current state of the science is this: if you are undiagnosed and undergoing genomic studies, there is a 1 in 3 chance of finding a mutation we can attribute the disease to. But why 1 in 3? Can we do better? ”



– Alan Beggs, PhD, director of The Manton Center for Orphan Disease Research at Boston Children's

Children's. Out of their meeting, CLARITY Undiagnosed was born.

CLARITY UNDIAGNOSED

CLARITY Undiagnosed became a call to arms for the five patient families featured in the documentary. Applying next-generation sequencing and genomic analysis, teams from around the world worked to answer one question: Why are these patients sick?

“We wanted to put the power of genomics into action,” says Dr. Beggs. “The patients in the challenge were the toughest of the tough. They all had extensive previous workups and a slew of the country's best physicians reviewing their cases.”

The crowdsourcing approach of the international challenge brings together the brightest minds in clinical and research genomics. With the world's experts focused on the same small set of patients, organizers hoped for a breakthrough.

“The current state of the science is this: if you are undiagnosed and undergoing genomic studies, there is a 1 in 3 chance of finding a mutation we can attribute the disease to,” says Dr. Beggs. “But why 1 in 3? Can we do better?”

According to Dr. White, who led the winning Nationwide Children's team, undiagnosed patients face three possibilities with each genomic study:

Door #1: They receive a specific diagnosis for which there is a known treatment.

Door #2: They receive a specific diagnosis for which there is currently no known treatment, and their clinical care remains focused on symptom management while they wait for more research. This outcome is still extremely helpful because it ends the odyssey to find the cause and also, often provides the family with accurate information about the risk of the disorder happening again in the family.

Door #3: Nothing turns up. This is, of course, disappointing for the families and the medical professionals. However, the disorder could still be genetic because the current belief is that, at most, 50 percent of such disorders can be detected using this technology.

“One of the important things to keep in mind for these

families is that knowing the cause of their illness — even if it doesn't lead to a therapy — is life changing,” says Dr. White. “We were driven by the desire to give these families answers.”

GETTING TO WORK

The research teams participating in the CLARITY Challenge were given whole genome sequences for each of the patients in question and selected affected and unaffected family members. From there, it was up to each team to analyze and interpret the findings and ultimately, generate a report containing meaningful information to be shared with the families.

Next-generation sequencing produces incredible amounts of raw data to be analyzed before a clinical team can begin to apply the data to diagnosing the patient. Churchill, a novel computational pipeline developed by Dr. White and his lab, expedites this genomic analysis without compromising quality or accuracy.

“Churchill has been tested time and time again and found to be an unparalleled tool for providing fast, accurate analysis of genomics data,” says Dr. White. “By using this tool, we could move on to the next step quickly and with confidence.”

The next step, explains Dr. White, was to annotate each patient's genetic variants — sites in their genome that differed from the gold standard human reference genome — in order to narrow the list to the 200 to 300 variants that may be functionally relevant to their disorder. Then, they were faced with the daunting task of analyzing those few hundred variants to determine if any of them could be implicated in a disease.

This prioritization process was a complex, cooperative effort between the research and clinical teams.

“The bioinformatics component, the sequencing and even the analysis — with the help of Churchill — is constantly getting better, faster and cheaper,” says Gail Herman, MD, PhD, principal investigator for the Center for Molecular and Human Genetics at The Research Institute at Nationwide Children's and clinical leader on the CLARITY team. “However, taking the analysis data and figuring out which variants might be implicated in disease processes is a challenging endeavor requiring extensive collaboration between research and clinical teams.”

“ One of the important things to keep in mind for these families is that knowing the cause of their illness — even if it doesn’t lead to a therapy — is life changing. We were driven by the desire to give these families answers. ”

— Peter White, PhD, director of the Biomedical Genomics Core in The Research Institute at Nationwide Children’s



“These are the most clinically complex cases, overall, I’ve ever seen,” Dr. Herman continues. “With the informatics and computation getting better, a big differentiator in genomics analysis is clinical skills. We have top-level clinicians here, and we threw everything we had at these cases.”

THE IMPORTANCE OF REPORTING

In the CLARITY Undiagnosed challenge, reporting was a key component of the competition.

“The first CLARITY challenge was about data, science and gaining knowledge,” explains Dr. Beggs. “But CLARITY Undiagnosed was all of that and how to bring it back to the patient and their medical team.”

When presenting genomics results to patients and their families, the way the information is presented is very important, says Dr. Beggs. In particular, physicians and researchers need to talk about the boundaries of what they know: sensitivity and specificity.

“Dr. White’s team did this well. The technical and clinical reports and the genetic counseling letter for families were outstanding examples of how we need to share the

results of genomics studies with physicians and families in a meaningful and accessible way,” says Dr. Beggs.

Using guidelines developed by the American College of Medical Genetics and Genomics (ACMG) for classifying sequence variants and for reporting secondary findings, all of the data were gathered into the reports and the letters.

According to Dr. Herman, Nationwide Children’s long history of providing state of the art clinical genetics patient care and their multidisciplinary approach to the challenge provided the necessary groundwork to stand out in terms of reporting.

“Multidisciplinary is a term that’s probably overused, but that’s what our team was,” adds Dr. Herman, who is also a professor in the Department of Pediatrics at The Ohio State University and past president of the American College of Medical Genetics. “To do this work, multidisciplinary is what you need.”

“The main objective of CLARITY Undiagnosed was to merge the research and clinical sides of the problem. Nationwide Children’s picked up on this concept and

CLARITY Undiagnosed Challenge Registrants

1. Bina Technologies (Redwood City, CA)
2. Centre for Genomic Regulation (CRG) (Barcelona, Spain)
3. Clinical Institute of Medical Genetics (Ljubljana, Slovenia)
4. Codified Genomics, LLC (Houston, TX)
5. Emory University School of Medicine (Atlanta, GA)
6. Enlis Genomics (Berkeley, CA)
7. Geisinger Health System (Danville, PA) and SimulConsult (Chestnut Hill, MA)
8. Gene.us (Austin, TX)
9. Genomatix Software GmbH (Munich, Germany)
10. Institute for Systems Biology (ISB) (Seattle, WA) and Inova Translational Medicine Institute (ITMI) (Falls Church, VA)
11. intelliseq (Krakow, Poland)
12. Invitae Corporation (San Francisco, CA)
13. Mendelics (Sao Paulo, Brazil)
14. Miti Medicine Inc. (Cambridge, MA)
15. Nationwide Children's Hospital (Columbus, OH)
16. QIAGEN (Redwood, CA)
17. Rare Genomics Institute (Hanover, MD)
18. Seven Bridges Genomics (Cambridge, MA)
19. SNPedia (Potomac, MD)
20. SolveBio (New York, NY)
21. Stanford University (Stanford, CA)
22. University of Southern California (Los Angeles, CA)
23. University of Utah (Salt Lake City, UT)
24. Tel Aviv University (Tel Aviv, Israel), and Variantyx Ltd (Ashland, MA)
25. Tute Genomics (Provo, Utah)
26. WuXi NextCODE Genomics (Cambridge, MA)

really embodied it — particularly with their inclusion of the patient letter,” says Dr. Moritz, who was also part of the challenge planning committee. “It’s science, but it’s about the patient.”

To bridge the gap between physicians and family and to mimic the type of care they would provide to a family seen at Nationwide Children’s, the three genetic counselors and physicians on the CLARITY team included genetic counseling letters to the families. These letters compassionately explained the work the team had done and what was found in language a lay person could understand.

“Having a letter following up the genetic counseling conversation is very important, and a lot of research has been done to show its importance,” says Dr. Beggs.

In this case, the letters were supplied in lieu of face-to-face counseling.

“Because we were not able to meet with the families in person, it was crucial for us to provide the letters,” says Elizabeth Varga, MS, LGC, a licensed genetic counselor who is also an adjunct assistant professor of Pediatrics at Ohio State. “The letters were very similar to patient letters we do for any patient who has had genetic testing.”

In any genetic study, but especially in genomic studies, secondary — originally called incidental — findings are common. When researchers perform genomic testing, they get data not only about potential disease-causing genes related to the patient’s current disorder or illness, but also about genes that might carry unrelated long term risks for their own or their relatives’ health. Examples include genes associated with a strong predisposition to cancer or potential sudden cardiac death.

“ Multidisciplinary is a term that’s probably overused, but that’s what our team was. To do this work, multidisciplinary is what you need. ”

— Gail Herman, MD, PhD, principal investigator for the Center for Molecular and Human Genetics in The Research Institute at Nationwide Children’s



Though searching for those genes was not the objective, researchers have a clinical and ethical obligation to communicate the secondary results to the family.

The President’s Commission on Bioethics and ACMG recently recommended, if patients so choose, a search for those genes whenever clinical genomic sequencing is performed.

“In genetic counseling, you have to think about the ethical, social, familial and reproductive risks for the conditions and risk factors in the report,” Varga says.

“You have to consider the problem of secondary findings,” agrees Dr. Herman. “When we get to clinical applications of genomics, it will be important to consider: What do you look for? What do you report? The more you include in the report, the more clinical and counseling time will be required. This is not just a matter of ethics but of cost and practicality. You have to balance the power of genomics with other considerations.”

NEXT STEPS

“At the end of the challenge, no previously described human diseases were identified,” says Dr. Beggs. “In several cases, the results provided a likely basis for the patient’s disease, but more research is needed to confirm causation.”

In one family, Dr. White’s team found a de novo mutation, which he suggests has a strong likelihood of being implicated in the disease process.

The gene GSK3A, while not linked to any known human disease, is implicated in a pathway that regulates a gene known to cause a certain disease. This particular patient suffers from symptoms consistent with the disease.

“We don’t know this is the cause, but we were able to pose an actionable hypothesis,” says Dr. White.

This seemed to be the overall trend.

It’s important to remember that while genomics is a powerful tool for diagnosing rare diseases, it usually doesn’t stand on its own. Once a candidate for pathogenesis is identified, functional testing to prove causation is needed to confirm the finding in most cases. This is typically accomplished through *in vitro* studies or animal models.

“When you find a genetic variation in so many patients with the same phenotype, you suspect association,” explains Dr. Beggs, “So you can make a hypothesis, but to really know causation, you need to do more work.”

“ The key to our success was our team. Having clinical and research professionals on the team enabled us to present concise, meaningful data in an approachable and useful way. ”

– Peter White, PhD, director of the Biomedical Genomics Core in The Research Institute at Nationwide Children’s

This additional effort is critical for expanding the knowledge base that could ultimately lead to answers for families. But it takes time. It takes resources. And it takes persistence.

In competing with leading institutions from around the world to provide meaningful genomic results to five families living with undiagnosed illnesses, Dr. White’s team created a model for genomic study. Not only did they reinforce the importance of making information accessible to physicians and families, but they also brought new hope to the families whose cases were presented.

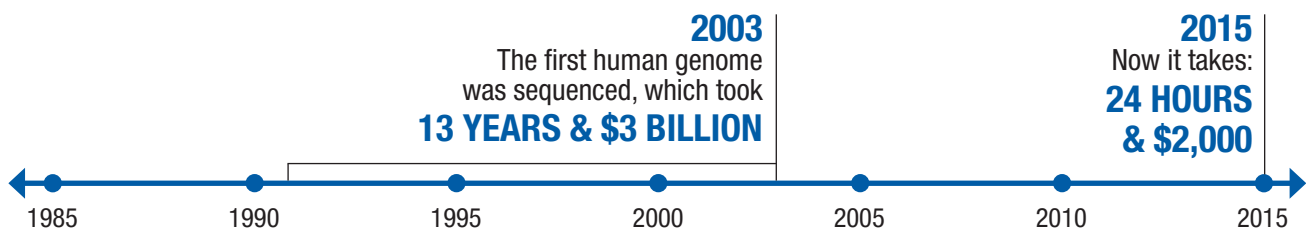
“The key to our success was our team,” says Dr. White. “Having clinical and research professionals on the team enabled us to present concise, meaningful data in an approachable and useful way.”

Dr. White and his team plan to build on their success and continue to apply all they have learned. Using the CLARITY Undiagnosed prize money and a grant through The Nationwide Pediatric Innovation Fund, a new research genomics program at Nationwide Children’s has been launched.

“We showed we could do it,” says Dr. Herman. “Let’s keep going.”

GENE SEQUENCING TIMELINE

The Human Genome Project, completed in April 2003, gave science the ability, for the first time, to read the genetic blueprint of a human being. But now, analyzing that genomic data is the main obstacle to its use.



Continue the conversation. Visit PediatricsNationwide.org/Achieving-CLARITY for additional content, including videos, the UNDIAGNOSED movie trailer and more.

Living Undiagnosed

To spend a few minutes talking with Dr. Moritz is to get a window into the life of someone with an undiagnosed illness. During our conversation, Dr. Moritz shared some important insights into what the medical community can do to help patients with undiagnosed diseases.

“One of the important things for doctors to ask patients with undiagnosed diseases is ‘How do you function?’”

Dr. Moritz says. “When conventional medical testing fails to pinpoint the cause of a patient’s symptoms, many doctors will throw up their hands and suggest the patient is suffering from a psychiatric condition. But one major difference between a psychiatric illness and a physical one is how you function.”

“Undiagnosed patients are trying to live to the best of their abilities,” she explains. “They are often accomplishing amazing things despite their limitations and uncertainty about the future. However, patients with severe anxiety and other psychiatric conditions cannot function. They become more paralyzed by their symptoms than an undiagnosed person does.”

Besides the unresolved symptoms, unanswered questions and uncertain future, patients with undiagnosed illnesses also must chart their course through a medical system that is not designed to treat people without diagnoses.

“The medical system cannot treat undiagnosed patients the same way it treats patients with a diagnosis,” says Dr. Moritz. “First, there’s the need for research and clinical collaboration. Second, you can’t diagnose someone with an unknown, unsolved, undiagnosed illness in a 20 minute visit. Doctors need to have a way to be paid for the research, the thinking, the solving and collaborating.”

Dr. Moritz also says doctors need to feel comfortable not knowing: “A scientist who doesn’t know is one who discovers.”



Photo credit: “Undiagnosed” Documentary

Dr. Moritz preparing to conduct an interview for the documentary UNDIAGNOSED

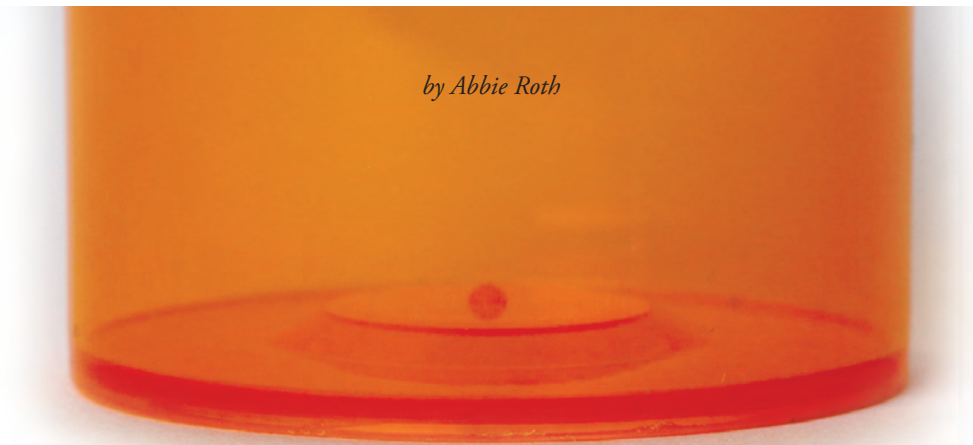


Rx Pharmacy

Everywhere Street
Everywhere, USA

Taking Aim at the Opioid Problem

by Abbie Roth



Pediatric specialists offer practical advice for protecting vulnerable patients from a growing epidemic.

The opioid epidemic in the United States is so widespread that even parents and teachers are now being issued opioid overdose kits complete with naloxone.

It's in rural communities, suburban neighborhoods and inner cities. It's so far-reaching that physicians and non-experts alike are being called to work together to save a generation. And the answers to hard questions are not illuminating a clear path to a solution.

Now, clinician-researchers at Nationwide Children's Hospital are working with regulatory groups and an organization-wide taskforce to take on the growing opioid problem. The newly formed Opioid Safety Taskforce began gathering and tracking baseline data, working with the community and legislature, and educating families in early 2016.

The state of Ohio has one of the highest rates of painkiller prescriptions in the country, with physicians writing enough prescriptions for opioids on average to give at least one script to every person in the state. The Opioid Safety Taskforce's first objective was to survey prescribing physicians to generate a baseline of prescribing practices.

"We need to get a sense of where we are as an organization and a community," says Sharon Wrona, DNP, administrative program director of the Comprehensive Pain Management Clinic at Nationwide Children's. "Looking at the survey results, we're able to identify some areas where

practice differs from the recommendations and best practices that we've been using at our hospital. Because the Comprehensive Pain Clinic is on the front lines of treating children and adolescents with chronic pain, we've developed best practices here that help us to protect and support our patients."

Changing Guidelines

According to the Centers for Disease Control and Prevention (CDC), existing guidelines for prescription opioid use vary. Primary care providers also report insufficient training regarding prescribing practices of opioid pain medication.

This prompted the CDC to develop new prescribing guidelines, which were released in March 2016 after months of controversy.

The CDC guidelines, which are focused on opioid use for chronic pain excluding end-of-life care and cancer, recommend that opioids not be treated as a routine first choice for pain management and that they be offered only for short periods of time and in low doses after other modes of treatment have failed. This is a sentiment with which Dr. Wrona whole-heartedly agrees.

"Opioids are not our first-line choices for chronic pain," she says. "We use steroids, nonsteroidal anti-inflammatory drugs, tricyclic antidepressants, antiseizure medications, muscle relaxants, as well as complementary strategies such as aromatherapy, massage, acupuncture, and physical therapy. We also use psychology and talk therapy as a component of pain management."

“ When we write the prescription, we need to talk about what to do with any leftover pain medication. Education and access are key to getting patients and families to participate in safe disposal practices. ”

– Timothy Smith, MD, director of the Comprehensive Pain Management Clinic at Nationwide Children’s

“Cancer is the main exception to the rules when it comes to managing chronic pain,” says Timothy Smith, MD, interim director of the Comprehensive Pain Management Clinic. “When it comes to managing cancer pain, the benefits of opioids are known to outweigh the risks. Controlling cancer-related pain is essential to supporting a child through cancer treatment.”

State-level prescribing guidelines fall in line with the national CDC guidelines, calling for physicians to prescribe only a minimum number of pills, discouraging automatic refill and recommending reevaluation of patients prescribed opioids at certain checkpoints.

But none of the existing guidelines are specific to pediatric patient populations.

“The pediatric population is a diverse group with complicated needs,” says Dr. Wrona. “Additional guidelines are needed for children and adolescents.”

Best Practices

At Nationwide Children’s Comprehensive Pain Management Clinic, clinicians have been creating and following guidelines and best practices regarding opioid prescription and monitoring.

▶ OPIOID AGREEMENT

One of the first things Drs. Smith and Wrona recommend for practices or clinics that treat patients with opioids is an opioid agreement. While this type of agreement is not legally binding, it serves as a contract among the patient, provider and parent. The agreement dictates that the patient will only get medications from the clinic and will submit to drug tests.

“It’s not a perfect solution, but it lays the groundwork for the patient-provider relationship,” says Dr. Wrona. “The opioid agreement starts the conversation and makes clear our expectations.”

▶ RISK ASSESSMENT AND AWARENESS

Dr. Smith suggests performing risk assessments, such as the Screener and Opioid Assessment for Patients with Pain (SOAPP), annually. “This is just one way to assess and track risk. It is also critical to talk about risks with your patients and families,” he says.

“Be aware. Know what’s being done with the medications you prescribe,” says Dr. Smith. “It’s unfortunate, but in some cases, it’s the parents diverting the meds.”

▶ OARRS REPORTS

Since 2012, physicians have been encouraged to use Ohio’s Automated Rx Reporting System (OARRS)

to see a patient's other prescriptions for controlled medications. OARRS is a database that stores all controlled substance dispensing and personal furnishing information.

"We recommend that providers check the OARRS report at every patient encounter, especially when prescribing opioids," says Dr. Wrona. "Armed with the information in the report, you may be better able to discourage 'doctor shopping' for pain medications."

"We check the OARRS report for our patients at every visit," adds Dr. Smith. "We are able to see if they are getting medications from any other prescribers and how often they are filling their prescriptions. Patients and families may be less than forthright about other prescriptions they have from other providers if they are diverting or abusing the medications."

Reviewing the OARRS report with the patient and family may be a way to open the conversation about safe habits, non-opioid adjunct therapies and risk factors.

► **STORAGE AND DISPOSAL EDUCATION**

Doctors have been heavily criticized for prescribing more pills than a patient may need, particularly after surgery or in an acute pain situation. Because many people don't know how to properly dispose of their prescription pain medications, the leftovers typically sit in the medicine cabinet, unlocked and easily accessible.

To prevent accidental ingestion or theft, the FDA recommends storing medications, including controlled substances, in lock boxes. When the medication is no longer needed, it should be disposed at a drug take-back site. "When we write the prescription, we need to talk about what to do with any leftover pain medication," says Dr. Smith. "Education and access are key to getting patients and families to participate in safe disposal practices."

"Drug take back days occur two to three times a year around Ohio, and many police stations — as well as a few pharmacies — are starting to install take back boxes," says Dr. Wrona.

According to Dr. Smith, the biggest barrier to safe disposal is security. "Many times, prescribers don't want the responsibility of being a drug take-back site

or having lock boxes for safe disposal in their facilities, because it is a liability and they could become targets for robberies."

When Addiction Happens Anyway

Guidelines are essential because, despite problems with misuse and abuse, opioid pain medication has a place in the physician's arsenal. And not everyone who uses prescription opioids will go on to abuse them or become addicted.

However, it can be difficult to know who will go from use to abuse. And, if addiction does occur, providing access to treatment is equally important to preventing opioid abuse.

"It's important to remember that many patients use opioid pain medications — sometimes for extended periods of time — without crossing the line from use to abuse," says Steven Matson, MD, who leads the Medication Assisted Treatment for Addiction (MATA) Program at Nationwide Children's. "We know that there is something uniquely biological about addiction, and it can be difficult to know what the triggers will be that will flip that switch."



— *Timothy Smith, MD, interim director and Sharon Wrona, DNP, administrative program director of the Comprehensive Pain Management Clinic at Nationwide Children's*

“ Most of these kids need something that looks like a serious substance abuse program. We work with community organizations and behavioral health specialists to ensure kids are getting the help they need. ”



– Steven Matson, MD, leader of the Medication Assisted Treatment for Addiction (MATA) Program at Nationwide Children’s

The MATA Program is an outpatient program for adolescents and young adults aged 14 to 21 years who are addicted to prescription opioids or heroin.

“Most of these kids need something that looks like a serious substance abuse program,” says Dr. Matson, who is also section chief of Adolescent Medicine at Nationwide Children’s. “We work with community organizations and behavioral health specialists to ensure kids are getting the help they need.”

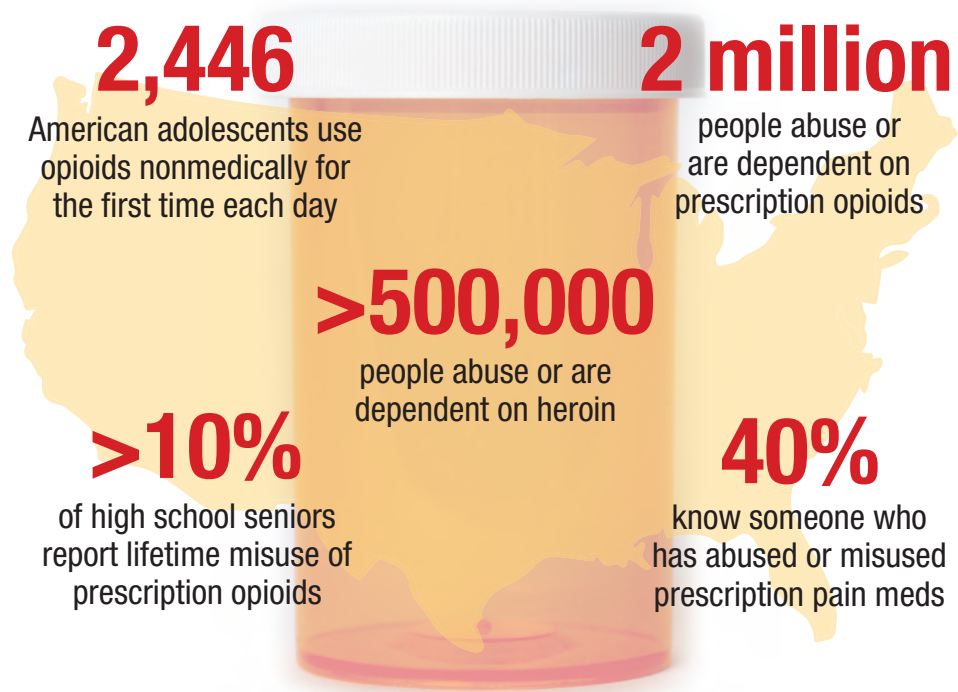
An end to the epidemic of opioid abuse and addiction will come from all sides: regulations, guidelines, prescribing practices, treatment opportunities and social awareness and support. The problem is complex, and millions of lives are at stake.

“No single intervention is going to fix the problem,” says Dr. Wrona. “But, providers who are writing prescriptions and helping patients manage pain, stressors and overall wellbeing are in a unique position to generate change.”



Join the conversation. How do you think new guidelines should address prescribing practices? Tweet us @NCHforDocs #opioidguidelines.

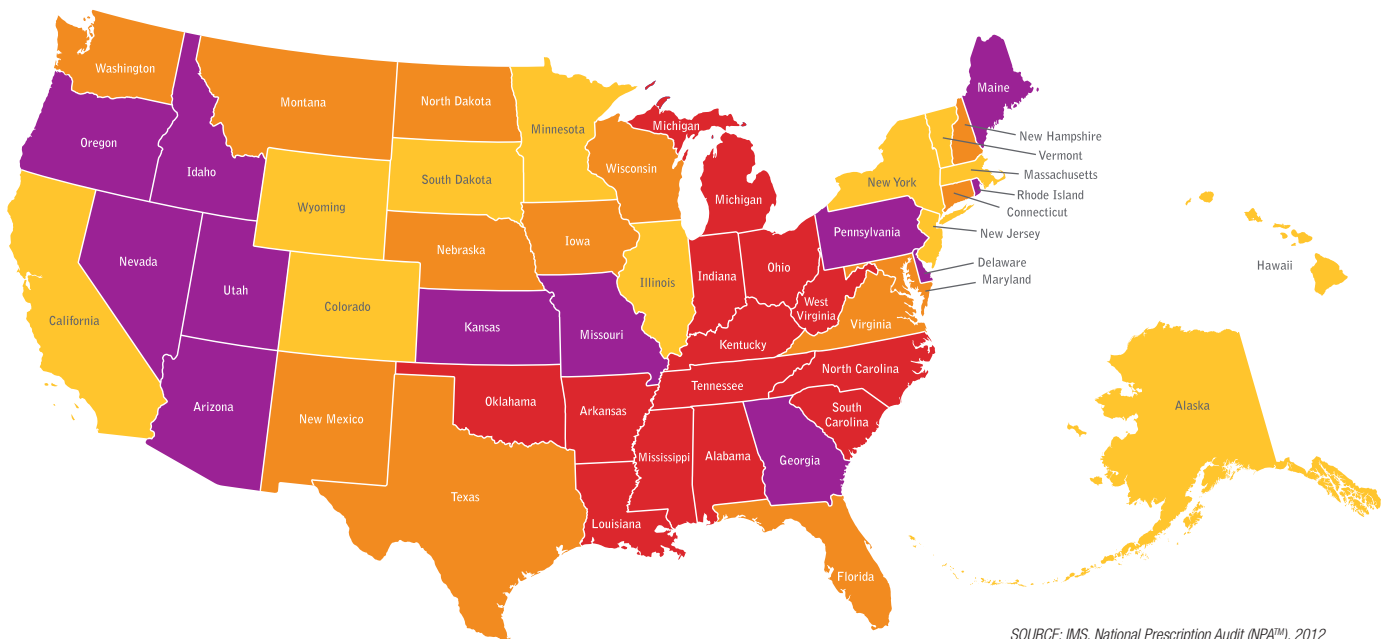
OPIOIDS IN AMERICA



SOME STATES HAVE MORE PAINKILLER PRESCRIPTIONS PER PERSON THAN OTHERS

Number of painkiller prescriptions per 100 people:

■ 52 – 71
 ■ 72 – 82.1
 ■ 82.2 – 95
 ■ 96 – 143



SOURCE: IMS, National Prescription Audit (NPA™), 2012

Remote Control Treatment

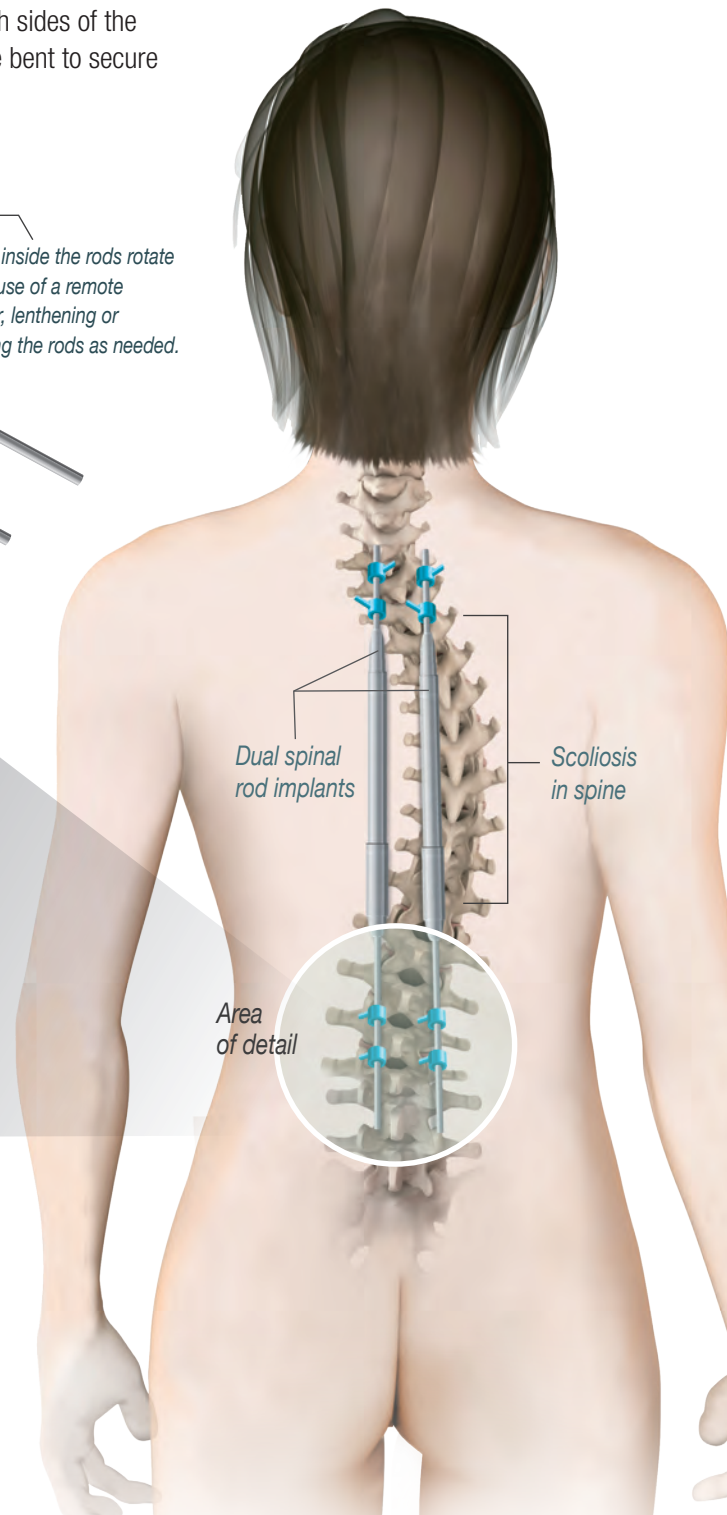
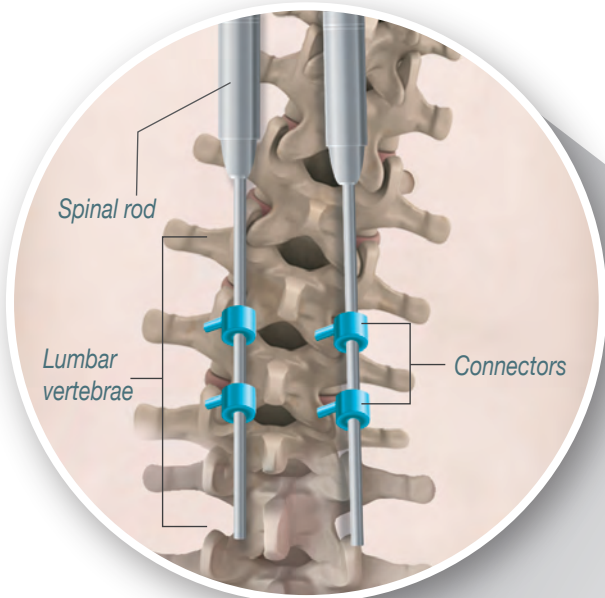
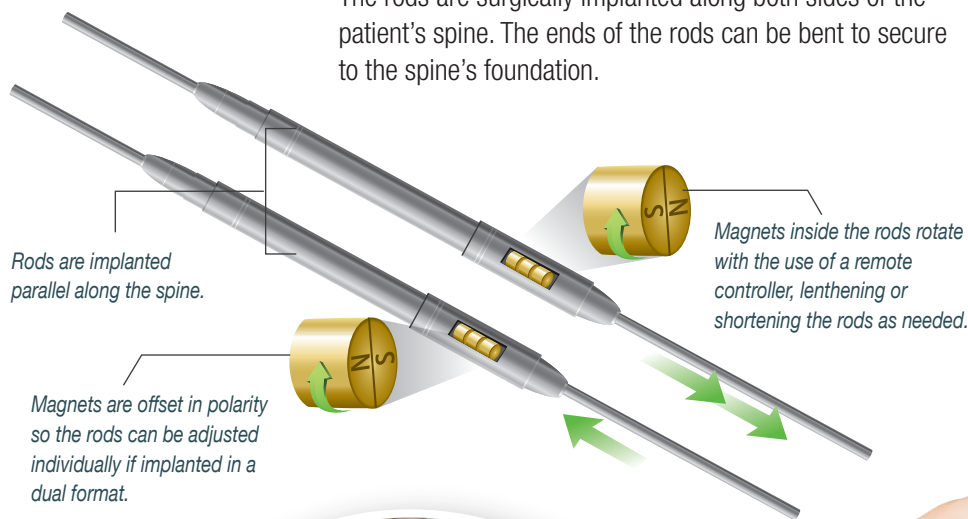
Magnetic growing rods help patients who have early-onset scoliosis avoid repeated surgeries

A common surgical treatment for young children with severe early-onset scoliosis is the implantation of growing rods or expandable titanium ribs. The devices are lengthened as the child grows, helping to straighten the spine. Lengthening involves surgery under general anesthesia every six months.

Magnetic Expansion Control (MAGEC) rods can be lengthened without an invasive procedure, however. After being implanted surgically, the rods are lengthened magnetically with an external remote control. This takes place during short outpatient visits and causes little or no pain.

► The Magnetic Growing Rods

The rods are surgically implanted along both sides of the patient's spine. The ends of the rods can be bent to secure to the spine's foundation.



► Implanting the Rods

Rods are secured using fixation devices such as screws and hooks. The rods may be attached to the rib cage and spine, or to the spine only.

Sources: Walter P. Samora, MD, and Allan C. Beebe, MD, Department of Orthopaedics, Nationwide Children's Hospital; Ellipse Technologies, Inc.

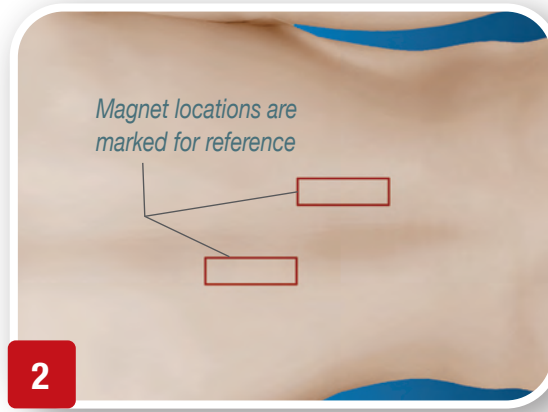
Graphic by: Christina Ullman, Ullman Design

► The Magnetic Growing Rods

The rods are surgically implanted along both sides of the patient's spine. The ends of the rods can be bent to secure to the spine's foundation.



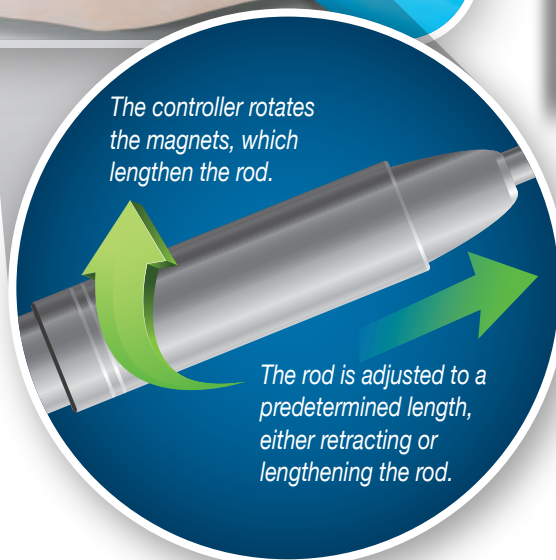
The magnets in the rods are located along the patient's spine.



The locations are noted on the patient's back for the external magnetic controller.

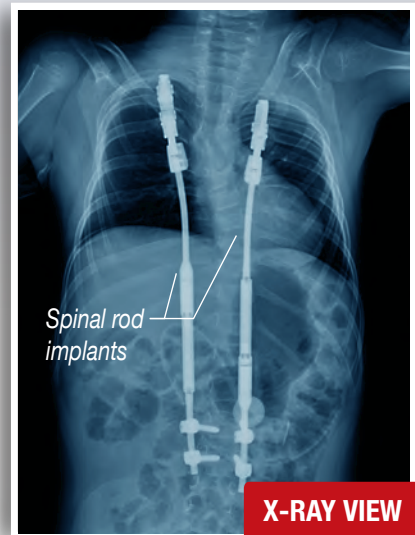


The external magnetic controller is placed over the patient's back. The controller locates the magnets through magnetic attraction, then is placed firmly over the area. The unit is controlled manually to lengthen the rods. Typically, rods are lengthened 3 mm every two months.



► Confirming the Adjustment

Lengthening the rod is confirmed through an X-ray of the patient's spine.



► Nationwide Children's and Magnetic Growing Rods

The FDA approved the magnetic growing rod system in 2014. Nationwide Children's Hospital performed its first MAGEC procedure in June 2015 and has now completed ten implantations.

Using Social Media to Advance Care

As the use of social media has grown, so has the medical community's understanding of how it can be harnessed for health care. From collaborating with peers and educating the public to building your career, physicians have a growing responsibility and growing presence in the social media arena.



David R. Stukus, MD

Section of Allergy and Immunology, Nationwide Children's Hospital

 @AllergyKidsDoc



Sarah A. Denny, MD

Department of Emergency Medicine, Nationwide Children's Hospital

 @sdennymd

Whether you embrace it, agree with it, disagree with it, or don't understand it, social media is here to stay. Our world has rapidly evolved into one in which information and opinions can be shared across continents in real time via multiple platforms.

I was motivated to start using Twitter by the constant barrage of misinformation I was hearing from not only patients but also referring physicians. It didn't take long to realize that the use of search engines for health-related information results in a flood of anecdotes from strongly opinionated and/or influential individuals, false promises of miracle cures, and professional looking websites that may provide information, only to sell a product for profit.

I decided to offer my voice to the public as a source of trustworthy, evidence-based information regarding the conditions I treat, including asthma and various allergic conditions. The response was immediate and overwhelmingly positive. I have received countless "thank yous" from parents seeking reliable information. In addition, I have established relationships with colleagues from across the world.

Additionally, I have received invitations to write posts and grant interviews from over 50 different outlets, including The Huffington Post, The New York Times, and WebMD, all of which serve to get my message to an even larger audience. I find this to be not only exceptionally rewarding and beneficial to my career but tremendous fun as well.

Ultimately, I believe that Twitter has made me a better doctor. Communicating complicated health information in 140 characters or less has taught me how to better explain information to patients, focus my message and improve my writing.

.....

I almost had to laugh when I was asked to write about social media. I hardly consider myself an expert; in fact, I naively thought that Facebook and Twitter were just a passing phase of which I wanted no part. But over time, I have realized that social media is here to stay. And as physicians, we need to take an active role in the social media conversation.

The biggest opportunity for physicians on social media is to educate the general public. There is no doubt that a significant number of people obtain their medical information from the internet — and I don't mean WebMD. I am in multiple Facebook groups, and I am shocked at the constant exchange of medical

misinformation that occurs. If physicians are not part of the social media conversations surrounding health care, people will continue to consider Jenny McCarthy and their neighborhood parents' group reliable sources of medical information. Our patients and their families are on social media, we also need to be there as a reliable source of health information, news and opinion.

Additionally, when engaging on social media, you are also building your practice and your brand. Sharing your research, blog posts and other articles of interest can help establish your reputation among patients and peers. By engaging on social media and building your brand as a physician, you are also providing a little personality to the alphabet soup behind your name. If families feel that they already know you a little, they may be more likely to come see you over the competition.

Whether your goals are combatting misinformation, growing your brand or recruiting patients, social media is an important tool for sharing your message.

Social media opens the door of opportunity for innovative solutions to common problems. Back in 2006, I faced one of those problems: how to adequately answer patient and family questions in the short time a busy office practice affords. I found many families craved evidence-based answers that were not dumbed down but still offered in terms they could understand. Of course this takes time, and I found myself repeating the same lengthy discussions. How could I provide the short answer in the exam room, while pointing families who want to know more in the right direction?

My answer came in the form of podcasts.

Prior to my career in medicine, I had worked as a disc jockey at a roller skating rink and two radio stations. And the emergence of podcasts got me thinking about it again. What if I recorded a series of episodes for parents? They would get detailed versions of the short explanations I provide in the exam room, and I could answer follow-up questions on subsequent visits. It might work!

I began listening to podcasts about making podcasts and learning the ins and outs of audio equipment, RSS feeds, internet servers, building websites and working with iTunes. The project took on a life of its own, and I realized this would be a great opportunity to share evidence-based information with a national audience of parents.

Fast forward 10 years: PediaCast is produced each week in a dedicated recording studio at Nationwide Children's Hospital. We have had millions of listeners, representing all 50 states and over 100 countries. Last year, we spun off an additional podcast — PediaCast CME — aimed at providers and available for free AMA PRA Category 1 credit.

Despite the success, my original premise remains: provide evidence-based information, don't dumb down the science, explain in terms parents can understand and put a practical spin on the presentation.



Michael D. Patrick, MD

Section of Emergency
Medicine and Medical
Director of Interactive Media,
Nationwide Children's Hospital

 @PediaCast

 www.facebook.com/PediaCast

 www.linkedin.com/in/mipatrick

PediaCast.org

PediaCastCME.org



Join the conversation. Visit PediatricsNationwide.org/features to vote in our social media poll.

Help us advance the conversation on child health.



Follow *Pediatrics Nationwide* on Twitter @NCHforDocs

to stay up-to-date on pediatric research, clinical advances, practice tools, case studies, patient education and live tweets from professional conferences. Join the community of physicians and health care providers dedicated to advancing the conversation on child health.

Join the conversation. Visit PediatricsNationwide.org for exclusive online content, physician commentaries and more.



Neurologists Urged to Consider MCA When Evaluations Don't Support Claims

by *Kevin Mayhoad*

Medical child abuse (MCA) is highly variable, but neurologists are in a position to help detect up to half of these cases, according to researchers at Nationwide Children's Hospital. Consistent with the authors' clinical experience, studies estimate that abusive caregivers make up, exaggerate or induce neurological symptoms in 40 to 50 percent of MCA cases.

PediatricsNationwide.org/medical-child-abuse

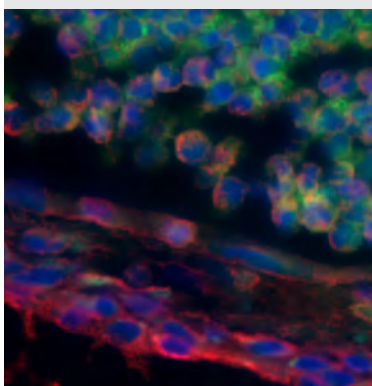


The Smallest Victims of the Opioid Crisis

by *Abbie Roth*

They didn't choose to take drugs, but they are paying the price. Infants born to mothers addicted to opioids face a difficult start to life. Care for these infants and support for the mothers to obtain prenatal care and addiction treatment during and after pregnancy is critical to improving outcomes for these families.

PediatricsNationwide.org/neonatal-abstinence-syndrome



Novel Approach Obtains Protein Signatures for Host and Pathogen With One Small Sample

by *Abbie Roth*

In the first comprehensive study of its kind, researchers have found a method to simultaneously analyze both host and bacteria protein signatures from a single tissue sample smaller than the average human biopsy. The technique described in the paper — two-dimensional liquid chromatography-tandem mass spectrometry — could change how researchers study infectious diseases.

PediatricsNationwide.org/Protein-Signatures

“Success is not final, failure is not fatal: it is the courage to continue that counts.”

– Winston Churchill

CITATIONS

Hearing Without Cochlear Nerves

Noritaka K, Yagmurli K, Matsuo S, Miki K, Abe H, Rhoton A. Auditory brainstem implantation: anatomy and approaches. *Neurosurgery*. 2015 Jun;11:306-321.

The Hearing Review (2015 February 18): ABI Trial Helps Children Born without Hearing Nerve. <http://www.hearingreview.com/2015/02/abi-trial-helps-children-born-without-hearing-nerve/>

Signaling Pathway Changes May Flag CAVD, Offer Target for Therapies

Huk DJ, Austin BF, Horne TE, Hinton RB, Ray WC, Heistad DD, Lincoln J. Valve endothelial cell-derived Tgfb1 signaling promotes nuclear localization of Sox9 in interstitial cells associated with attenuated calcification. *Arteriosclerosis, Thrombosis and Vascular Biology*. 2016 Feb; 36(2): 328-338.

Identifying Characteristics Associated With Timely Follow-Up Psychiatric Care

Fontanella CA, Hiance-Steelesmith DL, Bridge JA, Lester N, Sweeney HA, Hurst M, Campo JV. Factors associated with timely follow-up care after psychiatric hospitalization for youths with mood disorders. *Psychiatric Services*. 2016 Mar; 67(3): 324-331.

Predicting Risk for Chronic Renal Disease in Children

Beeman SC, Cullen-McEwen LA, Puelles VG, Zhang M, Wu T, Baldelomar EJ, Dowling J, Charlton JR, Forbes MS, Ng A, Wu QZ, Armitage JA, Egan GJ, Bertram JF, Bennett KM. MRI-based glomerular morphology and pathology in whole human kidneys. *American Journal of Physiology Renal Physiology*. 2014 Jun 1;306(11):F1381-F1390.

On the Front Lines

Daniel H, Butkus R for the Health and Public Policy Committee of the American College of Physicians. Lesbian, Gay, Bisexual, and Transgender Health Disparities: Executive Summary of a Policy Position Paper From the American College of Physicians. *Annals of Internal Medicine*. 2015 Jul 21;163:135-137.

A Novel Approach to Pediatric Fecal and Urinary Incontinence

Schober M, Ching C, Peters K, Alpert SA. Novel use of pudendal neuromodulation in a pediatric patient with caudal regression and partial sacral agenesis for refractory bowel bladder dysfunction. *Urology*. In press.

Vaccine Fails to Reactivate Immunity to Hepatitis C Virus

Callendret B, Eccleston HB, Satterfield W, Capone S, Folgori A, Cortese R, Nicosia A, Walker CM. Persistent HCV replication despite priming of functional CD8+ T cells by combined therapy with a vaccine and direct acting antiviral. *Hepatology*. 2015 Oct 29. [Epub ahead of print]

Kelly C, Swadling L, Capone S, Brown A, Richardson R, Halliday J, von Delft A, Oo Y, Mutimer D, Kurioka A, Hartnell F, Collier J, Ammendola V, Del Sorbo M, Grazioli F, Luisa Esposito M, Di Marco S, Siani L, Traboni C, Hill AV, Colloca S, Nicosia A, Cortese R, Folgori A, Klennerman P, Barnes E. Chronic Hepatitis C Virus infection subverts vaccine induced T-cell immunity in humans. *Hepatology*. 2015 Oct 16. [Epub ahead of print]

The Collapse of Biofilms?

Goodman SD, Obergefell KP, Jurcisek JA, Novotny LA, Downey JS, Ayala EA, Tjokro N, Li B, Justice SS, Bakaletz LO. Biofilms can be dispersed by focusing the immune system on a common family of bacterial nucleoid-associated proteins. *Mucosal Immunology*. 2011 Nov;4(6):625-637.

Brockson ME, Novotny LA, Mokrzan EM, Malhotra S, Jurcisek JA, Akbar R, Devaraj A, Goodman SD, Bakaletz LO. Evaluation of the kinetics and mechanism of action of anti-integration host factor-mediated disruption of bacterial biofilms. *Molecular Microbiology*. 2014 Sep;93(6):1246-1258.

Garrison AT, Abouelhasan Y, Kallifidas D, Bai F, Ukhanova M, Mai V, Jin S, Luesch H, Huijgens RW 3rd. Halogenated phenazines that potently eradicate biofilms, MRSA persister cells in non-biofilm cultures, and Mycobacterium tuberculosis. *Angewandte Chemie International Edition*. 2015 Dec 1;54(49):14819-14823.

Taking Aim at the Opioid Crisis

Koh, H. Community Approaches to the Opioid Crisis. *JAMA*. 2015 Oct. 13;314(14):1437-1438.

IMS, National Prescription Audit, 2012

Ohio Mental Health & Addiction Services. Opioid Prescribing Guidelines. Available online: <http://mha.ohio.gov/Default.aspx?tabid=828> (accessed Mar 2016).

Centers for Disease Control and Prevention. Draft CDC Guidelines for Prescribing Opioids for Chronic Pain. Available online: <http://www.cdc.gov/drugoverdose/prescribing/guideline.html> (accessed Mar 2016)

National Institute on Drug Abuse. Monitoring the Future Study: Trends in Prevalence of Various Drugs. Available online: <https://www.drugabuse.gov/trends-statistics/monitoring-future/monitoring-future-study-trends-in-prevalence-various-drugs> (accessed Mar 2016)

Achieving CLARITY

Corsmeier DJ, Herman GE, McBride KL, Flanagan KM, Pyatt RE, Varga E, Hashimoto S, Fitzgerald-Butt SM, Kelly BJ, Fitch J, Kuck H, Moosavinasab S, Huang Y, Lin S, White P. CLARITY Undiagnosed Challenge Final Report. The Research Institute, Nationwide Children's Hospital. 2015.

Clarity Undiagnosed. www.childrenshospital.org/clarity-undiagnosed (accessed Mar 2016)

Remote Control Treatment

Ellipse Technologies, Inc. <http://ellipse-tech.com/magec-us-spinal-deformity-correction/>

Pediatrics

NATIONWIDE

Advancing the Conversation on Child Health

Publishers

Jan Arthur
Tonya Lawson-Howard

Editor/Writer

Abbie Roth

Staff Writers

Tiasha Letostak
Jeb Phillips

Contributing Writers

Anne FitzSimons
Kevin Mayhoad

Art Director and Designer

Tanya Burgess Bender

Photographers

Brad Smith
Dan Smith

Illustrator

Christina Ullman

PEDIATRICS NATIONWIDE is published by Nationwide Children's Hospital, 700 Children's Drive, Columbus, Ohio 43205-2696. All opinions and recommendations stated in these articles are those of the authors and interviewees – not necessarily of the editors, the medical staff or the administration of Nationwide Children's. Inclusion of products, services or medications in this publication should not be considered an endorsement by Nationwide Children's. These articles are not intended to be medical advice and physicians should be consulted in all cases.

The material contained in this journal is the property of Nationwide Children's Hospital. No articles may be reproduced in whole or in part without the written consent of Nationwide Children's Hospital. For permission to reprint any articles, for additional copies and for information regarding the material contained herein, please contact Nationwide Children's Hospital at (614) 355-0485.

Disclaimer: All images in PEDIATRICS NATIONWIDE are used for artistic or illustrative purposes only. The persons displayed appear voluntarily and do not necessarily reflect the subject matter in real life. Copyright 2016 by Nationwide Children's Hospital. All rights reserved.

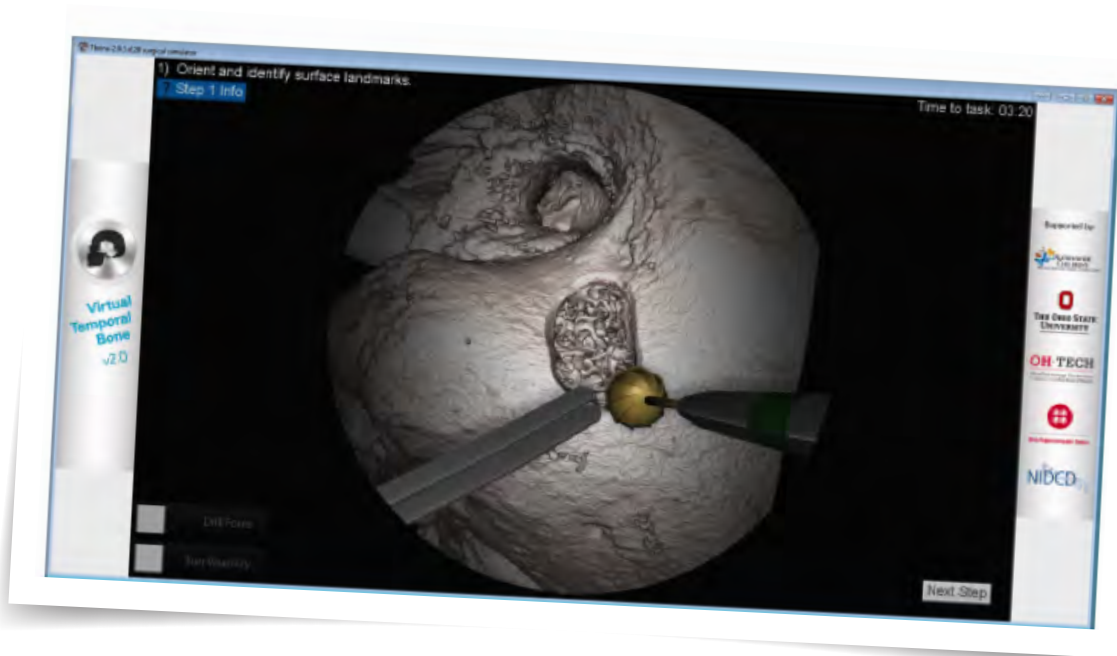


**NATIONWIDE
CHILDREN'S**

When your child needs a hospital, everything matters.™

Nationwide Children's Hospital
700 Children's Drive
Columbus, Ohio 43205-2696

NONPROFIT ORG.
U.S. POSTAGE
PAID
COLUMBUS, OH
PERMIT NO. 777



SIMULATING SURGERY WITH HIGH-PERFORMANCE COMPUTING

Mastoidectomies are common yet complex surgeries in the field of ENT that involve drilling into the temporal bone. Gregory Wiet, MD, and his team are applying high-performance computing to the field of otolaryngology through the development of a simulation environment for teaching surgical techniques related to the temporal bone. Since validating the program as a training tool in their 2012 publication, the team, which includes a national consortia of test sites, has been building on the program's success by refining the resolution of the bones, building an expansive library of bones including a neonatal temporal bone, improving the haptic feedback algorithms and developing metrics by which to score the simulations. The research is funded by the NIH/DCD through an R01 grant.

Read more about the progress the team is making at PediatricsNationwide.org/surgical-simulation.