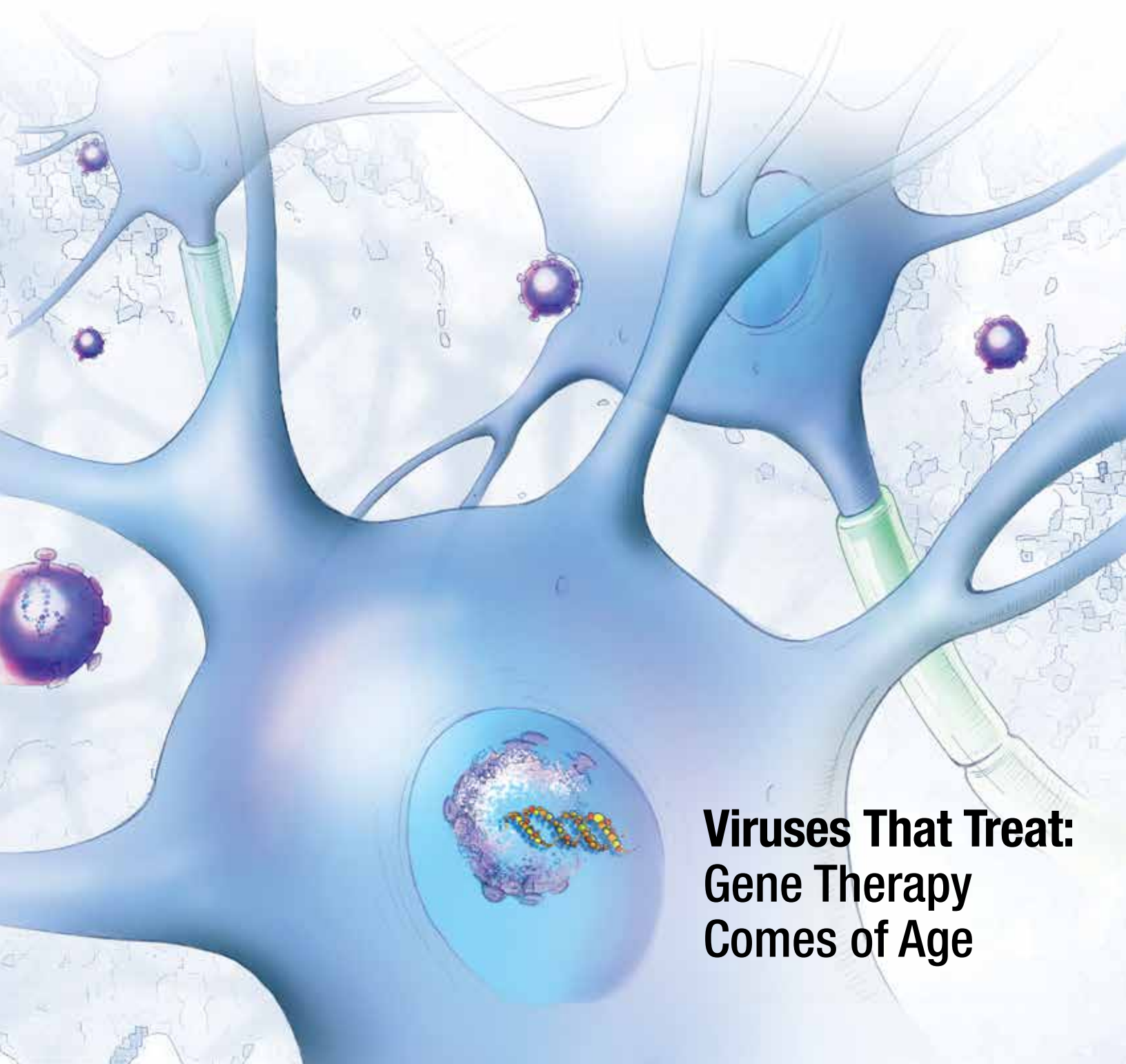


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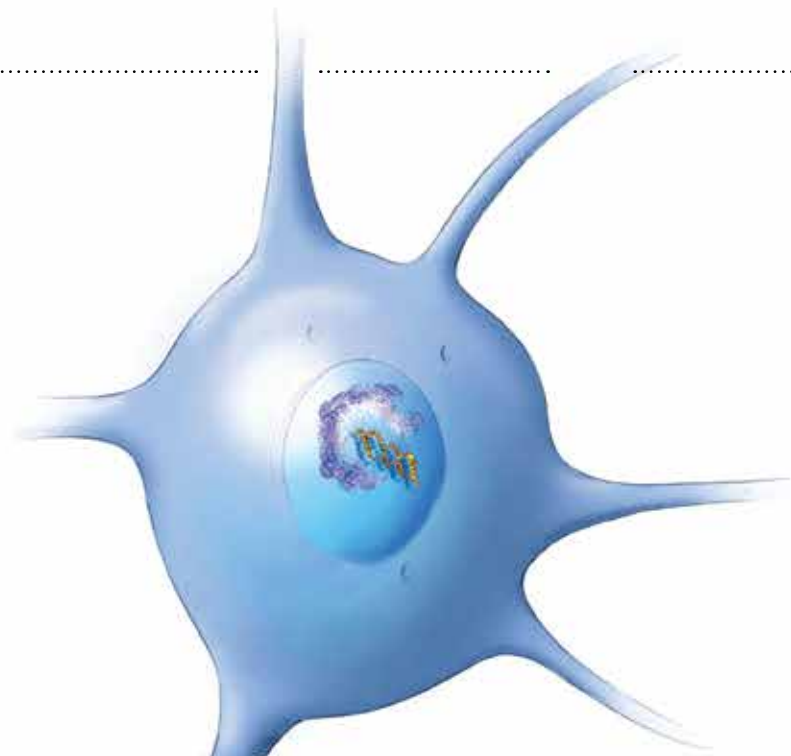
Pediatrics

NATIONWIDE

Advancing the Conversation
on Child Health

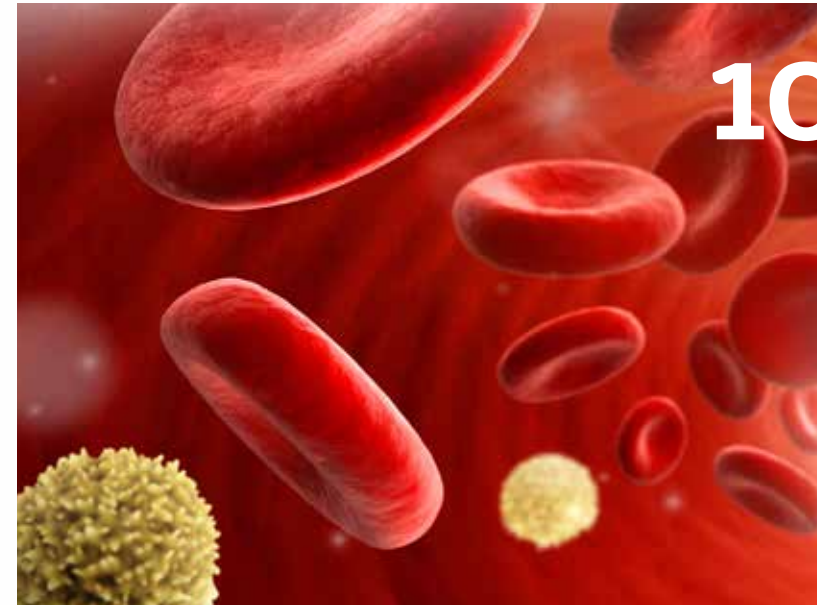


**Viruses That Treat:
Gene Therapy
Comes of Age**



18 VIRUSES THAT TREAT: GENE THERAPY COMES OF AGE

Through virus-mediated gene therapy, researchers are working to treat, cure or even prevent genetic diseases. The discovery, published in 2009, that adeno-associated virus serotype 9 (AAV9) vectors could cross the blood-brain barrier when injected into the vascular system and deliver genes directly to motor neurons has led to numerous innovations for targeted gene therapies for spinal muscular atrophy, Sanfilippo syndrome and others. AAV9 has also shown to be effective for targeting muscles and is the basis for gene therapies targeting muscular dystrophies.



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“The effect of inappropriate exposure to antibiotics lasts a lifetime.”

— Preeti Jaggi, MD, medical director of Stewardship and Optimization of Antimicrobial Prescribing at Children’s Healthcare of Atlanta (page 12)

“It’s not just that we don’t have evidence to support the treatment [for PDA]; we also have a lot of evidence that the treatment is not effective. That’s a stronger conclusion.”

— William Benitz, MD, chief of Neonatology at Lucille Packard Children’s Hospital at Stanford University (page 26)

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Reevaluate the Evaluation of Febrile Infants?

For decades, complete blood cell counts have been the go-to way to identify babies at high risk for serious bacterial infections. But recent research shows the popular lab test isn't as useful as everyone thought.

The Pediatric Emergency Care Applied Research Network (PECARN) has worked for the past decade to both evaluate new technologies and reevaluate standard of care for fever and infections. In a recent *JAMA Pediatrics* paper, the group revealed important findings: traditional complete blood cell (CBC) thresholds — with standard cutoffs for white blood cell count, absolute neutrophil count and platelet count — do not effectively identify very young infants with invasive bacterial infections.

“The majority of young babies presenting with acute fever are going to have something pretty benign, but a small group can have a serious infection. It’s important to identify that needle in the haystack,” says Octavio Ramilo, MD, chief of the Division of Infectious Diseases at Nationwide Children’s and an author on the publication. “We thought babies with higher white cell counts were more likely to have serious bacterial infections, but it turns out this standard lab test was not as helpful as we thought.”

PECARN’s investigators at 26 hospitals nationwide prospectively evaluated 4,313 previously healthy infants younger than 2 months of age who presented to emergency departments with fever. All babies had blood cultures and either cerebrospinal fluid cultures or a 7-day follow-up visit to confirm the cause and course of their fever. Standard CBC cutoff values were not accurate predictors of invasive bacterial infections, correctly identifying only 7-27 percent of true cases.

Even when the research team optimized CBC thresholds using the new data from study participants, including CBC values from 97 babies with confirmed invasive bacterial infections, the cutoffs could not discriminate between infants with and without invasive bacterial infections with high accuracy.

“It’s possible that CBCs used to be better predictive measures than they are now,” suggests Dr. Ramilo. “The causes of fever and infection in these young infants have changed over the last few decades. Vaccines and new protocols for treating infants born to mothers with fever may be making it even more challenging to detect which babies have severe bacterial infections.”

Despite the newfound shortcoming of this common lab test, Dr. Ramilo expects physicians will still use CBCs as part of their standard work-up — he just recommends they do so with a greater understanding of the limitations.

“We know now that CBCs can’t be relied on in isolation to make decisions,” says Dr. Ramilo, who is also a principal investigator in the Center for Vaccines and Immunity at Nationwide Children’s. “This study proves we need to develop new tools for identifying babies with serious infections more quickly and precisely.”

PECARN already has such efforts underway. The group’s 2016 *JAMA* publication announced their collective progress toward the use of transcriptomics — RNA biosignatures — to identify babies with bacterial infections with up to 90 percent accuracy. The researchers are currently validating the tests in a larger cohort to improve and prepare it for clinical practice.

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— Katie Brind’Amour, PhD, MS

How to Identify and Treat Blood Clots in Pediatric Patients With Cancer

New guidelines will help doctors recognize and treat children at risk of venous thromboembolism.

Prevention of blood clots is well described in adult cancer patients, but data on the problem in pediatric cancer patients is limited. In a new publication initiated at the request of the International Society of Thrombosis and Hemostasis, researchers provide guidance for identifying children most at risk of venous thromboembolism and choosing the best preventative treatment.

When it comes to determining which pediatric cancer patients are most at risk of cancer-associated blood clots, it’s up to physicians to evaluate the specific combinations of risk factors for each patient.

Risk factors include patient age, with adolescents and young adults at higher risk of venous thromboembolism, and the use of central venous catheters. Certain cancers, such as leukemia, are associated with higher rates of venous thromboembolism than others. Some chemotherapy agents, notably asparaginase, are also known to be associated with higher clot risk.

“A lot of it is going to be a clinical gestalt of the patient,” says Brian Tullius, MD, a pediatric Hematology/Oncology fellow at Nationwide Children’s Hospital and one of the paper’s authors. “We recommend an individualized risk assessment be performed on every patient that you care for as an oncologist.”

If a physician determines that prophylactic treatment is necessary, Dr. Tullius and his colleagues recommend using low-molecular-weight heparins. These medications

are already in use for both clot prevention and treatment in pediatric cancer patients. They have been shown to be safe, easy to use, reliable and effective in children.

“The first and foremost thing we’re hoping for from this paper is more research,” says Dr. Tullius. “More dedicated pediatric research will help us come up with better evidence-based guidelines for who exactly needs prophylaxis.”

One issue is that both cancer and clotting are rare in the pediatric population. “We really leave it up to clinical judgment because the data doesn’t support hard and fast recommendations,” says Dr. Tullius.

Beyond encouraging more research, the authors also hope the publication of these guidelines raises awareness of the risk for venous thromboembolism in pediatric cancer patients. It can lead to medical complications, treatment delays and even death — risks better known and understood in adults than in children.

“If any kids receive preventative treatment because of these guidelines and their clots are stopped, that is the ultimate goal,” says Dr. Tullius. “We want to save children undergoing cancer treatment from having bad outcomes from clots.”

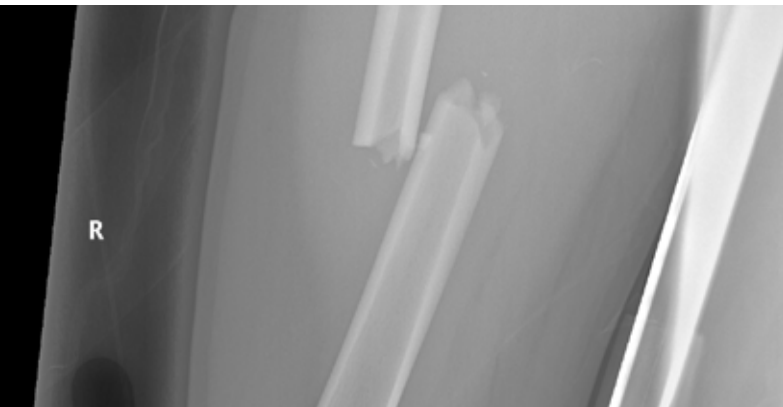
Tullius BP, Athale U, van Omme CH, Chan AKC, Palumbo JS, Balagtas JMS, for the Subcommittee on Hemostasis and Malignancy and the Subcommittee on Pediatric/Neonatal Thrombosis and Hemostasis. The identification of at-risk patients and prevention of venous thromboembolism in pediatric cancer: Guidance from the SSC of the ISTH. *Journal of Thrombosis and Haemostasis*. 2018;16:175-180.

— Mary Bates, PhD



Femoral Nerve Blockade May Reduce Need for Intravenous Opioids

Researchers find no differences in postoperative pain measures for patients receiving intravenous opioids and those receiving regional anesthetic.



Femur fractures often require surgical fixes and can be quite painful. Although traditionally treated with intravenous opioids, regional anesthesia may offer an alternative option.

In a new study, published in the *Journal of Pain Research*, researchers evaluated the efficacy of a regional anesthetic technique compared to intravenous opioids in treating pain following surgical repair of femur fractures in children. They found no significant differences between the two techniques on measures including postoperative pain scores and opioid requirements.

“Prior to four or five years ago, our general practice was to provide pain management to patients with femur fractures with opioids or narcotic pain medications,” says Nicole Elsey, MD, a physician on the anesthesiology and pain medicine team at Nationwide Children’s Hospital and one of the study’s authors.

More recently, Dr. Elsey and her colleagues have used a regional anesthetic technique called femoral nerve blockade in these patients.

“We found, anecdotally, that patients were doing better with regional anesthetic — fewer overall pain complaints, faster recovery and lower consumption of opioids,” says Tarun Bhalla, MD, a pediatric anesthesiologist at Nationwide Children’s, and an associate professor of anesthesiology at The Ohio State University College of Medicine.

To investigate these differences quantitatively, the team looked at a group of 17 pediatric patients undergoing surgical repair of a traumatic femur fracture. They assigned patients to one of two groups: general anesthesia with either a femoral nerve blockade or intravenous opioids.

Contrary to the team’s expectations, use of regional anesthetic did not significantly affect pain scores, intraoperative anesthetic requirements or postoperative opioid consumption.

There was a small, but not statistically significant, decrease in pain scores in the femoral nerve blockade group, suggesting a possible benefit to the technique. The small sample size, along with differences in age, mechanism and site of injury and initial post-injury care, could contribute to the lack of statistical differences between the two groups.

“Unfortunately, the study was difficult to perform given the various ways that femur fractures can be repaired,” says Dr. Elsey. “If we had a larger patient sample, we could narrow our scope to patients with the same type of femur fractures undergoing a specific type of fracture repair to try to determine what types of femur fractures benefit the most from regional nerve blocks.”

Although the study did not reveal any statistically significant benefits to femoral nerve blockades, the data suggest the technique is at least as effective as traditional pain management options. The team says that clinically, patients appear to benefit from regional anesthesia and it will continue to be an important treatment option.

“Even though we didn’t find statistical significance, we still provide regional nerve blocks to patients because, in this day and age, we take advantage of safe techniques that reduce the amount of opioids a patient receives,” says Dr. Bhalla.

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— Mary Bates, PhD

New Guidelines Offer Practical Tools to Treat GI Reflux

An international committee’s new recommendations reflect shifting opinions about acid-suppressive medications and include an expanded diagnostic algorithm.

While reflux-related complaints are heard often by pediatric gastroenterologists and primary care physicians, it can be difficult to tell when gastroesophageal reflux (GER) crosses the line into gastroesophageal reflux disease (GERD) — or how that disease should be treated in light of emerging research.

So a joint committee of the North American Society for Pediatric Gastroenterology, Hepatology and Nutrition (NASPGHAN) and the European Society for Pediatric Gastroenterology, Hepatology and Nutrition (ESPGHAN) has updated its reflux clinical practice guidelines for the first time since 2009.

Providers will find that among other changes, the recent publication places particular emphasis on reducing the use of acid-suppressive medication, says Carlo Di Lorenzo, MD, an author of the guidelines and chief of the Division of Gastroenterology at Nationwide Children’s Hospital. Dr. Di Lorenzo is one of three authors who also wrote the 2009 guidelines.

“Parents are understandably concerned when infants spit up or when children have troublesome symptoms that may be related to reflux, but we need to make sure we are correctly diagnosing the underlying issues and only using treatments that are likely to be effective,” says Dr. Di Lorenzo.

The guidelines, published in the *Journal of Pediatric Gastroenterology and Nutrition*, include 49 separate recommendations, from the correct definition of GERD to the proper use of the rare total esophagogastric disconnection.

The authors note four main ways in which the new publication diverges from the 2009 guidelines:

- In an effort to reduce acid-suppressive medication use, it recommends acid suppression courses of only 4 to 8 weeks for children with typical symptoms of GERD, then an assessment of efficacy (and an investigation into alternative causes of the symptoms if the treatment fails)
- It recommends that in infants, a change to protein hydrolysate or amino acid-based formula should occur before attempting acid suppression
- It includes a diagnostic algorithm for children with typical symptoms of GERD
- It suggests not immediately attributing respiratory and laryngeal symptoms to gastroesophageal reflux

The new guidelines also include a number of practical tools that may be especially helpful for primary care physicians, including a table of symptoms and signs that may indicate GERD; “red flags” that may suggest disorders other than GERD; a differential diagnosis for GERD; typical dosages of drugs often used to treat GERD; and a diagnostic algorithm to be used with infants.

“In some cases, the best course of action would be referral to a pediatric subspecialist, but that’s not always possible,” says Dr. Di Lorenzo. “We hope these new guidelines can help bring pediatricians up to date on the preferred ways of diagnosing and treating GERD.”

Rosen R, Vandenplas Y, Singendonk M, Cabana M, Di Lorenzo C, Gottrand F, Gupta S, Langendam M, Stalano A, Thapar N, Tipnis N, Tabbers M. Pediatric gastroesophageal reflux clinical practice guidelines: joint recommendations of the North American Society for Pediatric Gastroenterology, Hepatology, and Nutrition (NASPGHAN) and the European Society for Pediatric Gastroenterology, Hepatology, and Nutrition (ESPGHAN). *Journal of Pediatric Gastroenterology and Nutrition*. 2018 Jan 25. [Epub ahead of print]

— Jeb Phillips

IMPORTANT CHANGES IN THE GUIDELINES

- 1 Shortened duration of acid-suppressive medications
- 2 Try changing formulas before using acid-suppressive medications
- 3 Follow the new diagnostic algorithm for kids with GERD symptoms
- 4 Don’t immediately attribute respiratory or laryngeal symptoms to GERD

Is Whole Exome Sequencing the Future of Kidney Stone Management?

The first use of whole exome sequencing for monogenic causes of kidney stone disease reveals the diagnostic tool is ripe for clinical application.

In the first-ever study of whole exome sequencing for early onset kidney stone disease, an international team of researchers led by clinician-scientists at Boston Children's Hospital expanded on their prior finding that many early onset cases have a single-gene (monogenic) cause. The team's latest study identified seven novel mutations in genes known to cause kidney stone disease and changed the course of clinical management for 60 percent of the participating families in whom a monogenic cause was detected.

"For patients with recurrent stones, a severe phenotype, familial disease or early onset disease, I would highly recommend whole exome sequencing," says Ankana Daga, MD, clinical fellow of pediatric nephrology at Boston Children's and lead author on the study, published in *Kidney International*. Unlike kidney stone gene panels, whole exome sequencing looks at the patient's entire genetic background. "You'll be surprised at what you find and how that could change management of these patients."

Among families with kidney stone disease onset at less than 25 years of age who underwent whole exome sequencing, the study detected monogenic disease-causing mutations in nearly 30 percent (15 of 51 families). The team identified 19 total mutations in seven recessive genes, one dominant gene and one gene with both inheritance characteristics. Seven of the identified mutations were not previously known to cause disease. They also found a causative mutation in one of what may be 117 possible phenocopies of nephrolithiasis-causing genes.

"Nine of the 15 families in our cohort with a monogenic disease cause benefitted from the genetic findings," says

Dr. Daga. "The new information allowed their clinicians to better care for them either through preventative or therapeutic measures." The remaining families were already being appropriately managed for their underlying cause of disease.

"These findings may ultimately have a profound impact on clinical care," says John David Spencer, MD, a nephrologist at Nationwide Children's Hospital and principal investigator in the hospital's Center for Clinical and Translational Research. "Results from whole exome sequencing could alter daily medical or dietary management, enable more effective monitoring or prevention of potential systemic complications, and allow the creation of a screening framework for family members at risk for disease."

Prior to broader implementation of whole exome sequencing — which is considerably more expensive than panel sequencing — Dr. Daga and the project's principal investigator, Friedhelm Hildebrandt, MD, chief of nephrology at Boston Children's, plan to use the technology to investigate novel single-gene causes of nephrolithiasis and its pathogenesis to aid the development of targeted therapy for each patient.

"Our hope is that with more data presenting the potential of the technology for kidney stone disease management, it will become a feasible and common clinical assessment for all patients," Dr. Daga says.

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— Katie Brind'Amour, PhD, MS

Finding Monogenic Disease-Causing Mutations

15 CASES WERE SOLVED FOR GENES KNOWN TO CAUSE KIDNEY STONES



12 of 15 FAMILIES HAD RECESSIVE MUTATIONS



3 of 15 FAMILIES HAD DOMINANT MUTATIONS

Starting the Conversation on Sickle Cell Disease and Reproductive Health

Adolescents and young adults with sickle cell disease — and their caregivers — care about future fertility. But what should doctors tell them?

Until just a few decades ago, sickle cell disease (SCD) was often fatal in childhood. Now that more patients reach adulthood, clinicians and researchers need to ask — and answer — questions about fertility, parenthood and contraception. In a recent study led by physician-researchers at Nationwide Children's Hospital, adolescents and young adults with SCD and their caregivers reported interest in reproductive health topics, but very few reported ever receiving such information from their health care providers.

The researchers analyzed surveys completed by 18 patient-caregiver dyads during a 10-month period at Nationwide Children's. Two-thirds of all patient participants reported wanting future children, and 83 percent of caregivers hoped to have a grandchild in the future. However, only 16 percent of patients and 27 percent of caregivers reported receiving information about fertility, and only 11 and 22 percent of patients and caregivers, respectively, reported receipt of birth control information.

"As clinicians, we've focused on survival for so long that we don't have a great understanding of what people's goals and intentions are for parenthood later in life," says Susan Creary, MD, a hematologist at Nationwide Children's and senior author on the study, published in *Pediatric Blood & Cancer*. "No matter what patients decide about biological parenthood or fertility, sickle cell disease and its treatments have potential implications for patients' reproductive health."

Patients with SCD will pass on an affected gene to future children. Depending on their partner's status, this could result in a child with SCD or sickle cell trait. SCD also carries risks for women during pregnancy, and mounting research suggests that treatments used to manage the condition, such as hydroxyurea and bone marrow transplants, may impair fertility. Unfortunately, most respondents did not identify the disease or its treatments as potential barriers to fertility, and few patients reported interest in learning more about their birth control options.

"Even though the conversations may be difficult, providers need to know it's their responsibility to bring it up, because fertility and reproductive health are topics that need to be addressed in this population," says Leena Nahata, MD, an endocrinologist at Nationwide Children's and medical director of the hospital's Fertility and Reproductive Health Program. Dr. Nahata is lead author on the publication.

The researchers suggest that discussion and management of birth control may fit best with the primary care provider role and drug side effects and fertility preservation with subspecialists. However, they recommend that physicians not assume another clinician will broach the subject. They suggest informing families about emerging data and letting them know about available options, using fertility-related work in pediatric cancer as a framework.

"We need to be thoughtful about treatment and counseling in such a wide age range of patients with sickle cell disease," says Dr. Creary. "There's obviously a lot to talk about during appointments, so we are exploring a formal process for when and how to manage fertility-related conversations at Nationwide Children's."

Nahata L, Caltabellotta NM, Ball K, O'Brien SH, Creary SE. Desire for parenthood and reproductive health knowledge in adolescents and young adults with sickle cell disease and their caregivers. *Pediatric Blood & Cancer*. 2017 Sep 25. [Epub ahead of print]

— Katie Brind'Amour, PhD, MS



MAPPING THE WORLD OF PEDIATRIC SEVERE SEPSIS

Researchers work to reveal the many subtypes of pediatric sepsis — and what to do about them.

By Katie Brind'Amour, PhD, MS

Once upon a time, sepsis was just sepsis. Children experiencing septic shock and its aftermath — any resulting organ failure — were viewed as a fairly homogenous group of patients.

But now, thanks in a large part to the work of teams at Nationwide Children's Hospital, Cincinnati Children's Hospital Medical Center, Children's Hospital of Pittsburgh of University of Pittsburgh Medical Center, and their collaborators, researchers know better: Not all sepsis is created equal.

MULTIPLE AVENUES OF INVESTIGATION

"To the naked eye, children with sepsis look similar at the bedside," says Mark Hall, MD, chief of the Division of Critical Care Medicine at Nationwide Children's and a frequent collaborator in multi-institutional pediatric sepsis research. "But there are pathophysiological changes happening in critically ill patients that are not apparent, even through most traditional lab testing."

Uncovering these unique subtypes of sepsis has been a labor of love for many of the physician-scientists in this field. Each team has an area of emphasis, and each vein of exploration has made significant inroads toward an improved understanding of sepsis pathophysiology and risk stratification.

Collaborative efforts involving Dr. Hall and spearheaded by Hector Wong, MD, director of the Division of Critical Care Medicine at Cincinnati Children's, for example, have resulted in risk stratification tools known as PERSEVERE and PERSEVERE-XP, which use serum biomarkers and

clinical sepsis phenotypes to develop a prognosis. With each subsequent study and the incorporation of more precise prognostic markers, such as tumor protein 53 and mRNA, Dr. Wong and his colleagues near arrival at their destination: a clinically feasible, highly accurate predictor of pediatric sepsis-related mortality risk.

Another approach toward that goal is led by Joseph Carcillo, MD, professor of Critical Care Medicine and Pediatrics at the Children's Hospital of Pittsburgh, and his collaborators, including Dr. Hall. Their 2017 study in *Pediatric Critical Care Medicine* proffered a practical risk stratification table to predict pediatric sepsis-related mortality risk using C-reactive protein (CRP) and ferritin blood test results.

"Employing a 2 x 2 table at the bedside using two readily available tests like CRP and ferritin, we can now assess the severity of a patient's systemic inflammation mortality risk as well as the effectiveness of our therapies in reducing this risk," says Dr. Carcillo, lead author of the study. Children who reached CRP ≤ 4.08 mg/dL and ferritin ≤ 1980 ng/mL, for example, had a low risk for mortality in the study, even if they started with higher levels. Devoting resources to getting patients above those cutoffs down into the low-risk "safe zones" could help physicians track their progress toward an improved prognosis, he says.

GETTING THE LAY OF THE LAND

Together with research partner Jennifer Muszynski, MD, critical care physician and principal investigator in the Center for Clinical and Translational Research at Nationwide Children's, Dr. Hall has been unravelling the

immunobiology of severe sepsis and other critical illness or trauma for nearly 20 years.

"We study the function of white blood cells and the notion of critical illness-induced immune suppression in children, which we call immunoparalysis," says Dr. Hall. "It's a state of immune failure that can occur in the setting of many different critical illnesses, including septic shock, and can be measured via a number of laboratory tests."

To make the identification of patients with immunoparalysis easier, Dr. Hall and his team developed a specialized diagnostic assay. That immunoassay was used in more joint work with Dr. Carcillo, also published in *Pediatric Critical Care Medicine* in 2017, to identify one of several inflammation-related phenotypes of pediatric severe sepsis and their association with multiple organ failure, macrophage activation syndrome (uncontrolled systemic inflammation known as MAS), and death.

The immunoparalysis phenotype was the most commonly identified phenotype among children with severe sepsis, affecting 24 of 75 children with multiple organ failure and nearly two-thirds of all children with any phenotype used in the study. In general, children with any of the inflammation-related phenotypes were more likely to develop MAS and had a significantly greater risk of death than children with no such phenotype.

Drs. Hall and Muszynski have further explored the phenomenon of immunoparalysis in sepsis cases exclusively at Nationwide Children's, confirming that the immunoparalysis-associated multiple organ failure phenotype is common and associated with adverse sepsis outcomes. They expect to publish their data in 2018.

ALL ROADS LEAD TO IMPROVED SEPSIS MANAGEMENT

Although these recent studies of children with severe sepsis represent the largest such groups in the pediatric literature, Dr. Hall acknowledges the work is mostly associational. "We have to validate our findings in a multi-center cohort to make sure they're generalizable," he says. "And it's not yet clear that restoring immune function will lead to better outcomes. That has to be tested in clinical trials."

Sepsis trials in adults have already had some success in applying phenotype-specific therapies to reduce mortality. Clinical trials for immunoparalysis therapies (such as granulocyte macrophage-colony stimulating factor or immunosuppressant tapering) and other sepsis phenotypes have not been initiated yet in children with sepsis, but Dr. Hall expects they are not far off.

"We are going to uncover a whole world of subtypes of critically ill patients identifiable through testing who may respond to individual therapies," Dr. Hall predicts. "In time, it's our hope that identifying the distinct pathological sepsis subtypes will translate into better risk stratification, drug discovery and an explosion of treatment regimens that are unique to patients' individual pathophysiology. We all just have to keep working toward that end goal."

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"In time, it's our hope that identifying the distinct pathological sepsis subtypes will translate into better risk stratification, drug discovery and an explosion of treatment regimens that are unique to patients' individual pathophysiology."

— Mark Hall, MD, chief of the Division of Critical Care Medicine at Nationwide Children's



WEAVING AN ANTIMICROBIAL SAFETY NET

Stewards thread together monitoring programs and new protocols while trimming unwarranted tests and diagnostic speed.

By Kevin Mayhood

Studies estimate that 30 to 50 percent of antimicrobials prescribed in hospitals and up to 50 percent prescribed in outpatient settings are either unnecessary or inappropriate.

That's not only wasteful but harmful, say antimicrobial stewards.

Each prescription increases a patient's risk of suffering side effects, ranging from rash and dizziness to severe allergic reaction and *Clostridium difficile* infection, and speeds the growth of bacterial resistance.

Bacteria inevitably become resistant to antibiotics, but "The more antibiotics taken, the more certain resistant bacteria will emerge," says Josh Watson, MD, an infectious diseases physician and interim director

of Antimicrobial Stewardship (AS) at Nationwide Children's Hospital.

The Centers for Disease Control and Prevention estimate at least 23,000 Americans die each year from antibiotic-resistant infections. A report commissioned by the United Kingdom's government suggests that if resistance is not slowed and new drugs developed, 10 million people worldwide will die annually from drug-resistant infections by 2050, surpassing the predicted number of deaths caused by cancer.

Adding to the concern of antibiotic overuse, epidemiological studies suggest overexposure to antibiotics is associated with obesity, Crohn's disease, irritable bowel syndrome and autoimmune diseases.

"We're using antibiotics at such a high rate that we have room to decrease usage and have an impact," says Jason Newland, MD, associate professor of Pediatrics and Infectious Diseases at Washington University and director of the Antimicrobial Stewardship Program at Washington University St. Louis Children's Hospital.

Efforts at children's hospitals across the United States are showing progress and creating a complex and interconnected safety net evolving to reduce antimicrobial misuse. In addition to monitoring prescriptions, threads include a simple protocol to halt children from taking unneeded drugs, eliminating unnecessary testing that can lead to unneeded drug prescription, and more rapid and accurate diagnostics. Screening and testing children labeled allergic to penicillin is another. Ninety percent of them are not allergic and would likely benefit from effective narrow-spectrum antibiotics from the penicillin family.

"What we've seen for children's hospitals that have implemented an effective AS program is that it has core elements reflective of the CDC publication on AS," says Dr. Newland, who has studied AS programs across the country. "Administrative support is a must. A dedicated pharmacist — a full time equivalent dedicated to AS — is very valuable... You need a physician leader who's in the trenches with them and that requires dedicated time and financial support to perform AS. We've seen that programs with financial support have a greater decrease in improper antimicrobial use than those without financial support."

And, accepted practices must be changed or at least fine-tuned, he and other stewards say.

DAILY ROUNDS

"Hospitals and doctor's offices have traditionally used broad and powerful antibiotics 'just in case,' but it's likely we're doing harm with that strategy," says Sarah Parker, MD, a pediatric infectious disease physician

and medical director of the Antimicrobial Stewardship Program at Children's Hospital Colorado. Dr. Parker carries the CDC's message that each patient should receive "the right antibiotic, in the right dose, at the right time, for the right duration," to the hospital's health faculty daily.

The face-to-face AS program she and colleagues have developed, called handshake stewardship, cuts misuse of antibiotics while cutting costs. The program reduced antimicrobial use by 10 percent during its first four years. The savings amount to more than \$1 million annually, she says.

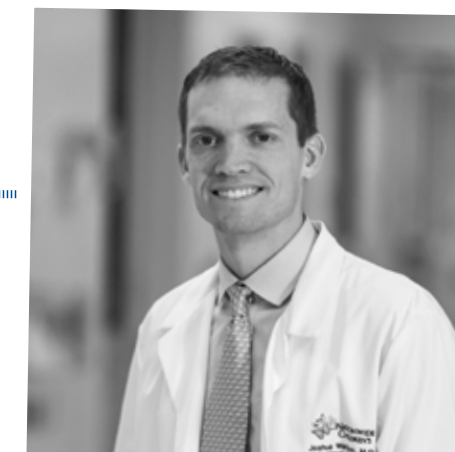
While some AS programs require hospital faculty to get prior approval for a prescription and others review only a sample of prescriptions, under handshake stewardship Dr. Parker and a pharmacist review every antibacterial, antifungal and antiviral prescribed at the hospital and available lab information at 24 and 72 hours. They then make daily rounds and ask questions about a list of patients that caught their attention and may make suggestions for more conservative options. Even if they don't have questions, the team talks with prescribers every day.

"This fosters better exchange," says Dr. Parker, who is also an associate professor of Pediatrics and Infectious Diseases at the University of Colorado School of Medicine. "Providers like it a lot more; they say they don't feel as policed."

Within the 10 percent overall decrease in antimicrobial usage the program has achieved, use of the broad-spectrum antibiotic vancomycin was reduced 26 percent and broad-spectrum meropenem 22 percent.

"The more antibiotics taken, the more certain resistant bacterial will emerge."

- Josh Watson, MD, interim director of Antimicrobial Stewardship (AS) at Nationwide Children's Hospital



A preliminary review of numbers through 2017 shows the hospital sustained the cuts and may have actually further reduced usage in some areas, Dr. Parker says.

Some programs review usage of only certain antibiotics, but Children's Colorado looks at all. By doing so, "We improved use of simple antibiotics," Dr. Parker says. "We found that amoxicillin was misprescribed a lot in the hospital. It was a great opportunity to teach. Prescribers then applied what they learned to more sophisticated antibiotics."

The rounds are a two-way street, Dr. Parker says, helping her understand what faculty in different departments face daily and enabling her to better help them with stewardship. The program has also helped spur collaborations among physicians, who produced studies to determine the most appropriate antibiotics for appendicitis and musculoskeletal infections.

OUTPATIENTS, TOO

Most stewardship programs began by focusing on patients who stay at the hospital, but the need is also clear in outpatient settings, physician-researchers at Nationwide Children's have shown.

Dr. Watson and Terry Barber, MD, medical director of Nationwide Children's offsite Urgent Care Centers, noticed urgent care physicians were prescribing antibiotics for a high number of children who had symptoms of a urinary tract infection (UTI) but whose urine culture, returned a few days later, was negative for infection.

Dr. Watson and colleagues came up with a simple protocol to follow-up with a child's caregiver. When urinalysis is negative and a clinician determines the antibiotic is unnecessary, a nurse calls the caregiver to

stop giving the drug to the child. If phone calls fail to reach the caregiver on two consecutive days, the nurse sends a letter to discontinue taking the medicine.

"It ended up being pretty smooth sailing," Dr. Watson says. "The urgent care doctors and nurses embraced it right away."

A study found that prior to implementation of the protocol, follow-ups to discontinue usage were documented in 4 percent of cases. That grew to 84 percent of cases. The protocol initially cut the number of days children were taking unnecessary antibiotics by 40 percent. As staff became accustomed to the steps and a lab nurse was designated to follow up with families, the number grew to 60 percent.

Nationwide Children's Emergency Department has since adopted the program. There, Dr. Watson and another team had found the same pattern. Only 55 percent of children prescribed antibiotics for UTI had positive cultures. Their goal is to make the protocol a standard routine as quickly as possible and at least match the reduction in unnecessary antibiotic exposure they've achieved in the urgent care centers.

DIAGNOSTIC STEWARDSHIP

"We need better diagnostic tools, and we need to do better with the tools we have currently," says Dr. Watson, who is also an assistant professor of Pediatrics at The Ohio State University College of Medicine.

Dr. Watson's teams are pursuing diagnostic stewardship to further reduce antibiotic usage, risk to children and costs.

He and colleagues are investigating whether antimicrobial peptides (AMPs) found in urine can be used as biomarkers of UTIs. Their initial study found that the AMPs HD5



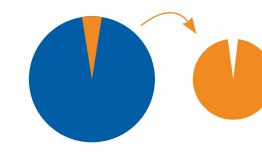
"Hospitals and doctor's offices have traditionally used broad and powerful antibiotics 'just in case,' but it's likely we're doing harm with that strategy."

- Sarah Parker, MD, medical director of the Antimicrobial Stewardship Program at Children's Hospital Colorado

EXCESSIVE ANTIMICROBIALS



20 - 50%
of antimicrobials prescribed
in hospitals and approaching
50%
in outpatient settings are
unnecessary or inappropriate.



10% of kids are labeled
as allergic to penicillin.
Of these **90%** will test
negative for the allergy and
can tolerate penicillin.



Costs to patients and the
health care system for those
labeled allergic to penicillin are
63%
higher due to use of more
expensive antibiotics and
more complications.

IN URGENT CARE CENTERS AT NATIONWIDE CHILDREN'S



A call-back program cut
unnecessary antimicrobial
usage for UTI by
60%



A protocol to stop swabbing the
throats of kids with a sore throat
and viral symptoms reduced
swabbing by **39%** and reduced
unnecessary antimicrobial exposure.

and HNP1-3 appear to improve the specificity without decreasing the sensitivity of the UTI test.

The researchers believe a combination of biomarkers will lead to tests that produce fewer false-positive results, and thereby reduce unnecessary antibiotic exposure. They are currently evaluating more biomarkers. They and urgent care physicians also are investigating how to identify children who can wait for results of a urine culture and start an antibiotic only if an infection is confirmed.

"Diagnostic stewardship also requires we order tests appropriately," says Preeti Jaggi, MD, an infectious disease specialist and former director of AS at Nationwide Children's. Dr. Jaggi is now medical director of Stewardship and Optimization of Antimicrobial Prescribing at Children's Healthcare of Atlanta.

At Nationwide Children's, she and Dipanwita Saha, MD, director of Quality Improvements in Urgent Care at Nationwide Children's and assistant professor of Pediatrics at Ohio State, found that the hospital's centers were swabbing the throats of nearly 2,300 children per

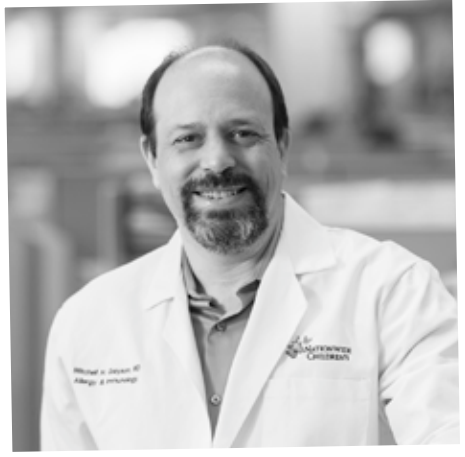
month and 74 percent of the tests were coming back negative for streptococcal pharyngitis.

"Clearly, we're swabbing too many," Dr. Saha says.

And among those with a positive result were children who received but didn't need an antibiotic, Dr. Jaggi says. "Twenty percent of kids carry group A streptococcus that causes them no harm."

Distinguishing who is a carrier and who has infection takes time and money for tests. To tackle overswabbing and overprescription of antibiotics, Drs. Saha and Jaggi refined the Licensed Provider Initiated Protocol used hospital-wide to guide when to swab. They spelled out symptoms of strep infection and said children with a sore throat and one or more of the symptoms should be swabbed. But, children who have a sore throat or one or more specific symptoms indicating a viral infection should not be swabbed, the revised protocol says.

With the changes in procedures, throat swabs in the urgent care centers dropped 39 percent, from 294 per 1,000



“Most people who get labeled with a penicillin allergy as a kid were taking amoxicillin or penicillin when they had a viral infection. They got a viral rash and were told that it was an allergic reaction to the medication. From then on, they are told to avoid penicillin and related antibiotics.”

- Mitchell Grayson, MD, director of the Division of Allergy and Immunology at Nationwide Children's

encounters to 180. Dr. Saha plans to submit a study of the refined protocol for publication later this year.

Not all physicians have been overswabbing. By reviewing medical claims records of children in 34 Ohio counties served by Nationwide Children's accountable care organization, Partners For Kids, Drs. Watson and Jaggi found that pediatricians and general practice physicians in the community are swabbing too few children.

“Children are being treated for streptococcal pharyngitis without a confirmatory test,” Dr. Watson says. “It seems that depending on the setting of care, either overtesting or undertesting can contribute to overuse of antibiotics.”

SPEEDING STEWARDSHIP

As diagnostics become more sophisticated, stewardship should be involved in implementing them, Dr. Parker says. In a recent study, researchers at Children's Colorado found that use of a commercially available rapid blood culture identification system (BCID) and rapid AS reduced the median time to optimal antimicrobial therapy from 60 hours to just under 27 hours.

Using a BCID, hospital staff identified the organism infecting a child's bloodstream in about an hour instead of the day or two traditional microbiology techniques require. Stewards reviewed and relayed the results and recommended the appropriate antimicrobial to the health care provider within 20 minutes.

Because resistance mechanisms vary among species, knowing the organism often allows the provider to use immediately a more targeted antibiotic instead of a broad-spectrum drug.

“When we receive results of susceptibilities tests a day or two later, we get the child on a narrower antibiotic,” Dr. Parker says.

The BCID has been proven capable but it's new. Without the AS intervention, “people were still inclined to wait for the old way before prescribing a new antibiotic,” Dr. Parker says. “We had to educate them. If we hadn't, we don't think there would have been uptake of the rapid system and we wouldn't have created change.”

For children who were diagnosed with the BCID, the mean duration of antimicrobial therapy was 367 hours compared to 475 hours for a control group that had been diagnosed using traditional techniques. Unnecessary antibiotic initiation for children with a culture containing organisms considered contaminants and not infections decreased from 76 percent to 26 percent.

Use of a BCID to distinguish likely contaminants from infection has also reduced hospital admissions at Nationwide Children's, says Dr. Watson. In the past, when a culture was positive and a Gram stain showed Gram-positive cocci, the child would be called back, admitted and placed on antibiotics until the bacterium was identified. Now, if the BCID identifies a common contaminant, staff will call and check on the patient, he says.

OVER-LABELING ALLERGIES

Another way hospitals are trying to get children on the optimal drug is by screening and testing children for penicillin allergy.

“Beta-lactam antibiotics, including penicillin, are among the cheapest and most effective,” says Mitchell Grayson, MD, director of the Division of Allergy and Immunology at Nationwide Children's. “If you can tell who's truly allergic, it improves the ability to use the right drug.”

He points to studies that have shown that as many as 10 percent of people are labeled as allergic to penicillin, but of those 10 percent labeled as “allergic,” more than 90 percent can still tolerate penicillin, and are indeed not allergic to penicillin.

“Most people who get labeled with a penicillin allergy as a kid were taking amoxicillin or penicillin when they had a viral infection. They got a viral rash and were told that it was an allergic reaction to the medication,” Dr. Grayson says. “From then on, they are told to avoid penicillin and related antibiotics.”

And that has costs. Eric Macy, MD, an allergy, asthma and immunology physician with Kaiser Permanente in San Diego, found that adults with a penicillin allergy history had longer hospital stays and more *C. difficile*, methicillin-resistant *Staphylococcus aureus* and vancomycin-resistant *Enterococcus* infections. The financial costs to patients and the health care system are up to 63 percent higher because these patients are treated with more expensive antibiotics, including fluoroquinolones, clindamycin and vancomycin, and have more complications.

Dr. Grayson and colleagues in Allergy and Immunology at Nationwide Children's have been evaluating and testing children labeled as penicillin allergic for years, and they have found almost none has a true penicillin allergy. The specialists are preparing a penicillin allergy information handout and decision tree, based partly on their screening experience. The tree asks physicians to consider the type or types of reactions the child has had after taking a beta-lactam, the timing of the reaction and when to consider referring a child for penicillin testing.

Dr. Grayson suggests general pediatricians and practitioners in particular should have the information. “The time to know whether children are allergic to penicillin is before they have an infection and need an antibiotic,” he says.

ADDING THREADS

Stewards are continuing to find ways to reduce antimicrobial usage. Drs. Watson and members of his AS team are using the Partners For Kids data to analyze antimicrobial prescribing for a number of conditions and diseases diagnosed and plan to give feedback to providers to help curb overprescription. The data, like the CDC's, shows more overprescribing in rural communities.

Other institutions are now implementing handshake stewardship, or aspects of the program. Dr. Parker suggests that AS can also be paired with a variety of rapid diagnosis technologies becoming available to get children on the appropriate medicine sooner.

In all aspects of stewardship, “We definitely must have more urgency,” Dr. Newland says. “In the last few years, the CDC, World Health Organization and the United Nations have made this a priority, but we need to do better reaching out into society. As doctors, we have to address this.”

The costs of doing otherwise are too high, Dr. Jaggi says. “The effect of inappropriate exposure to antibiotics lasts a lifetime.”

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VIRUSES THAT TREAT: Gene Therapy Comes of Age



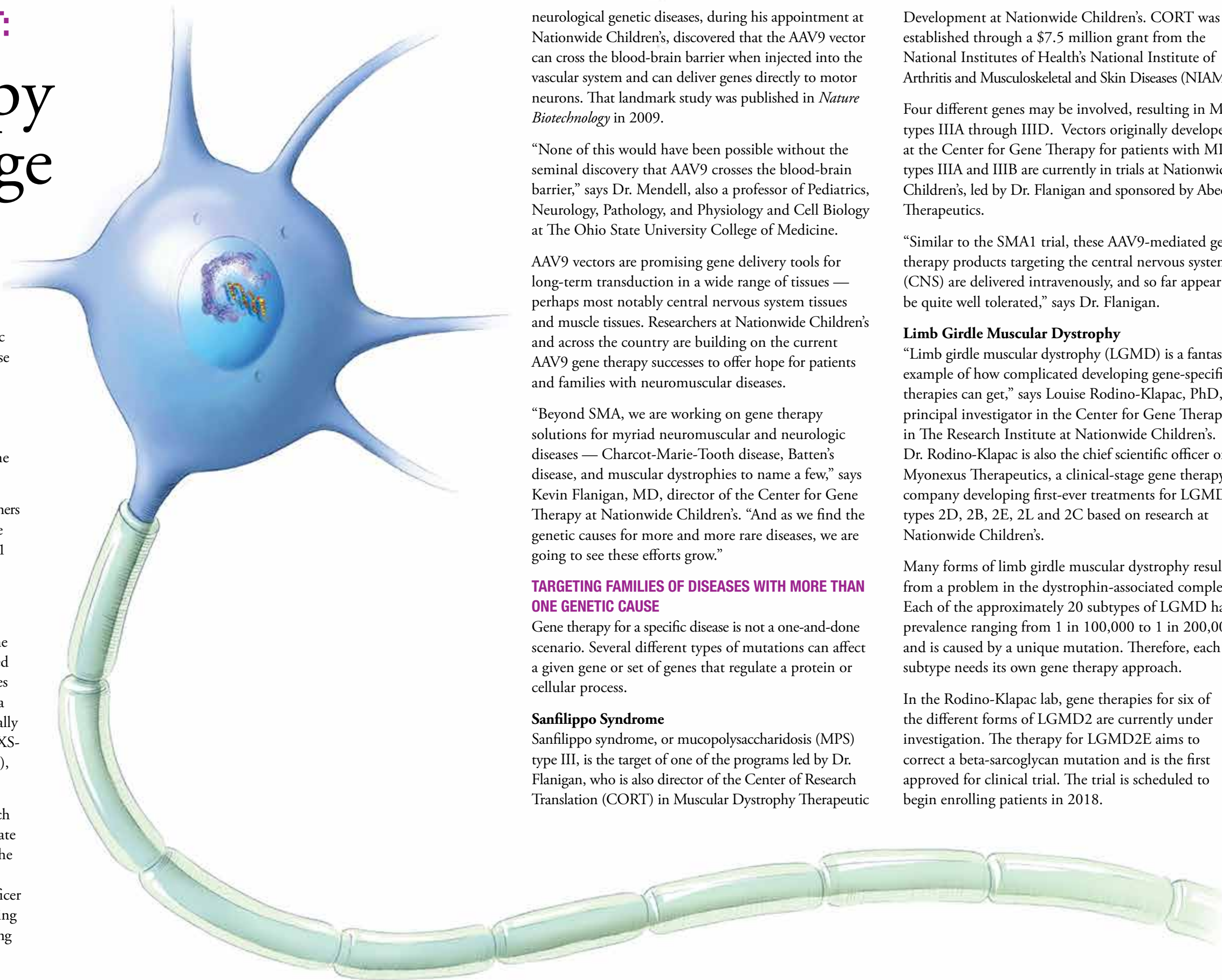
by Abbie Roth

Harnessing the ability of a virus to deliver genetic material to a cell to treat, cure or prevent disease has been the long-time goal of researchers working in gene therapy. Over the past 30 years, the journey to gene therapy has been fraught with challenges and roadblocks. But in 2017, after countless starts and stalls along the road, the field experienced many breakthroughs.

No breakthrough received more attention than when researchers from Nationwide Children's Hospital and The Ohio State University published the astonishing results of the phase 1 clinical trial of gene therapy for spinal muscular atrophy type 1 (SMA1) in the *New England Journal of Medicine*.

The SMA1 early phase trial, led by Jerry Mendell, MD, principal investigator in the Center for Gene Therapy in The Research Institute at Nationwide Children's, demonstrated extended survival and increased achievement of milestones previously unseen in the natural course of the disease — a devastating, progressive neuromuscular disease that typically results in death by age 2. An intravenous injection of AVXS-101, a modified adeno-associated virus serotype 9 (AAV9), delivered the survival of motor neuron (SMN) gene.

The trial builds on nearly 30 years of foundational research and collaboration. Arthur Burghes, PhD, of The Ohio State University, created the SMA mouse model that remains the standard by which all therapies are initially tested. Brian Kaspar, PhD, senior vice president and chief scientific officer at AveXis, a clinical-stage gene therapy company developing treatments for patients suffering from rare and life-threatening



neurological genetic diseases, during his appointment at Nationwide Children's, discovered that the AAV9 vector can cross the blood-brain barrier when injected into the vascular system and can deliver genes directly to motor neurons. That landmark study was published in *Nature Biotechnology* in 2009.

“None of this would have been possible without the seminal discovery that AAV9 crosses the blood-brain barrier,” says Dr. Mendell, also a professor of Pediatrics, Neurology, Pathology, and Physiology and Cell Biology at The Ohio State University College of Medicine.

AAV9 vectors are promising gene delivery tools for long-term transduction in a wide range of tissues — perhaps most notably central nervous system tissues and muscle tissues. Researchers at Nationwide Children's and across the country are building on the current AAV9 gene therapy successes to offer hope for patients and families with neuromuscular diseases.

“Beyond SMA, we are working on gene therapy solutions for myriad neuromuscular and neurologic diseases — Charcot-Marie-Tooth disease, Batten's disease, and muscular dystrophies to name a few,” says Kevin Flanigan, MD, director of the Center for Gene Therapy at Nationwide Children's. “And as we find the genetic causes for more and more rare diseases, we are going to see these efforts grow.”

TARGETING FAMILIES OF DISEASES WITH MORE THAN ONE GENETIC CAUSE

Gene therapy for a specific disease is not a one-and-done scenario. Several different types of mutations can affect a given gene or set of genes that regulate a protein or cellular process.

Sanfilippo Syndrome

Sanfilippo syndrome, or mucopolysaccharidosis (MPS) type III, is the target of one of the programs led by Dr. Flanigan, who is also director of the Center of Research Translation (CORT) in Muscular Dystrophy Therapeutic

Development at Nationwide Children's. CORT was established through a \$7.5 million grant from the National Institutes of Health's National Institute of Arthritis and Musculoskeletal and Skin Diseases (NIAMS).

Four different genes may be involved, resulting in MPS types IIIA through IIID. Vectors originally developed at the Center for Gene Therapy for patients with MPS types IIIA and IIIB are currently in trials at Nationwide Children's, led by Dr. Flanigan and sponsored by Abeona Therapeutics.

“Similar to the SMA1 trial, these AAV9-mediated gene therapy products targeting the central nervous system (CNS) are delivered intravenously, and so far appear to be quite well tolerated,” says Dr. Flanigan.

Limb Girdle Muscular Dystrophy

“Limb girdle muscular dystrophy (LGMD) is a fantastic example of how complicated developing gene-specific therapies can get,” says Louise Rodino-Klapac, PhD, principal investigator in the Center for Gene Therapy in The Research Institute at Nationwide Children's. Dr. Rodino-Klapac is also the chief scientific officer of Myonex Therapeutics, a clinical-stage gene therapy company developing first-ever treatments for LGMD types 2D, 2B, 2E, 2L and 2C based on research at Nationwide Children's.

Many forms of limb girdle muscular dystrophy result from a problem in the dystrophin-associated complex. Each of the approximately 20 subtypes of LGMD has a prevalence ranging from 1 in 100,000 to 1 in 200,000 and is caused by a unique mutation. Therefore, each subtype needs its own gene therapy approach.

In the Rodino-Klapac lab, gene therapies for six of the different forms of LGMD2 are currently under investigation. The therapy for LGMD2E aims to correct a beta-sarcoglycan mutation and is the first approved for clinical trial. The trial is scheduled to begin enrolling patients in 2018.



“Beyond SMA, we are working on gene therapy solutions for myriad neuromuscular and neurologic diseases — Charcot-Marie-Tooth disease, Batten’s disease, and muscular dystrophies to name a few. And as we find the genetic causes for more and more rare diseases, we are going to see these efforts grow.”

— Kevin Flanigan, MD, director of the Center for Gene Therapy in The Research Institute at Nationwide Children’s Hospital

“The preclinical results have blown us away,” says Dr. Rodino-Klapac, who is also an associate professor of Pediatrics at The Ohio State University College of Medicine. “Normally, we’re happy if 50 percent of the muscle fibers treated express the gene. In all of our preclinical studies, an excess of 95 percent of muscle fibers are expressing the gene. This makes us really hopeful about what the drug will be able to do for patients.”

Dr. Rodino-Klapac says there may be multiple reasons why the rate of expression has been so high in these preclinical studies, but she speculates that using self-complementary AAV (which was also used in the SMA1 trial) and the small gene size may be important factors.

Self-complementary AAV (scAAV) vectors contain complementary sequences that spontaneously anneal – or recombine – upon infection of the host cell. This technique works best for transfecting small genes, such as the SMN gene used in the SMA1 trial and the beta-sarcoglycan gene targeted in the LGMD2 trial, as the maximum gene length for scAAV is 2.4 kilobases (kb).

AAV GENE THERAPY APPROACHES FOR LARGE GENES

But what about large genes? While AAV gene therapy is limited by the vector’s capacity — only 4.8 kb — the research community is not deterred from tackling a gene therapy solution for the largest known human gene. Errors in the gene coding for dystrophin lead to Duchenne muscular dystrophy (DMD), one of the most well-known muscular dystrophies. The *DMD* gene’s cDNA is about 11.5 kb — roughly 2.5 times larger than the vector’s capacity.

Microgenes

While, the *DMD* gene is too large to insert in the vector, in two recently opened clinical trials, researchers are using a miniature version of the gene — microdystrophin. (See the figure on page 23.)

“The idea is that the smaller version of the gene will enable the cells to produce dystrophin that is ‘close enough’ to wild-type to dramatically improve the symptoms and survival of boys with Duchenne muscular dystrophy,” explains Dr. Mendell.

One trial at Nationwide Children’s, led by Drs. Rodino-Klapac and Mendell, will test the efficacy of Sarepta Therapeutics’ microdystrophin gene therapy product. Another trial, led by Barry Byrne, MD, PhD, director of the Powell Gene Therapy Center at the University of Florida, looks at a slightly different version of microdystrophin produced by Solid Biosciences.

“In our preclinical work, the micro-dystrophin has been effective in producing a near wild-type phenotype,” says Dr. Rodino-Klapac. “We are hoping for a profound effect in the phase 1 clinical trial, but we will have to see how effective the mini gene is compared to the full-length one.”

“To this point, we’ve had very little to offer these families,” says Dr. Mendell. “For 50 years, our only approved treatment for Duchenne muscular dystrophy has been prednisone. Our research aims to see if gene therapy is a safe and effective option for these patients and others with rare neuromuscular diseases in the future.”

The Nationwide Children’s clinical trial of microdystrophin for DMD will be the first use of intravenous (IV) gene therapy for any muscular dystrophy, according to Dr. Rodino-Klapac. “We’ll be starting with children aged 4 to 7 years old. This is still early in the disease process, and we hope that by intervening early, we can halt the progression of the disease. A second cohort, with children aged 3 months to 3 years, will enable us to see if we can prevent the onset of symptoms through the gene therapy.”

The team will be administering doses that were effective in preclinical studies. A control group of DMD patients will receive a placebo and be followed for one year. They will be offered treatment in the second year of the trial.

The University of Florida trial, currently recruiting participants, is open to children aged 4 to 17 years and utilizes a control group. “Our study design for this trial allows us to have matched controls in addition to the treatment group,” says Dr. Byrne, also a professor of Pediatrics and Molecular Genetics & Microbiology at the University of Florida. “The control patients will have the opportunity to receive the treatment later, based on the delayed start design. This provides a reasonable comparator of adverse events and benefits.”

Surrogate Gene Therapy

Another gene therapy strategy to treat DMD ignores the *DMD* gene entirely.

This is the surrogate strategy: Provide genes, delivered via viral vector, that encode proteins that can functionally compensate for the proteins that are missing in diseases. In the case of DMD, the GALGT2 genes are not in the right

place in the muscle cell normally to take on that role, but by directing overexpression through gene therapy, they can.

In 2009, Paul Martin, PhD, investigator in the Center for Gene Therapy at Nationwide Children’s and professor of Pediatrics and Physiology and Cell Biology at The Ohio State University showed that GALGT2 overexpression in skeletal muscle prevents injury in both mdx (muscular dystrophy pathology) and wild-type mice. Since then, researchers at Nationwide Children’s in cooperation with Sarepta Therapeutics have developed the technology into a product that is currently in a phase 1/2a clinical trial, which is the first arterial gene therapy trial in DMD.

“GALGT2 overexpression compensates for the lack of dystrophin in the context of DMD,” says Dr. Flanigan, leader of the clinical trial for GALGT2 at Nationwide Children’s. “By overexpressing synaptic dystroglycan binding partners in the skeletal muscles, such as utrophin, the muscles can function normally — even when dystrophin is absent.”

The GALGT2 surrogate approach offers a particular benefit that many gene therapies lack. This single substitute is expected to treat the majority of dystrophin gene mutations responsible for DMD, as well as potentially having applications in other muscular dystrophies.

Could Two Vectors Be Better Than One?

Like the *DMD* gene, the gene for dysferlin (*DYSF*) is too large to package in an AAV vector. However, using dual vector technology to increase the packaging capacity of AAV, researchers have developed dysferlin



“To this point, we’ve have very little to offer these families. For 50 years, our only approved treatment for Duchenne muscular dystrophy has been prednisone. Our research aims to see if gene therapy is a safe and effective option for these patients and others with rare neuromuscular diseases in the future.”

— Jerry Mendell, MD, principal investigator in The Center for Gene Therapy in The Research Institute at Nationwide Children’s Hospital

“It’s heartbreaking to exclude patients from a trial because they have antibodies to AAV. Our hope is that we will have a strategy to offer the therapy safely and effectively to patients who have had environmental exposure to the virus.”

— Louise Rodino-Klapac, PhD, principal investigator in the Center for Gene Therapy in The Research Institute at Nationwide Children’s Hospital



overlaps. This technique relies on homologous recombination to piece two plasmids delivered in separate vectors back together upon infection of the target cell. (See the figure on page 23.)

“The gene of interest, in this case *DYSF*, is divided between two transfer plasmids with substantial sequence overlap,” says Dr. Rodino-Klapac. “When administered together, both vectors enter the cell and the plasmids recombine and express the full-length gene.”

The broad scope of preclinical work with this technology for other genes shows mixed results, with the main concern being low efficiency of recombination. However, researchers hope that it will be an effective solution for some genes. In the case of *DYSF*, it has worked remarkably well, says Dr. Rodino-Klapac.

Dr. Rodino-Klapac is leading an intramuscular trial using a dual vector approach for dysferlinopathy — a muscular dystrophy affecting patients in their late teens or early 20s, with approximately one-third of patients becoming wheelchair bound within 15 years of diagnosis. LGMD2B and Miyoshi myopathy are the two most common forms of dysferlinopathy.

She is hopeful that an intravenous clinical trial could open in 2019.

MEETING THE CHALLENGES OF AN AAV GENE THERAPY FUTURE

“One consideration that is critical with these clinical trials is that, at present, the dose is a one-time thing for these kids. Currently, they won’t have a chance for another stronger dose. Once they are injected with vector, they build up an immunity to it and future doses won’t be effective,” says Dr. Mendell.

Likewise, if someone has environmental exposure to AAV9, they may have antibodies that would exclude them from the trial because of the likelihood that the therapy would be unable to get past the immune system.

“It’s heartbreaking to exclude patients from a trial because they have antibodies to AAV,” says Dr. Rodino-Klapac. “Our hope is that we will have a strategy to offer the therapy safely and effectively to patients who have had environmental exposure to the virus.”

Drs. Mendell and Rodino-Klapac and their colleagues at the Center for Gene Therapy at Nationwide Children’s have had success in using apheresis and immunotherapeutic mediations in animal models. The next step will be to design a clinical trial to test the process in patients.

“Solving the problem of re-dosing is vital to offering the best possible outcomes for patients and their families,” says Dr. Mendell. “Developing a solution is the right thing to do.”

Another step on the road to the future of gene therapy is newborn screening. Newborn screening identifies many genetic diseases that gene therapy aims to treat. And as more gene therapies become available, the number of genetic diseases on the screening list is likely to increase. So, when should gene therapy be given?

“We believe the sooner the child can get treatment the better the outcome,” says Dr. Mendell. “In our trial, those patients with SMA1 who were treated early are reaching milestones never seen in the natural history of the disease.”

When the gene therapy has the ability to not only stop the progression of a disease but — if given early enough — stop the onset of symptoms entirely, the question

seems to have a clear answer. However, given the lack of long-term studies for these new therapies, researchers don’t yet know how long the effects will last.

“That’s part of the re-dosing conversation,” adds Dr. Byrne. “As later onset diseases are identified in early life, no one is sure what to do with that information. But it seems likely that earlier intervention will lead to better outcomes.”

Treating smaller children also requires less vector. For the SMA1 trial, researchers gave the gene therapy to infants. In the upcoming DMD and LMGD trials, participants will be in the 4-to-12-year-old range.

“The requirements of using AAV gene therapy related to DMD in older, larger kids is stretching the resources of the existing technology,” says Dr. Byrne.

While researchers have shown safety and efficacy of AAV9 in numerous preclinical studies, and in the handful of early-phase clinical trials, the limits of the technology have yet to be defined. In a recent study

published in *Human Gene Therapy*, James Wilson, PhD, and colleagues report severe toxicity in large animal models following high-dose IV administration of the AAVhu68 vector expressing human SMN. During the Nationwide Children’s SMA1 trial, four patients had asymptomatic elevated liver enzymes attenuated with a course of prednisone. Dr. Mendell notes that no other side effects were observed during the trial.

Two factors may explain the marked difference in the results of the two studies. First, the vector used in the Wilson study is an AAV9 mutant, and while it is only two base pairs different from the AAV9 serotype, it hasn’t gone through the same testing as AAV9, says Jaysson Eicholtz, director of GMP (Good Manufacturing Processes) Operations at Nationwide Children’s. Additionally, different methods were used to quantify concentrations of vector in the gene therapy products produced at each clinical manufacturing facility (CMF).

“We don’t have an industry standard for this process,

CAN GENE THERAPY WORK FOR LARGE GENES?

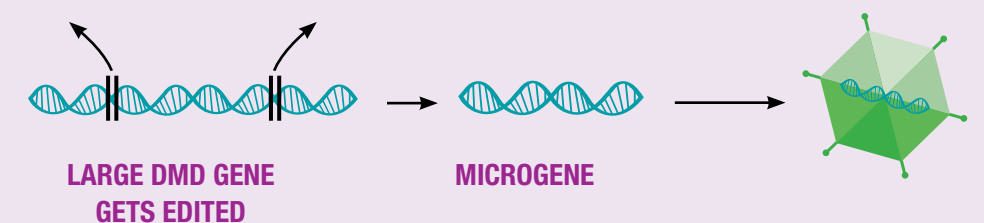
Small Vector, Large Genes

AAV vectors have a capacity of 4.8 kb. In contrast, the coding DNA for the *DMD* gene is roughly 11.5 kb — about twice the capacity.



Microgene Strategy

Some researchers discovered that by skipping certain exons, they could make a mini version of the *DMD* gene and still get a functional dystrophin protein.



Dual Vector Strategy

For the *DYSF* gene, which codes for the protein dysferlin, researchers can split the gene into two pieces with a section of overlapping code. Then, they package the two pieces into separate vectors that can be administered to the patient.



“I’m optimistic that we’ll meet the challenges that we’ve had. When I first came to Nationwide Children’s, we had to figure out how we could possibly make enough vector to do an IV clinical trial. Well, now we’re here, and we’re doing it. It’s not insurmountable. If the science is there, and the drug is effective, we’ll find a way ... How could we not?”

— Louise Rodino-Klapac, PhD, principal investigator in the Center for Gene Therapy in The Research Institute at Nationwide Children’s Hospital

but at Nationwide Children’s we use a manual process that has been consistent across all research, preclinical, toxicology and clinical lots,” says Eicholtz. “The digital droplet PCR method used on the products in the Wilson paper could result in concentrations of vector four times higher than the method we at Nationwide Children’s use for dosing.”

Dr. Byrne suggests that developing better and more consistent ways to measure concentrations across the industry will be an important step in bringing gene therapy to the clinic. “In a theoretical sense, you can do the math on the scale up... but until you actually do it, there’s a lot that you don’t know,” he says. “We still have a lot of work to do in developing analytics for bioavailability and potency. Those questions have been sorted out in the small molecule world, but we don’t yet have consistency for those tests in the gene therapy world.”

IF THE SCIENCE IS READY, WILL THE MARKETPLACE CATCH UP?

In today’s political and economic climate, every medical advancement is greeted first with excitement and optimism, followed quickly by the question “How much is this going to cost?” A month after approval, for example, Spark Therapeutics revealed it would charge \$850,000 for a one-time dose of its vision-loss gene therapy. This hefty price tag makes it the most expensive medication sold in the United States. Of course, negotiations with insurance companies take the pricing conversation further, including outcomes-based rebates.

“These are extraordinarily expensive therapies to produce,” says Dr. Flanigan, who is also a professor of Pediatrics and Neurology at The Ohio State University College of Medicine. “We’re going to have to figure out whether our model for this works in the long run. As

we accumulate more and more rare diseases treatable by gene therapy, costs upwards of \$1 million per dose may not be sustainable.”

Directly contributing to pricing is the challenge to commercialize and mass-produce the products. Scalability and manufacturing are key points in conversations with industry partners, says Dr. Rodino-Klapac. “It’s a bit different to make enough vector for hundreds of patients compared to a dozen patients in a trial.”

As vector products move into the marketplace, industry partners will be required to address the challenges of scale and distribution.

“I’m optimistic that we’ll meet the challenges that we’ve had. When I first came to Nationwide Children’s, we had to figure out how we could possibly make enough vector to do an IV clinical trial. Well, now we’re here, and we’re doing it. It’s not insurmountable,” Dr. Rodino-Klapac says. “If the science is there, and the drug is effective, we’ll find a way ... How could we not?”

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CAN GENE THERAPY TREAT DOMINANTLY INHERITED DISORDERS?

by Abbie Roth

Most applications of AAV-mediated gene therapy research are in recessively inherited rare diseases. The affected individuals have two copies of the “bad” gene, and receiving a copy of the “good” gene enables the cell to function (more) normally.

For dominantly inherited disorders, the goal is not to replace a gene that’s missing. There’s one bad copy of a gene in the cell, and it usually overrides the function of the good gene copy, explains Scott Harper, PhD, principal investigator in the Center for Gene Therapy in The Research Institute at Nationwide Children’s. “You want to eliminate the bad copy to allow the good copy to function normally.”

“Until about 12-15 years ago, we didn’t have good technologies to do that with gene therapy,” he says.

However, in 1998, Andrew Fire, PhD, and Craig Mello, PhD, published a study that described gene silencing by RNA interference in *Nature*. The work would later earn the two a Nobel Prize.

While Drs. Fire and Mello first described the phenomenon in the roundworm *Caenorhabditis elegans*, the cells of all complex organisms use RNA interference to regulate gene expression. Cells produce microRNAs, which are processed but do not code for proteins. They bind to other RNA in the cell and cause them to be degraded.

“We and a few others have been working on how to co-opt this natural system for our purposes,” says Dr. Harper. “We can take natural microRNAs, change the sequence, clone and package them in an AAV9 viral vector for delivery to a patient. And we can target any gene we want.”

In his case, Dr. Harper wants to target *DUX4* (double homeobox 4), the gene responsible for facioscapulohumeral muscular dystrophy (FSHD), a dominantly inherited muscular dystrophy with a widely variable phenotype. FSHD typically manifests in the second decade of life and progresses from there. However, early onset is possible.

“FSHD is complicated because there isn’t a uniform presentation of disease in patients,” says Dr. Harper. “Some patients may only experience muscle weakness in a localized area, such as the bicep. Others may have profound muscle weakness that impacts the whole body.”

Dr. Harper and his colleagues have been working to test the safety and efficacy of delivering interfering RNA targeted to *DUX4* in small animal preclinical studies. Their hope is to develop a treatment that could be delivered systemically or via intramuscular injection to effectively reduce *DUX4* expression in patients with FSHD.

“This whole line of research is relatively new,” Dr. Harper says. “In 10 years the FSHD field has identified the genetic cause of FSHD, and we and others have developed the needed animal models for the disease and now we’re looking at a strategy to use gene therapy to treat it. It’s exciting to see how the science is moving forward, and how what we learn regarding FSHD can be applied to other dominantly inherited diseases.”

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THE PDA CONUNDRUM

A patent ductus arteriosus is associated with increased morbidity and mortality, but common treatments are associated with poor outcomes as well. What is a neonatologist to do?

by Jeb Phillips

Until the mid-2000s, most neonatologists were pretty sure they knew how to handle a patent ductus arteriosus (PDA) in an infant born preterm – it needed to be closed as soon as possible.

This was the conclusion of decades of research demonstrating that:

- A patent (or open) ductus allows oxygenated blood from the aorta to leak into the oxygen-poor blood of the pulmonary artery, ultimately straining the heart and lungs

- PDA is associated with bronchopulmonary dysplasia, respiratory distress syndrome, intraventricular hemorrhage and many other problems, including increased mortality rates

- An open ductus can be closed by nonsteroidal anti-inflammatory drugs (NSAIDs) such as indomethacin, and failing that, by surgical ligation

So a widespread practice developed of trying indomethacin (or ibuprofen) closure in the first few days of a preterm infant's life, and if that didn't work, turning to surgery.

It makes sense. It's also a "conceptual trap," in the words of William Benitz, MD, Philip Sunshine professor in Neonatology and former chief of Neonatology at Lucile Packard Children's Hospital at Stanford University. Dr. Benitz is the first to admit that he, like the vast majority of his colleagues around the world, was caught in that trap for years.

"I thought I was doing the right thing," he says. "The whole experience has been humbling."

Yes, an open ductus arteriosus is a problem. But clinicians weren't asking other important questions, says Jonathan Slaughter, MD, a neonatologist at Nationwide Children's Hospital and principal investigator in the Center for Perinatal Research:

Is closing the ductus actually good for every preterm baby who has a PDA? If not, can we figure out the specific babies who would benefit?

"That's where we're stuck," says Dr. Slaughter. "We don't know which kids."

ESCAPING THE TRAP

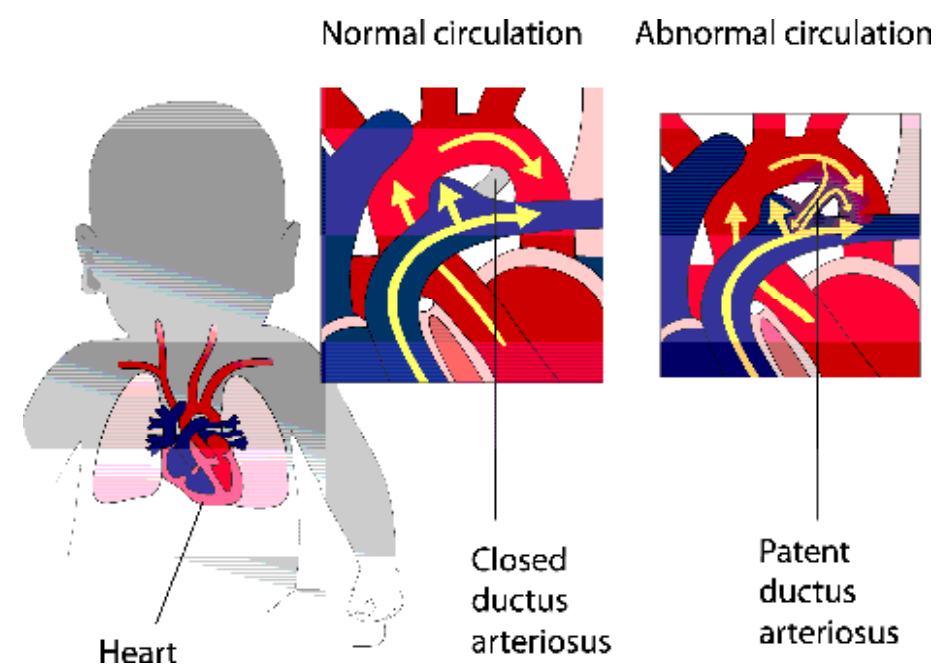
The answer to Dr. Slaughter's first question has become clearer. Closure is not good for every preterm baby with a PDA. It's probably not good for most of those babies, in fact.

The turning point was the 2007 re-analysis of data from the 2001 Trial of Indomethacin Prophylaxis in Preterm Infants, says Dr. Slaughter. It found an association between surgical ligation of the PDA and increased risks of bronchopulmonary dysplasia, severe retinopathy of prematurity and neurosensory impairment in extremely low birthweight infants.

A 2010 publication from Dr. Benitz also caught people's attention. He had been asked to present at a conference on his preferred practice – trying closure with indomethacin first, then moving to ligation – and he searched for evidence that the practice helped preterm infants. He couldn't find it in dozens of published studies.

"It's not just that we don't have evidence to support the treatment; we also have a lot of evidence that the treatment is not effective," he says. "That's a stronger conclusion."

Even though clinicians were trying to close a PDA as soon as possible, data had emerged before Dr. Benitz's review suggesting that most PDAs will spontaneously close without drugs or surgery. The evidence has only become stronger over time.



The ductus arteriosus is a blood vessel in the fetus that connects the pulmonary artery and aorta. It directs most of the blood directly from the right ventricle to the aorta, bypassing the fetal lungs. Once the infant is born, the ductus arteriosus should close.



“If you only treat the kids whose PDA definitely won’t close, then we may actually find a positive effect of treatment. That is personalized medicine that we’re not able to practice today.”

– Jonathan Slaughter, MD, neonatologist and principal investigator in the Center for Perinatal Research at Nationwide Children’s Hospital

A 2016 study from Dr. Slaughter and colleagues at Nationwide Children’s examined babies born at 28 weeks of gestational age or less who had PDAs. Some were treated with NSAIDs and some were managed conservatively. There was no difference in the odds of mortality or moderate-to-severe bronchopulmonary dysplasia between the groups.

A 2017 study in *Pediatrics* found that most PDAs in even the youngest and smallest babies – less than 26 weeks of gestational age and 750 grams weight at birth – will spontaneously close with conservative management.

Still, some PDAs don’t close for weeks or months. Some don’t at all. What should happen for those babies?

“We are left without strong data to guide the practice of evidence-based medicine,” says Carl Backes, MD, a member of The Heart Center and Division of Neonatology at Nationwide Children’s. “We have some data showing there are risks for heart failure, bronchopulmonary dysplasia and worsened outcomes with continued exposure to PDA. Alternatively, we have data showing that many ducts will close on their own without exposing infants to the risks of drug therapy and surgical ligation.”

Knowing which babies have PDAs that won’t close for months, or won’t ever close, would help.

WHO TO TREAT AND WHEN

While that 2017 *Pediatrics* study did show that most PDAs in preterm infants will close on their own, babies who were at least 26 weeks of gestational age and 750

grams at birth experienced spontaneous closure much more quickly. In contrast, the median time to closure was 71 days for babies born at less than 26 weeks and 48 days for babies with a birth weight of less than 750 grams.

A few babies in the study still had patent ducts at one-year follow-up. It may make sense, then, to focus on this subset of particularly small babies, says Dr. Backes. A PDA treatment algorithm that he helped develop at Nationwide Children’s does take into account a baby’s gestational age. It also assesses the “hemodynamic significance” of the patency by using eight clinical and echocardiographic criteria, such as a minimum PDA size of 1.5 millimeters and persistent hypotension requiring a cardiotropic agent.

The algorithm suggests not considering drug or procedure-based closure until at least 2 weeks of age for any baby, and potentially not even considering closure until after 30 days of age. In highlighted text is the sentence, “There is no evidence of any long-term benefit from treatments that close the PDA.”

Drs. Slaughter and Backes would like to create a spontaneous closure prediction model and are trying to secure National Institutes of Health (NIH) funding for it. Their idea is to regularly perform echocardiograms on preterm infants, collect biomarkers such as B-type natriuretic peptide and follow the babies out to at least 36 weeks of age, paying special attention to bronchopulmonary dysplasia (BPD) and mortality.

The combination of those variables could help the physicians learn which infants are most likely to have

a persistent patent ductus and which portion of those are most likely to be negatively affected by it. The biomarkers may add important information to the decision-making process.

“If you only treat the kids whose PDA definitely won’t close, then we may actually find a positive effect of treatment,” says Dr. Slaughter. “That is personalized medicine that we’re not able to practice today.”

HOW TO TREAT THEM

There are three traditional treatments for preterm infants with PDA that can result in closure. Conservative management, which may include fluid restriction and diuretics; NSAIDs, which have known renal and gastroenterological risks; and surgical ligation, with its own concerns.

A fourth has gained prominence in the last decade: catheter-based closure. It is considered among the safest interventional cardiac procedures in general and is the “procedure of choice” for PDA closure once an infant reaches approximately 4 kilograms. But only a handful of academic health care institutions, including Nationwide Children’s, regularly perform percutaneous closure on very small infants.

That’s not because others don’t have the ability; it’s because they have been waiting for a device specifically tailored to those infants, says Darren Berman, MD, co-director of Cardiac Catheterization and Interventional Therapy in The Heart Center at Nationwide Children’s.

Drs. Berman, Backes and colleagues have demonstrated that PDAs in small infants can be closed safely with a catheter-based approach. Nationwide Children’s is now one of eight United States centers participating in a prospective study called “Amplatzer Duct Occluder II Additional Sizes” (NCT03055858), investigating the use of a closure device in infants as small as 700 grams.

“We’re talking about the exact population that is likely to be most affected by a persistent PDA,” says Dr. Berman. “If we can show that this is the right device to close the PDA for them, then we can move on to the studies that we really need, asking, does this really benefit the patient?”

That’s a question clinicians once thought that they had figured out in the 1970s.

“We’re actually living through the answer right now,” says Dr. Berman.

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– Carl Backes, MD, The Heart Center and Division of Neonatology at Nationwide Children’s



How to Make a Viral Vector

The Research Institute at Nationwide Children’s Hospital is the home to a current Good Manufacturing Practices (cGMP) Clinical Manufacturing Facility (CMF) that operates according to FDA cGMP Guidelines to ensure the safety of manufactured biologic products.

THE SPACE

The CMF is a 9000-sq-ft space, including a 7500-sq-ft clean room suite with ISO Class 5/7/8 spaces and 1500-sq ft quality control lab and research production spaces. The presurization of the central corridor in the viral vector production suite allows the concurrent production of four distinct viral vector products. This allows the release of vector products for multiple clients in an expedited timeline. Biological drug

substances are manufactured according to the FDA Guidance for Industry cGMP for phase I investigational drugs, to ensure product safety, identity, purity and strength.

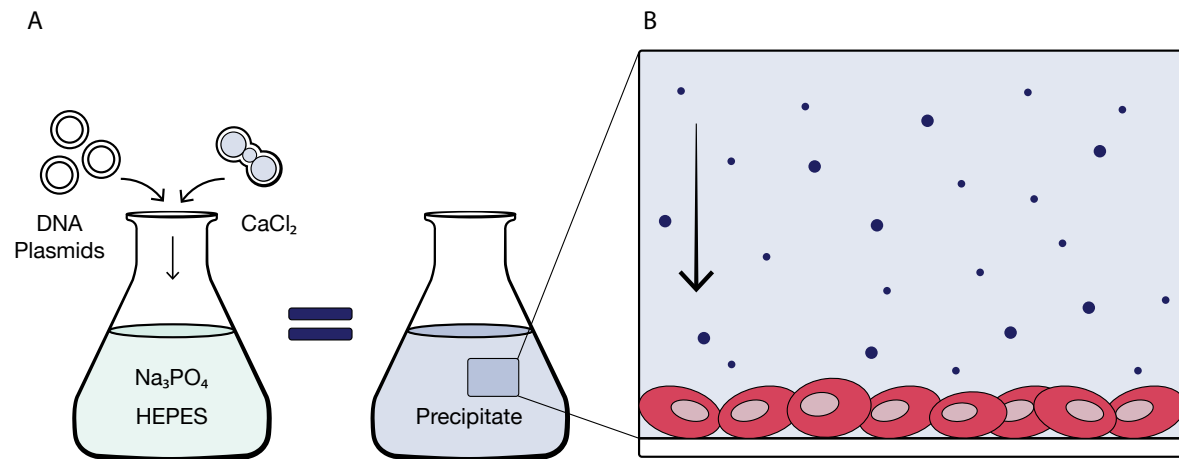
PRODUCTION CAPACITY

The current capacity for a single lot of AAV production is 20 36-layer HYPERstacks, which creates 6 billion cells ready for viral transfection and can yield upwards of 1E+15 vg/mL. The CMF can run three concurrent campaigns (lots) at one time.

THE PROCESS: TRANSFECTION

Transfection is the process by which the viruses acquire the modified genetic material, in this case, DNA. Transfection occurs in HYPERStack trains – groups of stacks of plastic cases wherein layers of HEK293 cells grow. HEK293 cells are a cell line derived from human embryonic kidney cells that are grown in tissue cultures.

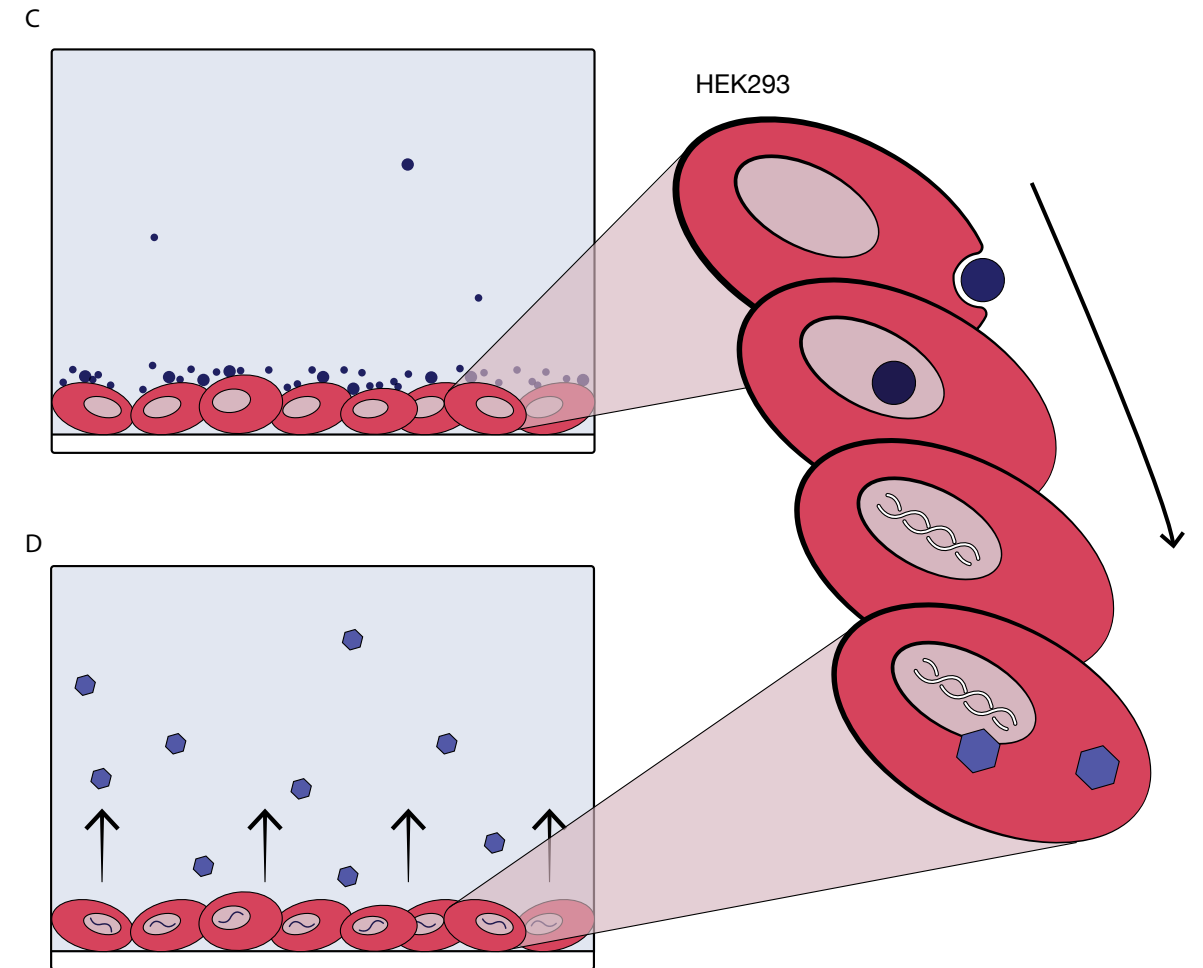
Through transient transfection, engineered plasmid DNA is introduced to the cells along with calcium chloride, sodium phosphate and HEPES, an organic chemical buffering agent. The HEK293 cells then function as small virus-producing factories. Once the process is complete, our team harvests the product and prepares it for purification by clarifying and concentrating the volume using tangential flow filtration.



A and B First, three DNA plasmids plus CaCl₂ combine **(A)** with HEPES and Na₂PO₄ solution to form a precipitate **(B)** in the solution added to the HEK293 cells.

C As the precipitate settles, it is taken up by the HEK293 cell into the nucleus. Then, the cells begin processing the virus.

D The HEK293 cells assemble the virus, releasing vectors with the desired genes into the media.



TANGENTIAL FLOW FILTRATION

Tangential Flow Filtration is a rapid and efficient method for separating and purifying the AAV vectors for the final drug product.

- Once the HEK293 cells have released the vectors into the media, the liquid is separated from the cells and filtered.

- The vector flow is parallel to the filter and is recirculated numerous times to remove large unwanted contaminating proteins.
- Diafiltration occurs to exchange the buffer and help release any vector that is retained on the filter.
- The vector is concentrated so the volume is reduced to aid in further downstream processing.

ACCESSING GENOMIC DATA FOR RESEARCH AND CLINICAL DIAGNOSTICS — MEETING THE CHALLENGE

What good is genomic data if it can't be shared efficiently?

By Rajeswari Swaminathan, MS

The genesis of DNA sequencing technology in the 1970s was a turning point in science, giving birth to a modern era in biology. Further, with the unfolding of the relationship between nucleic acid order and uniqueness across species, improvement in strategies to sequence this molecule continued at a rigorous pace.

In 1976, a bacteriophage became the first organism sequenced. Since then, consistent improvements in technology within the sequencing space have ultimately led to an avalanche of data, spawning the field of bioinformatics. The Human Genome Project began in 1990, and its completion in 2003 is a remarkable milestone in the history of medicine, contributing to our understanding of the molecular mechanisms underlying a multitude of human diseases. Through advanced next generation sequencing technologies, particularly whole exome and whole genome sequencing, genomic data is entering the clinical space.

Genomic data has the ability to be extremely informative, and the remarkable improvements in sequencing technologies have helped create a substantial pool of data. But what good is data that cannot be shared across applications and institutions?

HOW CAN WE SHARE GENOMIC DATA ACROSS RESEARCH INSTITUTIONS?

Currently, data generated within research laboratories are siloed, with many small pockets of geographically dispersed information. One of the main reasons for this limited accessibility is the privacy associated with genomic data. Although it is not considered personal health information according to HIPAA guidelines, it is possible to identify an individual using their genomic information. The Global Alliance for Genomics and Health (GA4GH) is trying to enable seamless data

integration and sharing by designing interoperable genomic application programming interfaces (APIs), termed genomic API. Google has adopted the framework proposed by GA4GH and created a functional product named Google Genomics. Although the first version of the API is in production and actively used by the research community, work is ongoing to add features and enhancements to the existing version.

The possibility of using a blockchain framework for secure storage and sharing of genomic data is also frequently discussed. Blockchain is the underlying technology behind cryptocurrencies, such as bitcoin, and is disrupting the financial industry with its demonstrated strengths in interoperability, transparency and auditability. Blockchain uses a decentralized, distributed ledger technology that eliminates the need to have an intermediary to verify transactions, thus empowering users depositing data to control its sharing. Every transaction performed gets added as a block to the chain, creating a historical footprint, which cannot be modified or deleted, preventing malicious attacks on the data. Although health care organizations are still in the infant stages of exploring this technology, blockchain has the potential to become the basis to transform health information technology.

HOW CAN WE MAKE GENOMIC DATA ACCESSIBLE IN THE CLINIC?

Genomic data is gaining visibility in the clinical space, especially in the diagnosis of genetic disorders. Currently, once a health care provider orders a genetic test, the samples are sent to a certified genetic laboratory that returns an analyzed, concise clinical summary report in the form of a PDF document. This report is mostly stored as a paper version but in some cases, it might be linked to the patient record in the electronic health record (EHR) as an attachment.

The emerging practice of personalized medicine requires the integration of genomic data with clinical information in the EHRs for the overall benefit of health care and improved patient outcomes. One of the benefits of this integration is the possibility of using the combined information for automated downstream clinical decision support (CDS). A major challenge to executing this action is the inadequate use of standards to represent genomic data. Genomic data comes in a variety of formats and sizes that would require a major reconstruction of the workflow within EHR. Another challenge is also the insufficient education of the clinical workforce related to how best to use genomic information for the benefit of the patient.

Despite these challenges, one area in which clinical integration of genomics data in the EHR for CDS has been successful is the emerging field of pharmacogenomics. Here, a patient's genomic information can predict his or her reaction toward specific drugs. Adverse drug reactions are a leading cause of morbidity and mortality during routine medical care. Identifying a genetic variant and linking it to the patient record allows the activation of downstream processes that can guide physicians toward prescribing the appropriate medication for a patient. At Nationwide Children's, we've rolled out a CDS system for the thiopurine-TPMT drug-gene pair. Although the effect of the TPMT gene on the metabolism of thiopurines is well documented for the pediatric population, the lack of prescribing physician knowledge about genomic test results prompted the development of an alert system within the EHR.

Genomic data is here to stay. Innovative solutions to overcome some of the challenges outlined here are required to enable the utilization of genomic information for the benefit of both clinical and research communities.

Rajeswari Swaminathan, MS, is a bioinformatician and systems programmer in Research Information Solutions and Innovation at Nationwide Children's Hospital



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Improving Exclusive Enteral Nutrition Adherence Among Children Newly Diagnosed with Crohn's Disease

by Kevin Mayhood

Using a quality improvement methodology, physicians at Nationwide Children's Hospital facilitated the use of exclusive enteral nutrition (EEN) among children newly diagnosed with Crohn's disease. Rates of EEN usage increased from a baseline of less than 5 percent to an average of about 50 percent. Of the 73 kids who started on EEN, half completed at least 8 weeks on the program. Of those, 71 percent achieved remission.

PediatricsNationwide.org/QI-Improves-EEN-Adherence



Solving the Puzzle of Transfusion-Related Immune Reactions

by Katie Brind'Amour, PhD, MS

With the initial safety challenges addressed and the technical barriers of donor blood storage and cleaning improved, critical care physicians and hematologists can examine the nitty gritty of the procedure: why do some patients fare better than others after a blood transfusion, when all else remains relatively constant? And even more importantly, could some of our transfusion practices do more harm than good?

PediatricsNationwide.org/Transfusion-Related-Immune-Reactions



Event-Related Potential as a Biomarker for Speech-Sound Differentiation in Preterm Infants

by Abbie Roth

Preterm infants are at increased risk for developmental delays, including hearing difficulties. Olena Chorna, MD, and Nathalie Maitre, MD, PhD, led a study that shows that event-related potential (ERP) in hospitalized preterm infants can be used as a biomarker of infant speech-sound differentiation, filling a gap in treatment-response biomarkers for auditory interventions. The researchers say ERP provides valid discriminative, responsive and predictive biomarkers.

PediatricsNationwide.org/Event-Related-Potential

“ Nothing in life is to be feared, it is only to be understood. Now is the time to understand more so that we may fear less. — Marie Curie ”

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Publishers
Jan Arthur
Tonya Lawson-Howard

Editor/Writer
Abbie Roth

Staff Writers
Jeb Phillips
Kevin Mayhood

Contributing Writers
Katie Brind'Amour, PhD, MS
Mary Bates, PhD

Art Director and Designer
Tanya Burgess Bender

Photographers
Brad Smith
Dan Smith

Illustrator
Mandy Root-Thompson

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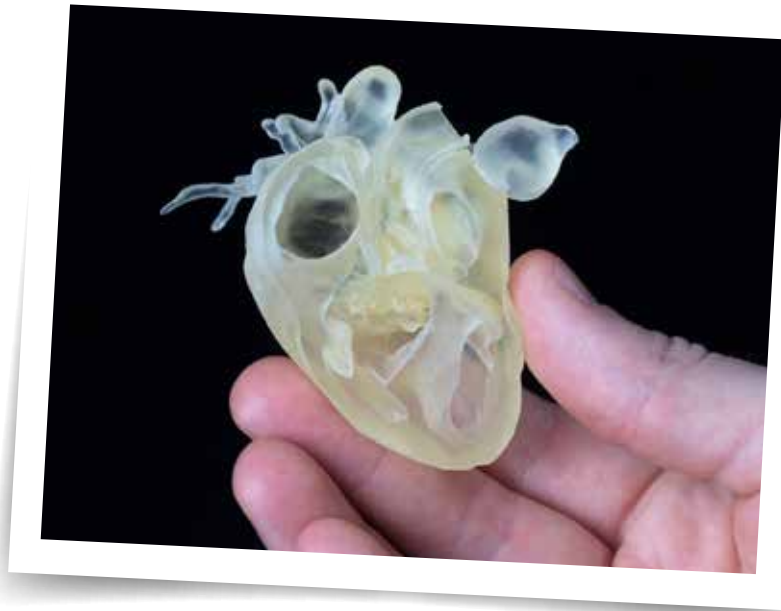


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A Heart in Three Dimensions

The 3D Printing Lab, part of the Pediatric Advanced Imaging Resource at Nationwide Children's Hospital, provides personalized diagnostic and treatment solutions for clinicians and patients. As one of only a handful of such centers in the country, the lab provides patient-specific treatment planning and device development services from a pediatric perspective. The program encompasses multiple surgical specialties, providing solutions for a variety of pediatric conditions.

For more about how 3D printing is benefiting patients and clinicians, visit PediatricsNationwide.org/3D-Printing