

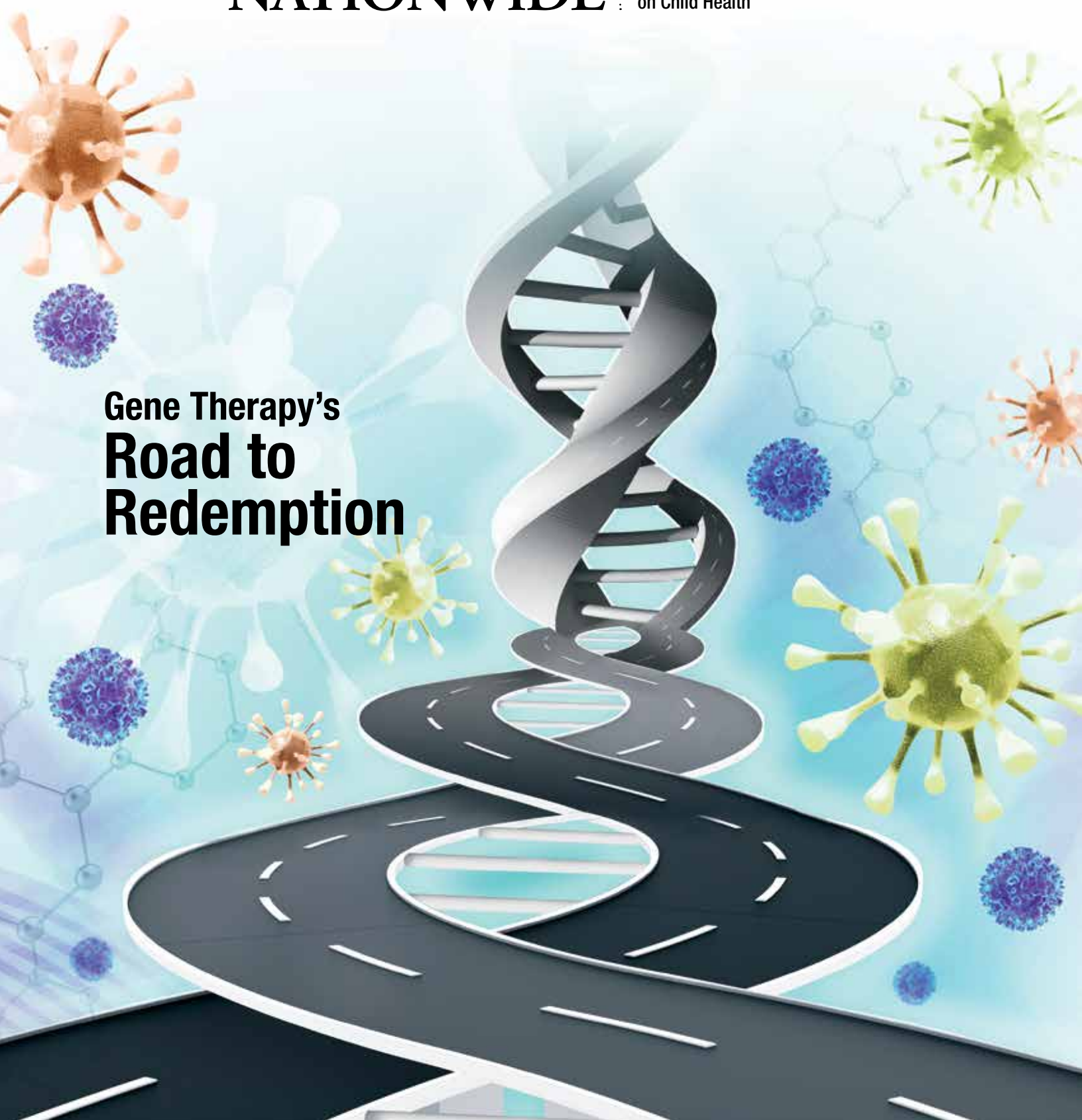
Spring/Summer 2014

# Pediatrics

NATIONWIDE

Advancing the Conversation  
on Child Health

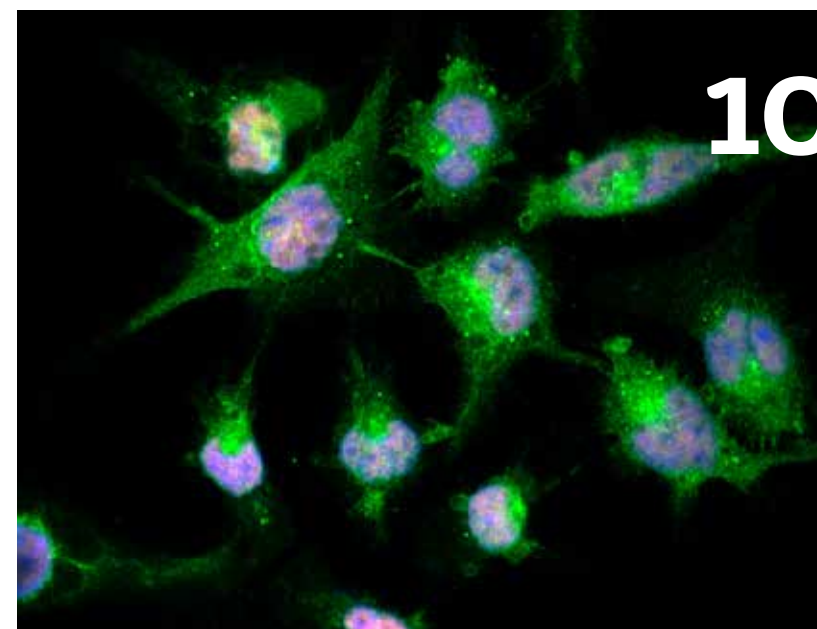
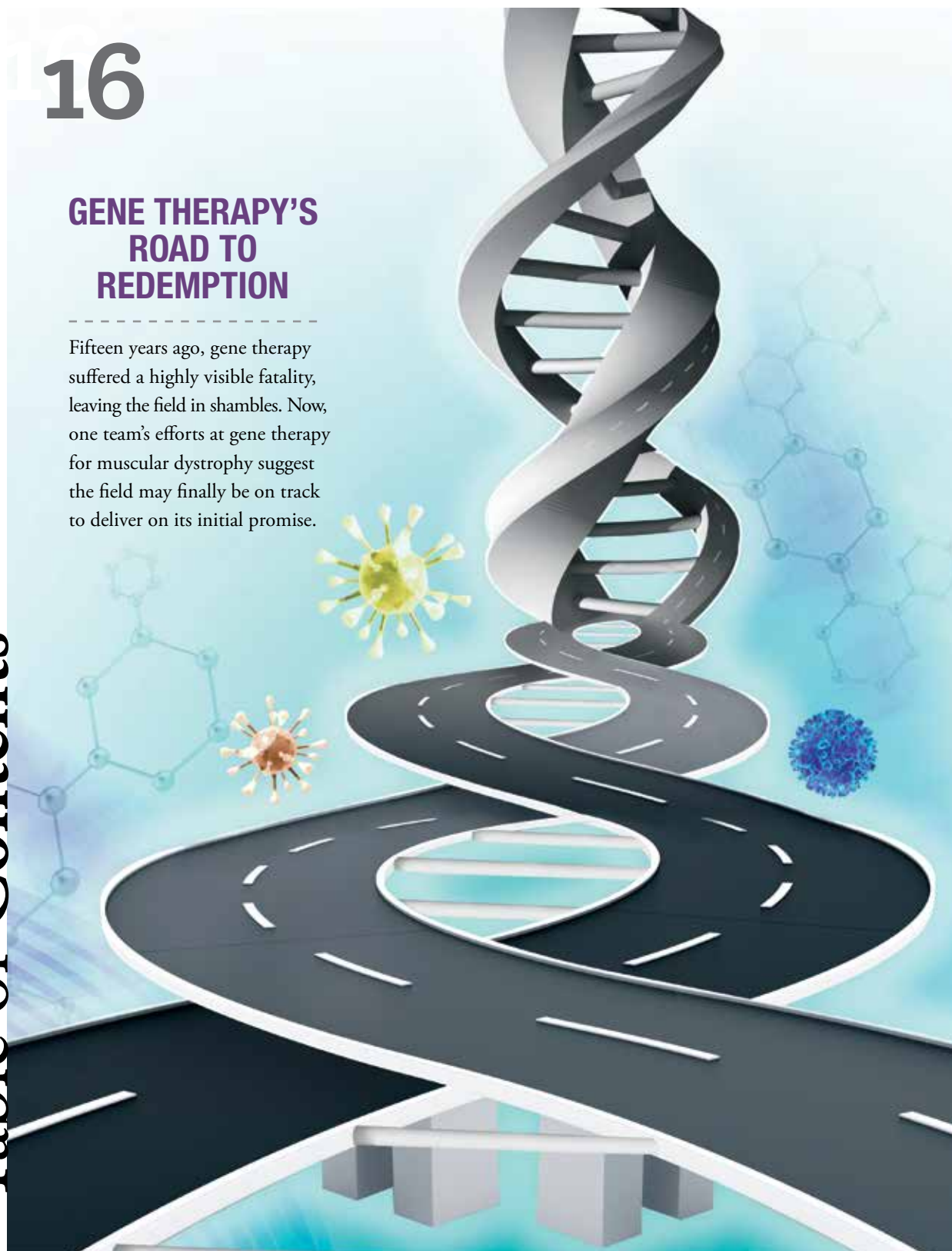
Gene Therapy's  
**Road to  
Redemption**



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**GENE THERAPY'S ROAD TO REDEMPTION**

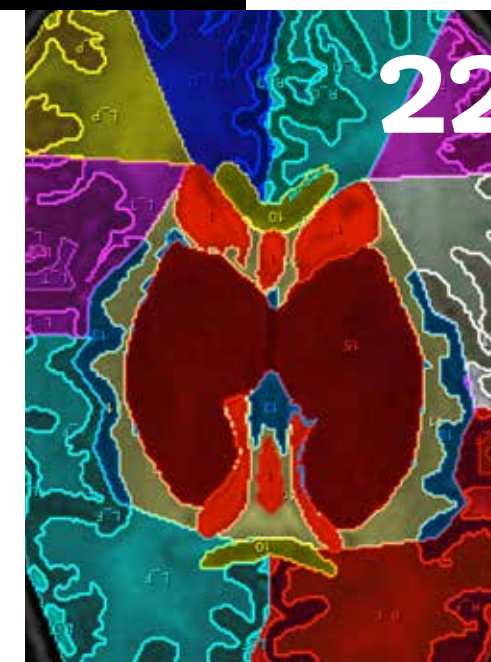
Fifteen years ago, gene therapy suffered a highly visible fatality, leaving the field in shambles. Now, one team's efforts at gene therapy for muscular dystrophy suggest the field may finally be on track to deliver on its initial promise.



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“The value of... transparency is that it holds us accountable to the standard of care that we believe in.”

– Paul Levy, MD, former CEO of Beth Israel Deaconess Medical Center (page 15)

“The diagnosis of NEC is very subjective, so having an objective test ... could have meaningful impact.”

– Karl Sylvester, MD, Lucile Packard Children's Hospital (page 7)



# CHIP at a Crossroads

Funding is running out for the Children's Health Insurance Program, a state-federal partnership that prevents low-income children from falling through the cracks.

Five years since it was reauthorized, the Children's Health Insurance Program is again facing an uncertain future. Funding for the state-federal partnership will run out next year, putting in jeopardy a program that has resulted in dramatic reductions in uninsured children.

CHIP, as it's commonly called, covers 8 million children whose families earn too much to qualify for Medicaid but not enough to afford high-quality private health insurance. Since the initial law was approved in 1997, the number of uninsured children in the United States has dropped by 40 percent to a record low of 7.2 million. In 2009, President Barack Obama reauthorized CHIP, expanding eligibility, simplifying enrollment and offering incentives for states to add more children to the program.

But the program could go away if Congress doesn't act soon. While Obama reauthorized CHIP through 2019, funding will end in October 2015. The Affordable Care Act, approved 13 months after the CHIP reauthorization, provided funding for the program but also cast doubt on its future. Under the ACA, children could be moved from CHIP to the ACA's health insurance marketplaces. That scenario concerns CHIP supporters. "CHIP is a

program that was designed for children," says Alison Buist, director of child health at the Children's Defense Fund in Washington, D.C. "It really does have appropriate health benefits and networks for children."

William Cotton, MD, medical director of the Primary Care Centers at Nationwide Children's Hospital, says CHIP — though not perfect — is a better option than trying something new. "Pediatricians are pretty scared about that," Dr. Cotton says. "We think CHIP has been very successful and that the Affordable Care Act won't cover children as well."

With states already planning for next year, Congress will need to act in the coming months to make sure children in the CHIP program don't lose their coverage. The idea, however, could face opposition. Though originally bipartisan, CHIP has become more controversial in recent years. President George W. Bush twice vetoed CHIP reauthorization legislation. Plus, the political fallout from the ACA makes any kind of health care proposal more controversial these days. "We have our work cut out for us," says Dr. Buist.

— Dave Ghose

## Diagnosis Focus

Up to one in 10 blood clots in women occur in teen contraceptive users.

When a teenage girl presents with chest pain, most doctors likely think first of anxiety, muscle injury or heartburn. In most cases, this is entirely appropriate. But if the girl is taking birth control pills, the problem could be a pulmonary embolism — and failing to diagnose it could be fatal.

More than half of all sexually active teen girls take combination hormonal contraceptives and many more teens take them to treat other health conditions. Contraceptive users are up to six times more likely to have a blood clot than non-users and recent data indicate that as many as one in 10 females who experience blood clots are younger than 20.

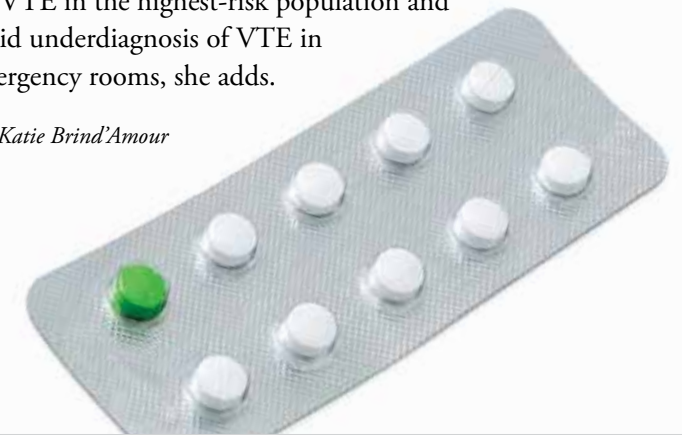
"I tell my patients that if they are otherwise healthy and walk into an ER with leg or back pain or shortness of breath, no one is ever going to think of a blood clot — they have to tell the doctor they're on a birth control pill," says Sarah O'Brien, MD, a hematologist at Nationwide Children's Hospital who studies venous thromboembolism (VTE) among contraceptive users.

Emergency nurses and physicians have the responsibility to respond appropriately as well, she says. "If the patient is on combined hormonal birth control, pulmonary embolism automatically has to be on the list of things to rule out," says Dr. O'Brien.

Dr. O'Brien's latest research suggests that reducing the incidence of VTE in teen girls could begin with thrombophilia screening of patients with a family history of the problem or who have other risk factors, such as smoking or obesity. But she cautions against screening too broadly. As many as 5 percent of U.S. Caucasians are carriers of the most common type of inherited thrombophilia, 90 percent of whom will never experience a complication.

Denying so many women the convenience of estrogen-containing birth control could actually cause more VTE-related problems than it avoids, Dr. O'Brien says, since the risk of blood clot during pregnancy is far greater than any increase from contraceptive use. Prescribing an estrogen-free birth control pill or finding alternative contraceptives are preferable solutions, she says. These changes could potentially reduce the risk for VTE in the highest-risk population and avoid underdiagnosis of VTE in emergency rooms, she adds.

— Katie Brind'Amour



## By the Book

AHA releases first evidence-based guidelines on anticoagulation in congenital heart disease.

Anticoagulation is a key element in managing patients with congenital heart disease. Despite the therapy's widespread use, there are no established guidelines on anticoagulants in this patient population, which often leads to inconsistency and guesswork in how and when to use the drugs.

A new document from the American Heart Association and the American College of Cardiologists is changing that with the first-ever evidence-based recommendations on preventing and treating thrombosis in all types of

congenital heart disease. The report, published in December in *Circulation*, is the result of an exhaustive review of published research on anticoagulation in children and adults. Dozens of cardiologists from around the country spent nearly three years on the project, part of a larger initiative by the two groups to develop a series of tools to help cardiologists better care for their patients.

"When writing guidelines, a group of experts is assembled and literature is reviewed," says Craig Sable, MD, chair of the AHA Council on Cardiovascular Disease in the

Young and a cardiologist at Children's National Medical Center in Washington, D.C. "In pediatrics, it is rare to have multicenter randomized controlled studies, so much of our guidelines are based on smaller studies or expert consensus."

The 82-page report addresses the more common questions about anticoagulant use, such as whether to give post-operative aspirin therapy to patients with single ventricle defects. In the past, some cardiologists would give their patients low-dose aspirin following surgery, while others might have used a higher dose and still others wouldn't have given aspirin at all. Under the new guidelines, low-dose aspirin is recommended.

The guidelines include suggestions for how to respond to complications that arise and what to do if that response prompts additional complications. Congenital heart disease is difficult to manage, in part, because each case is different. The new guidelines account for that, says Timothy Feltes, MD, a co-author of the new recommendations and co-director of The Heart Center at Nationwide Children's Hospital.

"Guidelines typically fit for 90 percent of the patients, but there's always going to be an exception," Dr. Feltes says. "This document tries to put together what's good for that 90 percent but also touches on many of the exceptions that we sometimes see."

— Kelli Whitlock Burton

# Supply and Demand

A major physician shortage is predicted by 2025. What does it mean for pediatrics?

Dire forecasts of physician shortfalls in the United States have many experts pondering how best to address the problem. In December, the journal *Academic Medicine* devoted an entire issue to the looming shortage, predicted by the Association of American Medical Colleges to peak in 2025 with 125,000 fewer doctors than the country will need.

What this means for pediatrics is unclear. Based on projected population growth, the AAMC estimates the combined fields of primary care pediatrics, family medicine and general internal medicine will be 46,000 doctors shy of meeting patient demand. Further, the American Academy of Pediatrics issued a statement in July 2013 citing a current shortage of pediatric subspecialists and an inadequate number of primary care pediatricians in rural and underserved communities.

“Within pediatric and other subspecialties, market forces often self-correct shortages and I think that’s what we’ll continue to see,” says Philip Saul, MD, physician-in-chief at Nationwide Children’s Hospital and chair of Pediatrics at The Ohio State University College of Medicine. In response to workforce studies a decade ago that called for more pediatric specialists in such areas as urology, neurosurgery and gastroenterology, medical schools expanded training programs and hospitals increased starting salaries to attract doctors to those areas.

Solving the shortage in general pediatricians may not be as easy, Dr. Saul says. The AAP statement noted several factors driving the need for more primary care pediatricians, including an increase in children with chronic health conditions, a rise in the number of pediatricians choosing to work part-time and an increase in patients due to the Affordable Care Act.

To address these issues, a number of medical schools have added primary care tracks and the AAP and others are pushing for more equality in government payments to pediatricians, which often are lower than payments for treating the same problems in adults. And then there’s federal support for resident training, called general medical education. The number of eligible residents was capped in 1997. It’s too soon to tell if increasing pressure from physician groups will convince Congress to make a change.

“The biggest barrier to increasing the workforce is GME funding, because it doesn’t matter if you produce more medical students if there’s nowhere to train them,” Dr. Saul says. “Hospitals have had to assume the cost over the cap and at some point, because of financial issues in the health care system, they won’t be able to do that anymore. We will just have to stay the course and see what happens.”

— Kelli Whitlock Burton

## 2025 Baseline Physician Supply and Demand Projections

PROJECTED NEED: 859,300

PROJECTED ACTUAL: 734,900

PROJECTED SHORTAGE: 124,400

Source: Association of American Medical Colleges

# Baby Steps

After decades of study, researchers are closer to understanding NEC.

Clinicians and scientists have been studying necrotizing enterocolitis, or NEC, for decades and here’s what they know for sure: Some premature infants get it. Some don’t. Some who get it need surgery. Some don’t. Some who get it will survive. Some won’t. The ability to predict disease severity remains, researchers say, frustratingly elusive.

“The biggest challenge with NEC is that you’ve got a whole neonatal intensive care unit full of preemies and only a few out of 100 are going to get it and you don’t know which ones,” says Lawrence Moss, MD, surgeon-in-chief at Nationwide Children’s Hospital and a founding member of a multicenter research consortium that’s studying NEC, an infection and inflammation of the intestinal walls. About 2,000 to 4,000 infants get the disease each year, making it the most common gastrointestinal illness in neonatal intensive care units. NEC is either managed with medicine and diet or with surgery, depending on severity.

“If we could figure out which babies with NEC are going to progress and need surgery and which ones are likely to do well with medical management,” Dr. Moss says, “we’d have a much better chance of helping these patients.”

The consortium has taken the first step in that direction by developing an algorithm to predict disease severity that uses both biologic and clinical markers. In a series

of studies published late last year, the team identified seven protein biomarkers found in urine that are either up- or down-regulated in patients with NEC. They also created a checklist of 27 risk factors to help predict disease progression.

They analyzed urine samples for the biomarkers and calculated risk factors for 119 premature infants at five hospitals around the country. Looking only at clinical criteria, the researchers accurately predicted disease severity just 40 percent of the time. But when they combined the presence of the proteins with the risk factors, their prediction rate rose to 100 percent.

“The diagnosis of NEC is very subjective, so having an objective test that could catch the disease early could have a meaningful impact on how babies are treated,” says Karl Sylvester, MD, an associate professor of surgery at Lucile Packard Children’s Hospital in Palo Alto, Calif., and lead author of the studies. “We are continuing to evaluate molecular markers that would speak to an infant’s predisposition for disease.”

These studies offer a snapshot of the proteins at one stage in each patient’s disease. The next step will be to look at protein levels over the course of the illness, information that could help scientists pinpoint what triggers NEC in the first place.

— Kelli Whitlock Burton



# A Knowledge Gap

Study suggests many pediatricians feel unqualified to treat genetic conditions.

Many pediatricians don't feel competent to treat patients with genetic disorders, according to a new study that raises questions about how to better prepare physicians for these cases.

Led by a team at the Children's Hospital at Montefiore in New York, researchers polled members of the American Academy of Pediatrics' Quality Improvement Innovation Network about the number of genetic tests they order, how often they discuss genetic testing and related medical conditions with their patients, their approach to collecting family histories and whether they felt they had sufficient training to treat patients with genetic conditions.

The study, published in the *American Journal of Medical Genetics*, found that most pediatricians ordered just three or fewer genetic tests per year and only 13 percent discussed the potential risks, benefits and limitations of genetic tests with patients and families seeking that information. More than half said they felt unqualified to provide even routine health care to patients with genetic diseases.

Treating genetic conditions in children often involves a team of medical professionals — including pediatricians. This, coupled with a shortage of practicing medical geneticists in the United States, could mean that doctors will see more patients with genetic disorders in their waiting rooms in the near

future, says Gail Herman, MD, PhD, president of the American College of Medical Genetics and Genomics.

“Medical schools and pediatric training programs often have different levels of genetics education built into their curriculums, so it's easy to see how some pediatricians would feel comfortable treating these patients while others aren't,” says Dr. Herman, who also is a physician-scientist in molecular and human genetics at Nationwide Children's Hospital. “But it does call attention to the need for more education during training and continuing education throughout a pediatrician's career.”

The ACMG offers several classes and workshops for physicians on genetics at professional meetings and through the group's website. Offering resources online is a great way to elevate the genetics know-how among practicing pediatricians, Dr. Herman suggests. Meanwhile, medical schools should consider a heavier emphasis on genetics in the training of students and residents.

“Genetics is quickly becoming the foundation for the treatment of many different medical conditions, and everybody is going to need to know it to some degree,” Dr. Herman says. “We must do more with our medical students and our pediatric residents in terms of genetic concepts and how to look at genetics in disease.”

— Kelli Whitlock Burton

# (Some Other) Mother's Milk

Women who can't breastfeed often turn to the Internet for breast milk. But is it safe?

As the daughter of a Wisconsin dairy farmer, Sarah Keim, PhD, has a keen grasp on the importance of testing milk for safe consumption.

“Government and industry have researched cow's milk processing, health concerns and benefits for over 100 years,” says Dr. Keim, a researcher at Nationwide Children's Hospital. “But our understanding of human milk is way behind.”

In an effort to fill that knowledge gap, Dr. Keim has launched a series of studies on breast milk and the growing business of milk sharing over the Internet. Thousands of mothers, convinced that human milk is essential for their infants, have turned to milk sharing — purchasing untested milk from online sellers, sometimes at a cost of more than \$3 per ounce. Not only is the practice expensive, Dr. Keim's latest research suggests that it may also be unsafe.

In a study published in the journal *Pediatrics*, Dr. Keim found that 74 percent of milk samples purchased online were contaminated either with disease-causing bacteria or high levels of bacteria in general, and 21 percent tested positive for cytomegalovirus DNA.

“Most milk-sharing websites try to educate about milk safety, but it doesn't seem to be working,” says Dr. Keim, principal investigator in the Center for Biobehavioral Health in The Research Institute at Nationwide Children's.

Many mothers who buy milk online from strangers receive products that arrive at temperatures ideal for bacterial growth. Nearly one in five samples in Dr. Keim's recent study was shipped with no cooling agent at all, and coliforms were detected in nearly half of the samples. What's more, because there's no way to confirm the source of milk bought online, it's possible the product isn't even human breast milk.

Milk sharing isn't new — many societies have a long history of wet nurses, both for necessity and convenience. But this Internet phenomenon may be

driven less by historical norms than by the grassroots trend toward all-natural diets and the success of a public health messaging campaign proclaiming that “Breast is best.”

“There is a lot of societal and peer pressure to breastfeed,” Dr. Keim says. “So some women are willing to go to great lengths to provide breast milk to their babies, even if it's not their own.”

Dr. Keim's latest research suggests that as many as 25 percent of women consider either providing or receiving shared breast milk postpartum, via family and friends, the Internet or a milk bank. Seventeen human milk banks exist in the United States and Canada, but they give priority to infants in neonatal intensive care units. Additional milk banks would help, but Dr. Keim believes the supply would still fall short of the public demand for breast milk.

So what's a mother who wants to give her newborn breast milk to do? One solution, she posits, is to change the messaging. Referral to lactation support before problems arise might spare many mothers the regret of failed breastfeeding and reduce the market for Internet milk-dealing sites, she says. Meanwhile, Dr. Keim adds, physicians should explain the potential dangers of milk sharing to their patients who are struggling to breastfeed their babies.

— Katie Brind'Amour







# OFF TARGET

ONCE CONSIDERED  
THE HOLY GRAIL FOR  
CANCER TREATMENT,  
TARGETED THERAPY IS  
LOSING ITS LUSTER.

by Katie Brind'Amour

The U.S. Food and Drug Administration usually takes about six months to approve cancer drugs. In 2001, Novartis' Gleevec made it through the process in less than three.

Its speedy regulatory success was based on striking results from clinical trials of patients with Philadelphia-chromosome positive chronic myelogenous leukemia, or CML, a rare cancer that affects 6,000 people a year. Gleevec, also known by its generic name imatinib, was designed to seek out and kill only cancer cells, leaving healthy cells untouched — and it accomplished the task with remarkable precision. Before Gleevec, CML's five-year survival rate was only 30 percent. But with the targeted therapy, 90 percent of patients were cured.

For nearly four decades, scientists had searched for a molecular therapy that would target cancer cells exclusively. It was the Holy Grail for researchers, and Gleevec was proof that it was possible. Tommy Thompson, then secretary of the U.S. Department of Health and Human Services, hailed the drug as a major scientific and medical breakthrough and announced a 12 percent increase in cancer funding for the National Institutes of Health. Things were looking up for targeted cancer therapy research.

Researchers analyzed the genome in dozens of adult and childhood malignancies, hoping that all cancers had a silver bullet oncogene like the one Novartis had discovered in CML. Time and again, they were disappointed. It appeared that CML's dramatic response to targeted therapy was an anomaly.

Deflated, many believers in targeted cancer therapy began to have doubts. How could something that once seemed like such a sure thing turn out to be so wrong?

## A MISLEADING BEGINNING

Targeted therapies aim to inhibit certain molecular functions specific to cancer cells. Some block enzymes that otherwise instruct cells to reproduce with abandon while others attempt to directly program cancer cell death or prevent the growth of blood vessel infrastructure around tumors. The goal is to kill only oncogenic cells, unlike standard chemotherapy, which destroys fast-replicating cells indiscriminately. In theory, the side effects of targeted therapies are less severe than those of traditional cancer treatments.

CML's "miracle" drug worked by accurately targeting an abnormal enzyme in and around cancer cells that

promotes uncontrolled growth of tumors, inhibiting the enzyme's function and resulting in slowed cell growth and eventual death. But scientists now know that Philadelphia-chromosome positive CML is rare in two key respects. First, its cause (an abnormal chromosome pattern produced by genes leads to overexpression of the targeted enzyme) is the same in both adults and children with the disease. Second, this irregularity is causative instead of a consequence of the disease.

Unlike CML's simple enzymatic "on" switch, any given disease may have multiple pathways that can cause malignant transformation in a cell. Nearly all types of cancers result from a complex network of genetic, cellular and environmental interactions. Couple that with the ability to adapt and use other pathways to grow and reproduce, and the target does more than just move — it morphs into another target altogether.

"What is alarming is how quickly a cell adapts to using another pathway," says Peter Houghton, PhD, director of the Center for Childhood Cancer and Blood Diseases in The Research Institute at Nationwide Children's Hospital. "It's like a balloon. You squeeze it in one place and it pops out in another. Cells can change malignant pathways, probably in minutes when they're under stress."

This explains why many targeted therapies for childhood cancer have resulted in only short-term improvements. Even excellent initial responses may disappear three months later as resistance develops.

"Just because they're molecularly targeted doesn't mean you're not going to get resistance," explains Dr. Houghton, who also directs the National Cancer Institute's Pediatric Preclinical Testing Program, which is based at Nationwide Children's.

The next logical strategy becomes blocking multiple pathways to decrease the chance of resistance, but oncologist Timothy Cripe, MD, PhD, warns of escalating toxicities with combined targeted therapies. Shutting off a cancer's alternate malignant pathway options may impact healthy cells that need those processes to function normally. "A better approach may be to combine targeted therapies with traditional cancer treatments," says Dr. Cripe, chief of the Division of Hematology, Oncology and Blood and Marrow Transplant at Nationwide Children's. "But really outmaneuvering cancer means thinking more long-term than initially anticipated, seeing the bigger picture."

## CHILDHOOD CANCER BY THE NUMBERS

**\$5 billion:** total NCI 2012 budget  
**\$208 million:** childhood cancer NCI research funding in 2012

**39+** FDA-approved targeted therapies for child and adult cancers

**45+** child and adult targeted therapies being studied in clinical trials

**1%** of all U.S. cancer diagnoses are in kids

**15,780:** new childhood cancer diagnoses expected in 2014

**1,960:** child deaths from cancer expected in 2014

**1 in 285:** children diagnosed with cancer before age 20

**80%** five-year survival rate

**95%** probability of 15-year survival among patients surviving five years

**50%** decline in childhood cancer death rate since 1975

Source: National Cancer Institute and the American Cancer Society

### KIDS VERSUS ADULTS

Some researchers have attempted to transfer findings from adult clinical cancer trials to the treatment of children with the same diagnosis, hoping to spread the wealth from effective therapies in the adult world. But a single cancer can have dozens of subtypes, each with its own malignant actor, and the molecular cause of an adult cancer may differ significantly from the cause of the same disease

in kids. This throws a major wrench into the pursuit of curative therapies for childhood cancers, Dr. Cripe says, since advancements in pediatric oncology often depend on progress in the adult world.

“In pediatrics, there don’t appear to be a lot of specific cancer ‘on’ switches like there are in many adult cancers,” Dr. Cripe says. “In many cases, the genome is relatively quiet. When there are no obvious molecular triggers, it’s hard to develop a targeted therapy.”

Scientists will have to figure out which childhood cancers have viable targets for molecular therapies — and whether they match targets in adult cancers — before there can be productive sharing between the world of adults and kids, he says. But even in the case of common triggers, targeted therapies considered effective from the viewpoint of adult oncology may fall short of expectations in pediatrics.

“When you talk of extending a 6-year-old’s life by three months, I think you put it in perspective,” says Dr. Houghton. “A brief extension of life is not the end goal of pediatric cancer research. We have to look at molecularly targeted drugs in the context of curative therapy.”

Ideally, children survive decades after a cancer diagnosis, so long-term effects of targeted therapies also matter. Growth, fertility and quality of life cannot be ignored when developing and testing such treatments.

“Right now, there are few data to show the long-term side effects of many of the targeted agents in children, so we don’t yet know what a lifetime of these drugs might do,” says Lia Gore, MD, founder and leader of the Experimental Therapeutics Program at Children’s Hospital Colorado and co-director of the Pediatric Oncology Experimental Therapeutics Investigators’ Consortium. “Hitting some targets may have deleterious effects on normal mechanisms of childhood growth and development.”

Beyond the biological challenges in developing targeted therapies for pediatric cancers, the financial difficulty of developing drugs specifically for rare diseases and the understandable limitations on pediatric clinical trials can also restrict the field’s progress.

“It can be frustrating,” Dr. Cripe admits. “We’re left with the drippings of the adult world when it comes to new drugs and options for clinical trials.”

A small pool of potential trial participants further complicates the matter. About 13 million adults in the

United States currently have cancer, while only 35,000 children do. The fact that these children have many different cancers also means that, for any given molecular target, there may be only a handful of eligible children each year to test a particular experimental targeted therapy.

Even the most common pediatric cancer, acute lymphoblastic leukemia, is more than 20 different diseases on a molecular level. Further reducing the number of potential clinical trial participants is the fact that approximately 90 percent of children diagnosed with cancer each year in the United States respond well to existing initial treatments. Only those who are unresponsive or relapse are typically eligible to try experimental therapeutics.

“It’s a problem of our prior success,” says Michael Link, MD, professor of pediatrics at Stanford University School of Medicine. “It’s very difficult for an institutional review board to consent to a brand new therapy when the standard treatment, even with its side effects, still has an 80 percent chance of a cure.”

Adding a targeted therapy to standard cancer treatments partially ameliorates the challenge of a limited population for clinical trials, Dr. Link says, but it does nothing to address what is, perhaps, the most significant barrier to the future of targeted therapy in pediatric oncology: money.

“More important than the lack of federal funding for pediatric oncology research is the lack of pharmaceutical company interest,” says Dr. Link, past president of the American Society of Clinical Oncology and the first pediatric oncologist to have held that position. “Unlike adult cancers, all childhood cancers are rare; it would be nice if there were a better incentive for developing drugs for what are essentially orphan diseases.”

### HOLDING OUT HOPE

Dr. Houghton has devoted more than 20 years to the search for a molecular-level solution to treat these rare diseases. He admits he’s disappointed with the current lack of evidence to support targeted therapeutics for most childhood cancers. But he also isn’t ready to give up.

“I do believe that at some point we will be able use effective targeted therapies to tailor treatment to the

“MORE IMPORTANT THAN THE LACK OF FEDERAL FUNDING FOR PEDIATRIC ONCOLOGY RESEARCH IS THE LACK OF PHARMACEUTICAL COMPANY INTEREST.”

— Michael Link, MD,  
Stanford University School of Medicine

particular molecular characteristics of patients’ tumors,” he says.

Biology has offered a tough reality check for the field’s proponents but still provided enough success to leave researchers cautiously optimistic.

“Targeted therapy is in its infancy in pediatrics,” Dr. Gore says. “We have a long way to go to understand what targeted agents are most promising, how to use them with or without current standard therapies and what the long-term effects of targeted therapies will be.”

Many molecular targets remain unexplored, and slow but steady progress in the field may yet offer targeted drugs an auspicious — albeit limited — future in childhood cancer treatment.

“We just have to be smart enough to get from where we are now to that future of using highly effective targeted therapies,” says Dr. Link. “I can’t believe that 20 years from now we won’t be targeting cancers in this way.”

However the future of such therapies for pediatric cancers may take shape, the road to their development is likely to be winding. Emerging methods of cancer research, such as immunotherapy and viral therapy, are gradually garnering more scientific attention and federal funding, shrinking the spotlight on targeted therapy.

“I think targeted therapy will be a strategy in the future of pediatric cancer treatment,” says Dr. Cripe, whose viral therapy research aims to specifically infect and kill cancer cells without having to find and turn off their oncogenic drivers. “It won’t be the magic bullet, but it will definitely be a part of the oncologist’s arsenal.”



Join the conversation about targeted therapy. Can targeted cancer therapy live up to its promise? Lend us your voice at [PediatricsNationwide.org](http://PediatricsNationwide.org).



# AIMING FOR ZERO

Efforts to eliminate preventable harm in pediatric care are making progress. But can we make it to zero?

by Kelli Whitlock Burton

440,000  
210,000  
98,000  
44,000

0

In October 2008, Richard Brill, MD, stood in a silent conference room, waiting for his audience to digest the news he'd just delivered: hundreds of significant harm events are identified each year at Nationwide Children's Hospital, and nearly every one of them could be prevented.

The group before him, the institution's board of directors, knew that incidents of preventable patient harm are an unfortunate reality in the health care industry. But hearing the numbers aloud made the reality all the more real.

Conversations such as this were happening in hospital board rooms across the country at the time, a reaction to the 1999 Institute of Medicine (IOM) report *To Err is Human*, a 287-page study that found between 44,000 and 98,000 people in the United States die each year in hospitals from preventable medical errors. This report was among the first to publicize the serious consequences associated with medical errors.

The response to the report was fast and fierce. News media reported the figures. Congress convened hearings and health care industry leaders testified about plans to reduce the numbers. But it wasn't long before the furor quieted and things appeared to go back to business as usual.

A handful of hospital executives, Dr. Brill among them, were not content to let the issue die. As the chief medical officer at Nationwide Children's, Dr. Brill felt strongly that the problem couldn't be addressed on a national scale until individual institutions tackled the problems from within. So in 2008, he found himself convincing the board of directors that just reducing the number of serious harm events wasn't enough. The goal, he argued, had to be eliminating them altogether.

## TO ERR IS HUMAN

When the IOM report was published, many leaders in the industry decried its findings, says Paul Levy, MD, former president and chief executive officer of Beth Israel Deaconess Medical Center in Boston.

"The first thing hospitals and health care leaders often say when a report like this comes along is that the data are wrong," Dr. Levy says. "Or, they may say, well maybe the data aren't wrong but our numbers are higher because our patients are sicker."

In 2007, Dr. Levy, now retired, became the first hospital executive in the country to report all of his hospital's quality and safety data on its intranet, despite resistance from his staff and board. At first, Dr. Levy says, they feared posting the data would drive patients away. But his co-workers soon embraced the idea.

"The value of the transparency is that it holds us accountable to the standard of care that we believe in," Dr. Levy says.

## ONE TOO MANY

Despite the success at Beth Israel Deaconess, few other adult hospitals in the country followed suit. Indeed, Dr. Levy says, the first move toward transparency and eliminating patient harm came in the pediatrics field, with Ohio paving the way.

In early 2009, the state's eight pediatric institutions, including Nationwide Children's, launched the Ohio Children's Hospitals' Solutions for Patient Safety, a nonprofit network whose initial focus was on reducing surgical site infections and adverse drug events. Today, the organization has a much broader mission and reach, with 78 member children's hospitals around the country.

The same year the network launched, Nationwide Children's also unveiled "Zero Hero," the patient safety initiative that traces its beginnings to Dr. Brill's impassioned 2008 board presentation. In the program's first year, nearly 9,000 employees underwent comprehensive safety training. In 2011, Nationwide Children's became the first pediatric institution in the country to make its serious safety event statistics public.

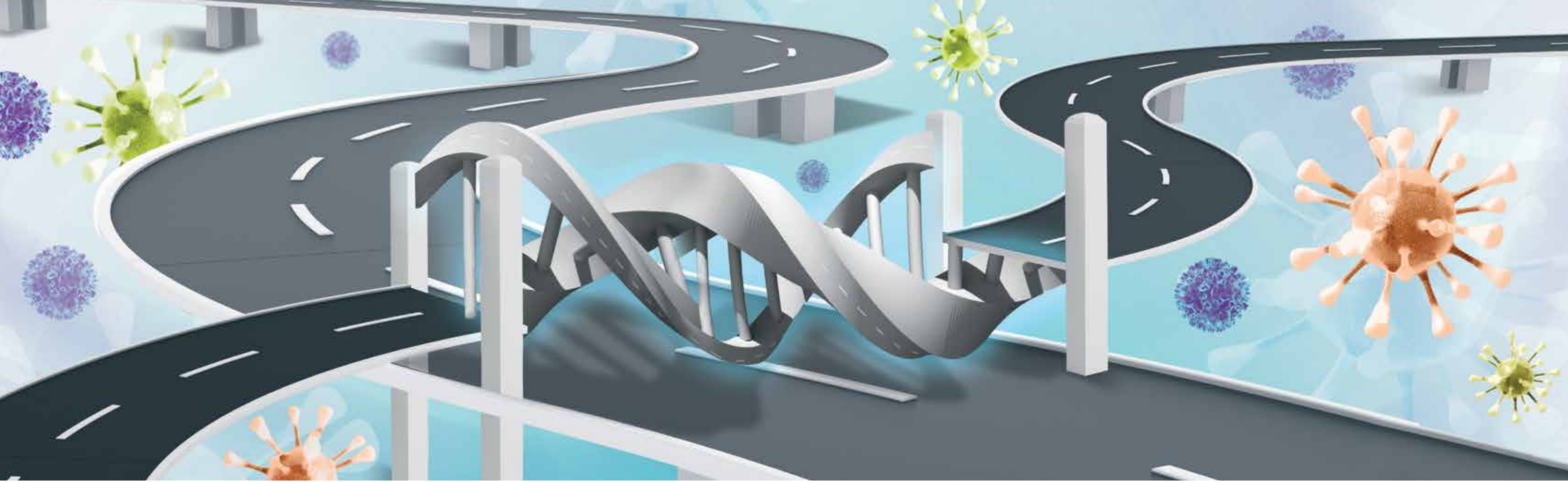
"Health care outcomes are only going to improve if everyone is willing to change long-standing habits and do that consistently, and being transparent is an important part of that," Dr. Brill says. "Health care has had a culture of secrecy for decades and I'm not proud of that. But I am proud of the fact that we at Nationwide Children's and now other children's hospitals around the country are focusing on improving outcomes and sharing data more transparently than ever before."

Five years after the program's official roll-out, "Zero Hero" has resulted in an 83.3 percent reduction in serious safety events, a 78 percent decrease in other serious harm and a 25 percent drop in hospital mortality. Getting to these results is a laudable effort, Dr. Brill says. "But there's always room for even greater improvement."

As if to underscore his point, a study published in September 2013 in *The Journal of Patient Safety* reported that the number of patient deaths in the United States due to medical errors may actually be between 210,000 and 440,000, as much as five times higher than the IOM estimate. When the latest report was published, some health care executives once again questioned the data. But that, Dr. Brill says, really isn't the point.

"Even one incident of preventable harm is too many."





# GENE THERAPY'S ROAD TO REDEMPTION

by Kelli Whitlock Burton

**D**uring the first few weeks of September in 1999, a 36-year-old air traffic controller from South Dakota and a 15-year-old high school student from Ohio checked into a hospital in Columbus, participants in the world's first gene therapy trial to treat muscular dystrophy. Each received copies of a gene engineered in the lab to mimic the function of one of their own genes that wasn't working correctly. The new genes were packaged neatly inside a viral vector that was injected into a muscle in the top of one foot.

The entire process took only 30 minutes but represented nearly 30 years of work by scientists such as Jerry Mendell, MD, the lead investigator on the clinical trial who was then the chair of neurology at The Ohio State University. Dr. Mendell had spent his career learning the finer points of how the neuromuscular disorder laid waste to muscle cells throughout the body. He and others had studied drugs that treated the symptoms of muscular dystrophy, but gene therapy aimed to do something those medications couldn't — treat the condition's underlying cause.

After decades of slow and uncertain progress, the field of gene therapy was finally moving forward. The National

Fifteen years ago, gene therapy suffered a highly visible fatality, leaving the field in shambles. Now, one team's efforts at gene therapy for muscular dystrophy suggest the field may finally be on track to deliver on its initial promise.

Institutes of Health approved a record number of new gene therapy clinical trials in 1999, Dr. Mendell's among them. Not only was his the first gene therapy trial for muscular dystrophy, it also was the first time this particular type of viral vector — an adeno-associated virus — had been used to deliver a gene in humans. Unfortunately, there would soon be yet another first for gene therapy.

Two weeks after Dr. Mendell began his study, an 18-year-old named Jesse Gelsinger, a participant in an unrelated trial at the University of Pennsylvania, died following an unforeseen and catastrophic reaction to the adenovirus vector used to deliver a gene for the

patient's rare metabolic disorder. Gene therapy had its first fatality.

As details slowly surfaced about Gelsinger's death, it became increasingly apparent that a series of missteps by scientists leading the trial was at least partially to blame. The leader of the Gelsinger study was also director of a lab at the university that produced and supplied a variety of viral vectors to researchers around the country. Until investigators from the Food and Drug Administration could determine why Gelsinger died, the agency suspended all gene therapy trials linked to that lab.

## The development of a \$2 million vector-manufacturing facility allowed scientists to use their own viral vectors for their gene therapy studies of muscular dystrophy. “Being able to do that was liberating.”

— Jerry Mendell, MD

Almost everything about the trials in Pennsylvania and Ohio was different: two different research teams, two different diseases, two different genes and two different viral vectors. But both vectors were made at the University of Pennsylvania. Dr. Mendell had to stop his trial.

Just four weeks after Dr. Mendell’s team took its momentous steps toward treating muscular dystrophy with gene therapy, the field faced a perilous future — if it had a future at all.

### FROM HUMBLE BEGINNINGS

Human gene therapy became a reality on Sept. 14, 1990, in a hospital room at the National Institutes of Health in Bethesda, Md., when a 4-year-old girl with the immune disorder adenosine deaminase (ADA) deficiency received an infusion of white blood cells engineered to contain copies of the gene she lacked. It was the moment of truth for gene therapy, a concept that first arose in the 1960s with the creation of DNA-splicing technology. The idea is simple: identify genes that malfunction and cause disease and replace them with functioning copies that will treat or even cure that disease. But as is so often the case in science, turning the idea into a reality is far more complex.

After initial success in animal studies, gene therapy met with a number of highly publicized failures in the 1990s (among them the very first trial at the NIH, which only produced temporary gene expression in the girl with ADA deficiency). It had a long list of critics, including former NIH Director Harold Varmus, who in 1995 issued a report criticizing some in the scientific community for making what he said were premature claims of gene therapy’s success. The biggest stumbling block in almost every failed trial proved to be finding a vector that would transport the engineered gene to the targeted cells safely and efficiently. The death of Jesse Gelsinger illustrated that point on an international stage.

Gelsinger enrolled in a phase I clinical trial at the University of Pennsylvania for gene therapy to treat

ornithine transcarbamylase deficiency, a rare metabolic disorder that causes ammonia to amass in potentially lethal levels in the bloodstream. The teenager from Arizona was admitted to the hospital on Monday, Sept. 13, and received the treatment that morning. Later that afternoon, he had a stomach ache and spiked a fever of 104.5. He awoke Tuesday disoriented and jaundiced and by that evening, had lapsed into a coma. He died two days later, a result of multi-system organ failure.

A federal investigation cited the scientists involved in the study for violating federal policies regarding the conduct of gene therapy trials. They were banned from working on any FDA-governed human clinical trials for five years. At the time, the University of Pennsylvania was one of the primary suppliers of viral vectors for gene therapy studies around the country. The fallout impacted every scientist in the field — including Dr. Mendell.

### A SEVEN-YEAR PAUSE

In the 1990s, there were a handful of scientists who knew muscular dystrophy well. Dr. Mendell was one of them. Muscular dystrophy is actually a group of more than 30 genetic diseases that weaken muscles in the arms, legs, spine and in some cases, the heart and lungs. The participants in Dr. Mendell’s 1999 trial were diagnosed with a particularly destructive form called limb girdle muscular dystrophy (LGMD) type 2D. They lacked functioning copies of the *alpha-sarcoglycan* gene and, along with most patients with other forms of muscular dystrophy, would likely end up in a wheelchair. The air traffic controller from South Dakota had only mild symptoms so far. The teenager could barely walk.

Dr. Mendell had investigated other treatment options, but he was convinced that gene therapy offered the best shot at a successful treatment for the neuromuscular disorder. The LGMD trial was his first attempt at human gene therapy for muscular dystrophy. When the NIH halted his and other gene therapy trials at the end of 1999, Dr. Mendell was left with the frustrating task of delivering the news

to the two participants, who saw the trial as their best chance at treatment.

“They were just devastated,” Dr. Mendell recalls. “We all were.”

It was seven years before that clinical trial would resume. During that time, Dr. Mendell joined the faculty in The Research Institute at Nationwide Children’s Hospital as director of the Center for Gene Therapy. His first aim was to make sure he would never again have to rely on an external lab for the vectors he needed for his studies. With support from hospital leadership, Dr. Mendell oversaw the development of a \$2 million vector-manufacturing facility. And in summer 2007, Dr. Mendell and his team re-launched the LGMD trial, this time using a homegrown adeno-associated viral vector.

“Being able to do that was liberating,” Dr. Mendell says. “One thing we’ve learned from our past experiences is that you must work with a vector-manufacturing facility that is just as precise as you will be as the principal investigator of the study. It was the only way we could oversee quality control and it was imperative for our studies to continue.”

### FINDING THE RIGHT VECTOR

Identifying the genes that cause disease and engineering healthy copies in the lab are not the challenges they once were, thanks to advances in genomics and sequencing technologies. But gene delivery remains a sticking point. To get the engineered genes, called transgenes, into targeted cells, scientists have used both nonviral vectors, such as liposomes and naked DNA, and viral vectors, including the adeno-associated virus Dr. Mendell has used in all of his gene therapy trials to date. Other viral vectors include retroviruses and herpes simplex virus. Adenovirus, the vector used in the ill-fated University of Pennsylvania study, has largely fallen out of favor.

Viruses exist for one purpose: to get inside cells and release their DNA. That, naturally, makes them a perfect vehicle for gene delivery. They are especially effective in gene therapy delivered *ex vivo*. In this case, a scientist draws some of a patient’s own cells, places them in cell culture, and injects them with the gene of interest, also called the transgene. Gene expression is confirmed and the cells are returned to the patient.

Not all diseases are good candidates for an *ex vivo* approach. In most cases, the cells that lack a functioning gene cannot be removed or collected outside the body.

To get the gene inside targeted cells in these conditions, scientists first package the gene inside a viral vector and then either inject it directly into the affected tissue or deliver it through the circulation, called vascular delivery. In 2008, a team led by Brian Kaspar, PhD, a principal investigator in the Center for Gene Therapy, used vascular delivery to illustrate that a type of adeno-associated virus called AAV9 could cross the blood-brain barrier, enabling scientists to deliver transgenes directly into the brain and cerebral spinal fluid.

The research, published in *Nature Biotechnology*, is the foundation behind a new strategy to treat spinal muscular atrophy (SMA) type I, the most common genetic cause of infant death. Patients with SMA lack a gene called *SMN*, which produces a protein vital to the health of nerve cells in the brain and spinal cord. In a phase I clinical study, which has received a new investigational drug status from the FDA and is funded by Sophia’s Cure Foundation, scientists will deliver an *SMN* transgene in infant patients with this devastating disease. Scientists are also conducting pre-clinical studies to see whether the AAV9-delivered *SMN* gene can be delivered through the cerebrospinal fluid. That work is funded by the Families of SMA and the National Institute of Neurological Disease and Stroke.

### BATTLING THE IMMUNE SYSTEM

Researchers in the Center for Gene Therapy will also soon launch a new trial in LGMD using another AAV vector, rh74, a virus isolated from rhesus macaque monkeys. This adeno-associated virus was developed at Nationwide Children’s and could address another key challenge to gene therapy: immune response. Other AAV viral vectors used in gene therapy are human viruses, which means that patients undergoing therapy may already have antibodies against the virus. The immune system recognizes the virus and launches an attack, killing the virus before it can deliver the gene it carries.

“Because rh74 is a non-human primate virus, there is less likelihood that human patients will already have antibodies to the virus, which is the ideal scenario,” says Louise Rodino-Klapac, PhD, a principal investigator in the center who will lead this new trial with Dr. Mendell. “Gene expression is inhibited by pre-existing antibodies because the antibodies block the AAV virus from entering the cells.”

Having rh74 in the tool box gives scientists another vector to choose from, which history suggests will be key to the



“You do everything you can to protect your patients but when mistakes are made, you study them, learn from them and do your best to never repeat them.”  
— Jerry Mendell, MD

success of gene therapy. Another secret to success, Dr. Mendell notes, is knowing that there is new knowledge to be gained from every experiment — even those that fail.

Such was the case with the world's first gene therapy trial in Duchenne muscular dystrophy (DMD), the most common form in children. Launched in spring 2007 and led by Dr. Mendell, the trial used a gene therapy product developed by scientists at the University of North Carolina to treat DMD, which is caused by a missing or defective gene that makes dystrophin, a protein vital for healthy muscle tissue. The gene that makes dystrophin is the largest known human gene, too large to package into conventional viral vectors. So the UNC scientists created minidystrophin, a smaller but functional version of the human gene.

Once a transgene is injected, it should start expressing protein within a week, with optimal expression occurring at about four to six weeks. However, when scientists examined muscle biopsies from patients in the DMD trial, they found no gene expression. The therapy had failed, but it taught the team a crucial new element about the disease.

Patients in the trial had large deletions within the gene that produces dystrophin. When the transgene was injected and made its way into muscle cells, the boys' immune systems attacked it. The immune response was striking — and puzzling. Because transgenes are meant to replace a gene innate to humans, immune reactions to the gene itself are rare. With the aid of Christopher Walker, PhD, director of the Center for Vaccines and Immunity at Nationwide Children's, the researchers discovered that the patients' T cells recognized parts of the dystrophin transgene as foreign because of the patients' own genetic deletions.

This is just one example of how the body's immune system has repeatedly thwarted gene therapy efforts. While studies continue to identify ways to molecularly manipulate immune response, Dr. Rodino-Klapac and

her colleagues have figured out how to level the playing field mechanically with plasmapheresis. Widely used to treat patients with autoimmune disorders, plasmapheresis removes blood from the body, filters out antibodies and returns the blood to the patient. The antibody loss is temporary; the body begins producing new antibodies within a few hours following the procedure.

In a study published in 2013 in *Molecular Therapy*, the team used plasmapheresis in a large animal model, then injected a virus packed with a micro-dystrophin gene developed to treat DMD, a slightly smaller version of the minidystrophin gene used in the original trial. When they examined the levels of micro-dystrophin gene expression in the animals, they found a 500 percent increase over gene expression in animals that did not receive plasmapheresis.

“One of the problems we are faced with moving forward is that when patients get the first treatment, their bodies will develop antibodies to the virus used to deliver the gene,” Dr. Rodino-Klapac says. “Using plasmapheresis on someone who previously received gene therapy could allow them to be treated again.”

#### THE JOURNEY CONTINUES

Much has been learned in the 15 years since Jesse Gelsinger died. “We learn new lessons from this work every day,” Dr. Mendell says. “You always find yourself wishing you were smarter than you were when you started, but that's part of science. You do everything you can to protect your patients but when mistakes are made, you study them, learn from them and do your best to never repeat them.”

Gene therapy may have been around for more than five decades, but as Dr. Mendell will attest, the field is still very much in its infancy. Only three gene therapy products have been approved for use — one in Europe and two in China. The United States has yet to approve a gene therapy product, although there are many in the pipeline. *The Journal of Gene Medicine* estimates there

are nearly 2,000 gene therapy clinical trials underway worldwide, with the vast majority in the United States.

Now, scientists also are looking at using gene technology to repair rather than replace mutated genes, silence overactive genes and retrofit patients' own immune cells with the tools they need to recognize and kill cancer cells. New genome editing studies are examining ways to remove dysfunctional genes and replace them with corrected versions, a copy and paste maneuver that takes gene replacement a step further than just adding corrected genes. This is crucial for disorders in which the malfunctioning genes are doing something harmful, as in some blood disorders, autoimmune illnesses and some types of cancer.

New drugs take years to reach the marketplace. Gene therapy takes years just to reach human trials. The

preclinical and toxicology preparatory studies for the upcoming LGMD phase I clinical trial with the new rh74 vector took two and a half years and more than \$1 million human clinical trials, and the price tag and time required to get the drug ready for FDA approval will likely double. Among the most painful aspects of this work, Dr. Mendell says, is telling parents and families to be patient. Indeed, it's something he has a hard time telling himself.

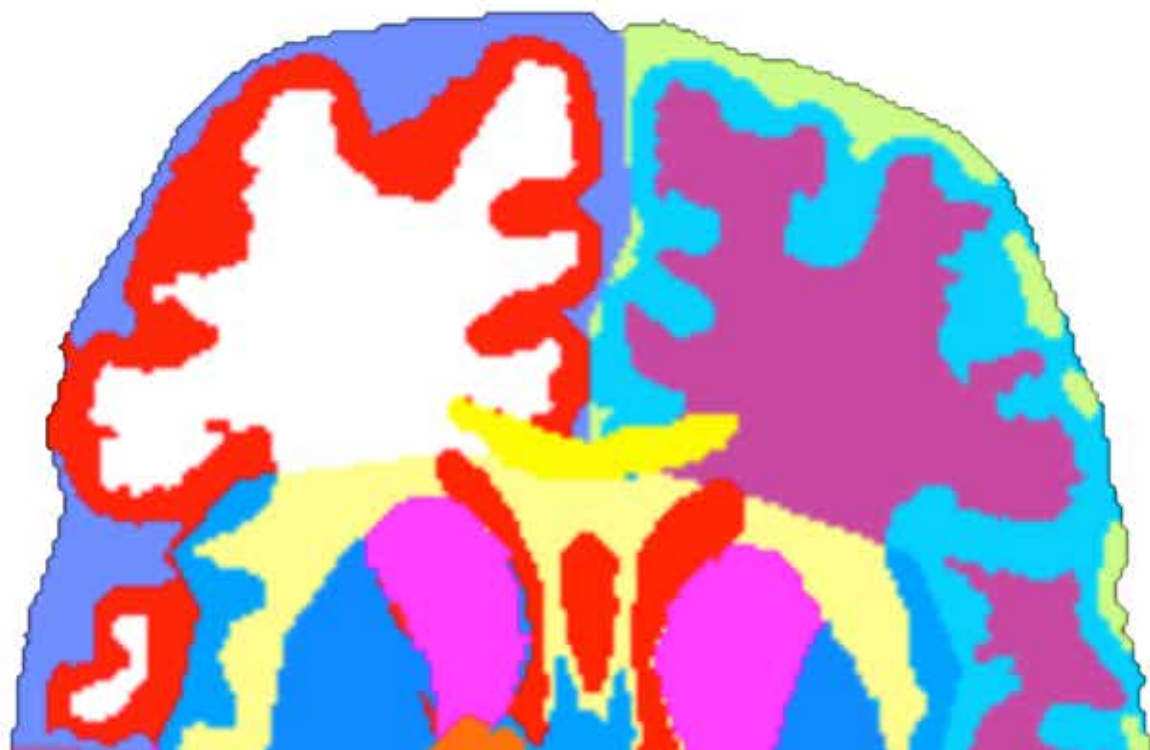
“I've been involved with muscular dystrophy research for 40 years and most of my contemporaries, people I've worked with in the past, are gone,” Dr. Mendell says. “I believe this is the best and safest approach for these patients and I am very determined to see it succeed before I'm gone, too.”

On a rare Saturday at home, Jerry Mendell, MD, finds himself in between the lab and trips to conferences to discuss his pursuit of gene therapy treatments for muscular dystrophy. Simon, a 4-year-old English Labrador, was an anniversary present to his wife, Joyce, to keep her company when he's away.



Join the conversation about the future of gene therapy. Does the potential of gene therapy outweigh the risk in all diseases? Or should it only be considered for treating single-gene disorders? Lend us your voice at [PediatricsNationwide.org](http://PediatricsNationwide.org).

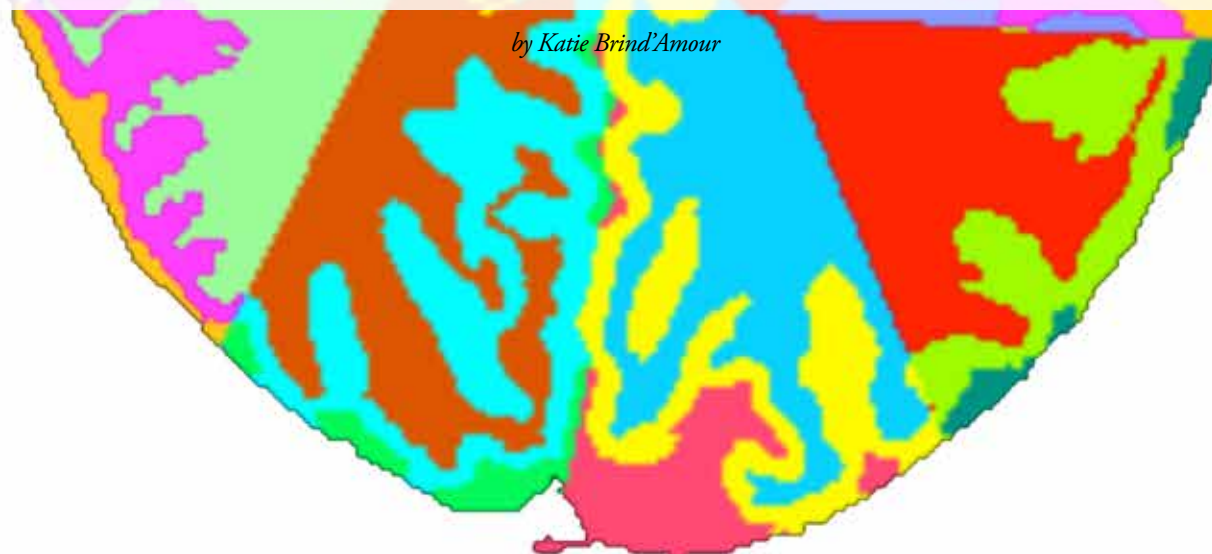




# EVOLUTION of an Atlas

**Adult brain atlases have existed for years. Why is it so crucial — and so difficult — to build one for preemies?**

*by Katie Brind'Amour*



**E**ven experts need maps. They give perspective, scale and orientation. They can show both current location and the final destination. And in the world of premature brains, they can offer vital information about subtle injury, developmental delay and opportunities for intervention.

But existing brain maps primarily feature adult brains, which have different landmarks. Newer maps of healthy, full-term infant brains have different scales and features than their less-developed preemie counterparts. So, how do you go about building a map for the premature brain?

This is a challenge neonatologist Nehal Parikh, DO, MS, has tackled at Nationwide Children's Hospital, taking brain mapping into uncharted territory. When he set out to develop an atlas of the premature brain, he first needed to overcome two not-so-simple problems: the subjectivity of MRI diagnostics and an entire profession's lack of knowledge about brain development in premature babies.

## ATLAS HISTORY

Clinician researchers started applying mapping techniques to aid our understanding of the human brain more than 150 years ago. Each map featured a single individual's characteristics in 2-D illustrations, drawn from cadaver brains. The most widely referenced series of paper brain maps, created in 1909 by German anatomist Korbinian Brodmann, guided surgeons and pathologists in their craft late into the 20th century.

Now, adult brain maps are organized into digital atlases that resemble a car's GPS in their level of sophistication — they can embed layers of information to tell users about brain segment density, volume, blood flow and genetics much like a car's computer can identify local restaurants and estimate travel time based on current speed. The most advanced adult brain atlases include population-based templates built by combining scans from hundreds of individuals to figure out what normal parameters are for each brain feature. "In adults, probabilistic, population-based brain atlases provide an assessment of the normal brain at different ages," says John Mazziotta, MD, PhD, executive vice dean of the David Geffen School of Medicine at the University of California, Los Angeles and father of the modern adult brain atlas. "Since the normal human brain varies in size, shape and configuration, having an average brain atlas provides a basis for determining subtle abnormalities, as these fall outside the range of normal variance."

Dr. Parikh has spent the past 10 years trying to achieve the same level of complexity in premature infant brain imaging. His first attempts to reduce the subjectivity of MRI interpretation, begun during his time in Houston at the University of Texas, involved an algorithm for manual, objective evaluation of neonatal MRI scans that appeared to indicate subtle injuries to the brain's white matter.

"I failed miserably," he admits. "But it did help me understand why radiologists weren't already objectively defining these injuries in preemies."

His techniques for researching the anatomy and abnormalities of the premature brain have since evolved to include digital automation processes. By starting with adult brain segmentation computer software developed by Ponnada Narayana, PhD, at The University of Texas Medical School at Houston, Dr. Parikh helped develop automated brain segmentation software for preterm infants. The technique required years of focused work to first reliably and reproducibly segment developing brain tissues and structures that lacked clear anatomic boundaries.

His new measures resulted in what would become the first layer of his atlas: one that allows the automatic, objective quantification of brain tissues and subtle but diffuse injuries not previously measured by traditional diagnostic imaging technology. Having removed some of the subjectivity from the MRI diagnostic process, Dr. Parikh, also a principal investigator in the Center for Perinatal Research in The Research Institute at Nationwide Children's, then turned his attention to the creation of a multi-layer, digital atlas of the premature brain.

## PEERING INTO THE PREMATURE BRAIN

Dr. Parikh's mission hinged on one task. He would have to study hundreds of MRI scans of preemies to define what the average premature brain actually looks like. These infant brains are obviously much smaller than those of adults, but they also contain more water, more immature structures and fewer connective networks.

To get from a series of scans to an actual template for an atlas, Dr. Parikh applied the same principle to mapping the premature brain as Dr. Mazziotta used to build his adult brain atlas. Numerous subjects' brain images were compared, manually segmented, measured for key parameters and averaged to obtain normal ranges. Ideally, a new brain image could then be contrasted with the population-based template to visually and mathematically identify abnormalities.



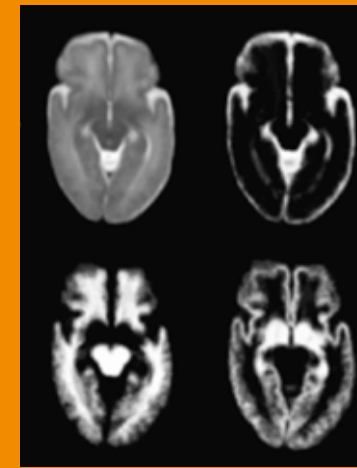
# BUILDING A BRAIN ATLAS



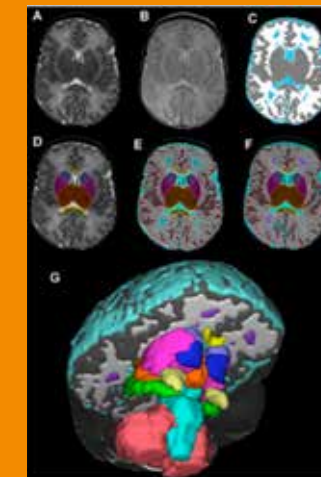
The team lifts the MRI-compatible infant incubator onto the MRI table. The 3.0 Tesla magnet is nearly twice the strength of standard clinical imaging machines.



The premature baby is monitored as the MRI physicist sets brain imaging parameters and collects the scans. The process takes about 40 minutes.



Dozens of scans are used to create an atlas with average results from the test population for the whole premature infant brain, cerebrospinal fluid and white and gray matter.



Each new scan undergoes various stages of processing, including standardization of raw conventional images, automated and manual segmentation and a final combined, corrected map.

Watch a video on Dr. Parikh's atlas creation and lend us your voice at [PediatricsNationwide.org](http://PediatricsNationwide.org)

"I spent a lot of time in the early years working with neuroradiologists and physicists, sending out emails to people I didn't know to see if they would share their neonatal imaging sequences with us to tailor them for our premature population," Dr. Parikh recalls. "The question is, how do you come up with the best atlas for such a unique group? I think that's an evolving issue as we continue to build on prior work."

Very little is known about the appearance of a truly normal premature brain. What is the difference between underdevelopment due to prematurity versus that due to injury? What is healthy for a preemie brain, especially if "healthy" isn't average?

To further complicate the matter, the premature brain doubles in size between 28 and 40 weeks postmenstrual age, literally making a brain atlas for this population a moving target.

"Right now, we're creating atlases with and without subtle injury, trying to see which one works out best in the end with outcome measures," Dr. Parikh says.

## ATLAS-MAKING IN ACTION

Despite the simultaneous efforts of a few teams around the world, the premature brain atlas is definitely a work in progress.

One way to tackle the challenge of building a useful atlas, Dr. Parikh explains, is to follow premature babies over time for functional outcome measures that correlate with the individual's brain images in infancy. This would tell researchers whether certain brain injuries and underdeveloped segments during infancy actually impact long-term development. A series of images on the

same children combined with functional outcome measures could offer the precision needed, Dr. Parikh says.

A second option, he suggests, is to build atlases constructed with images of premature infants at 28, 30, 32 and 40 weeks postmenstrual age and 3 months corrected age. This could provide a more appropriate picture of a developmental trajectory — with true clinical implications, Dr. Parikh says. His team is pursuing both options.

"If a baby's development falls off that trajectory, that may be a good predictor of delays and impairments down the road," he says. "It could also serve as an early indicator that this baby might benefit from intervention, instead of waiting two or more years for problems to appear."

This conviction comes from conveying his fragile patients in a special MRI-compatible incubator to the radiology department hundreds of times. Dr. Parikh uses their results to refine the science and to improve his clinical suggestions to anxious parents eager to have any advanced notice of potential developmental difficulties in their premature babies.

## MAPPING MOTIVATION

As a clinician, effective therapeutic intervention and improved long-term outcomes are Dr. Parikh's ultimate aims. As a clinical trialist, more efficient research and faster translation of results are his goals.

His probabilistic atlas already enables more objective, accurate diagnoses and increased sensitivity in the detection of subtle brain injury. But by embedding as much relevant information as possible into the program, the tool could have much wider use in neonatology. EEG data, brain tract volumes, functional

MRI measures, blood flow, genetic information, clinical risk factors, metabolite measures and neuron networking could all be added to his current atlas to improve the tool's diagnostic and predictive power.

"I want to be able to offer an accurate prognosis and better strategies to prevent the neurodevelopmental disabilities that affect 40 percent of these preemies," Dr. Parikh explains. "An atlas like this would have tremendous potential for predicting clinical outcomes and for enabling a new model for faster, more efficient research."

A wide range of embedded features could help measure intervention effectiveness within weeks or months instead of years. Therapies that aren't working can be quickly discontinued and substituted with another intervention.

"Until we develop that robust, multi-modal program, we can still work with the individual layers of that atlas to inform our clinical decision-making and research," Dr. Parikh says. "But the days of using automated MRI atlas diagnostics in routine clinical care of premature babies may be only five or 10 years away."



To create the preemie brain atlas, Nehal Parikh, DO, MS, reviews hundreds of images.



# A Brave New World of Data

According to William C. Ray, PhD, of the Battelle Center for Mathematical Medicine in The Research Institute at Nationwide Children's Hospital, novel techniques prototyped for understanding protein data could soon enable the visualization of large sets of demographic data, displaying contingency tables and group relationships through visual representations of positive and negative correlation, covariance and mutual exclusivity.

## ILLUSTRATING DATA

Massive, multi-dimensional contingency tables are a ubiquitous feature of biological data. From precision medicine to structural biophysics, understanding complex networks of dependencies in contingency data is critical to drawing knowledge from and making informed decisions about the data.

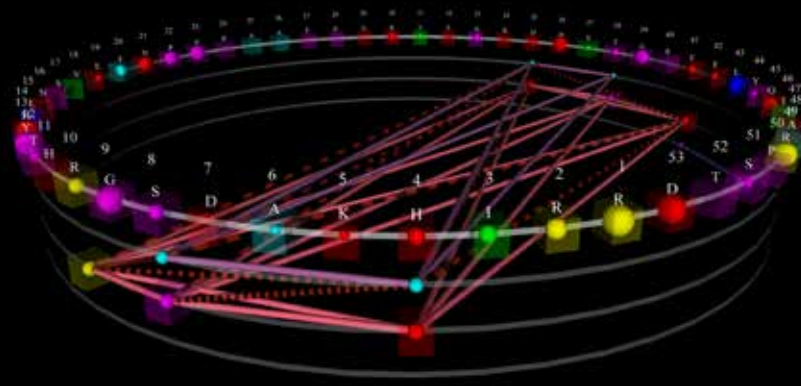
The many appearances of the Adenylate Kinase (ADK) protein lid domain and the inability of character sequences to show functional dependencies between the amino acid subunits highlight the need for data representations that are more sophisticated. But existing methods of creating precise molecular models are laborious, expensive and rarely successfully executed.



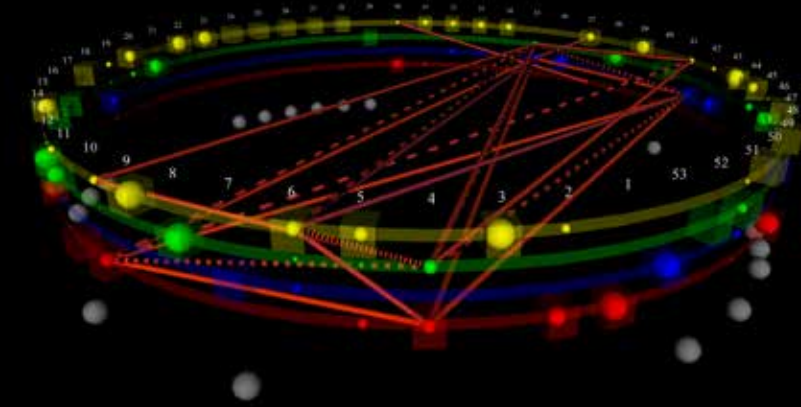
Protein data is often shown in this classic sequence alignment, with strings of letters for each amino acid in the order a cell assembles them.



Sequence logos depict a protein's amino acid sequences but lack information about its structure.

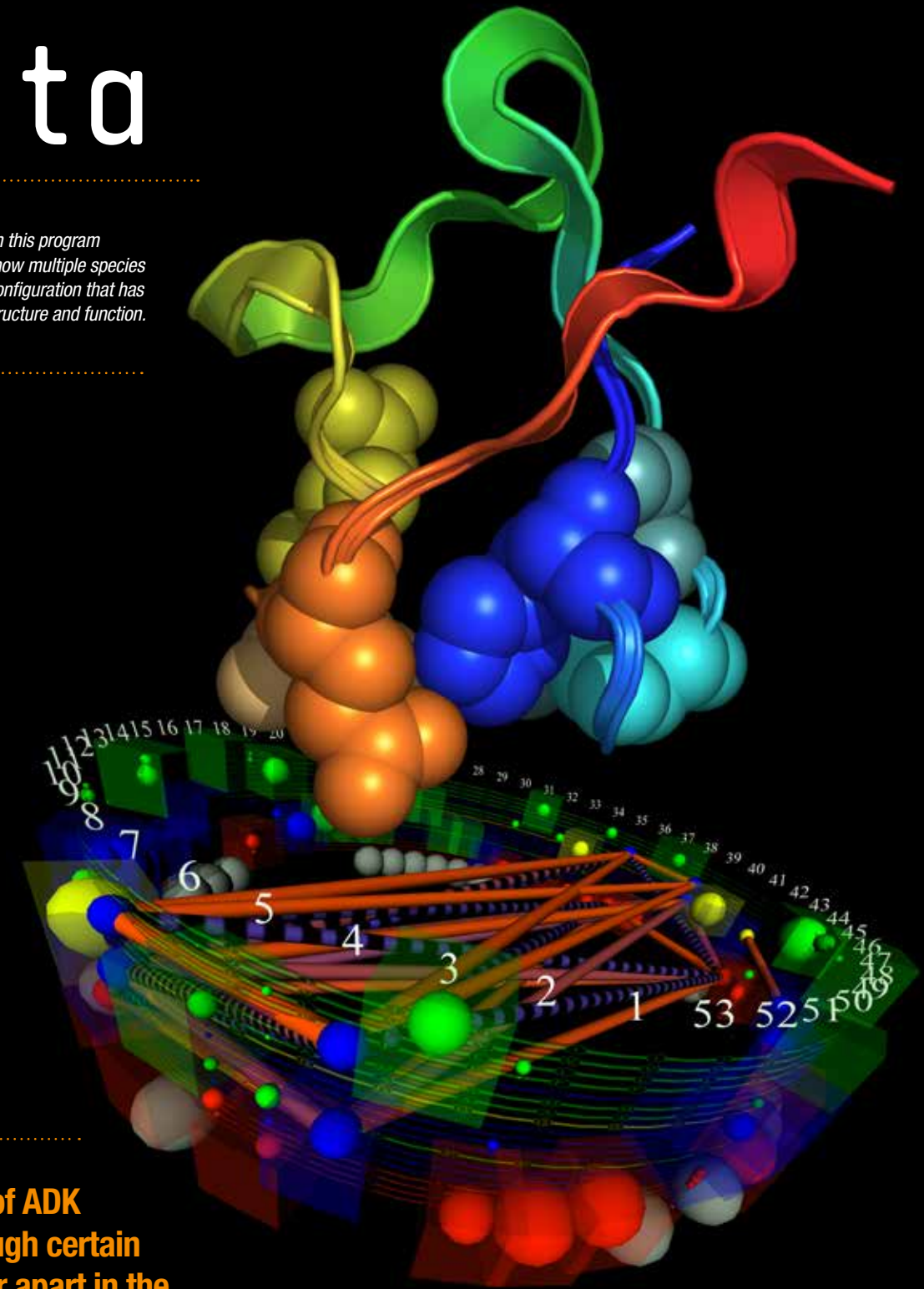


Dr. Ray's StickWRLD diagrams display ADK sequence relationships through stick and sphere connections in a 3-D digital model. Partitioning the data allows visualization of mutually exclusive patterns and the study of amino acid interactions that create ADK's structure and function.



Alternative representations enable amino acid grouping by physical categories to see whether relationships depend on properties such as charge or size.

Visually representing ADK data with this program allows researchers to understand how multiple species can share an identical molecular configuration that has different ways of maintaining its structure and function.



**This visualization of ADK reveals that, although certain amino acids are far apart in the protein sequence, they are nearby in the physical structure of the model. The data representation also identifies previously unknown amino acid interactions. StickWRLD models offer insight into structure and function requirements for proteins and hold similar potential for other fields with complex, interacting data.**



## Creating a Positive Impact on Child Poverty

Each issue of *Pediatrics Nationwide* will include thought-provoking questions and commentary from Nationwide Children's Hospital faculty as well as colleagues and peers from other pediatric institutions.

For the premiere issue, and in honor of the Pediatric Academic Societies roundtable focus on poverty, we posed the following question:



The great triumphs of pediatrics, health care and public health in improving infant mortality, infections, injury and chronic disease have not been shared equally in our society. Our poorest children have rates of disease and death similar to those of children from 50 years ago. Poverty mocks our best clinical efforts, even though many pediatricians and specialists struggle individually to provide better care to low-income patients.

Poverty takes its toll through the rapid accrual of multiple risk factors or the “social determinants of health” aimed at young children and their families. Violence, hunger, drugs and exposure not only affect developmental, psychological and health problems, but also the acceptance of health-risking behaviors like smoking and lack of exercise.

Traditional health services by themselves are not adequate to address these problems, nor can they work effectively for many chronic conditions in the face of these problems. Instead, community collaborations that engage multiple sectors like education, employment, justice and health care simultaneously in our most difficult neighborhoods will be necessary to make a dent in child and young family outcomes. In fact, there are promising data from cities like New York and St. Louis about how much child health improves for poor children when the requisite willpower is engaged.

Pediatricians and their health care institutions hold high moral, political and financial standing in most communities. Thus, they are well positioned to address what I believe is the single biggest issue related to poverty: the need for broad political, health and educational coalitions to change our highest-risk neighborhoods through a refusal to accept that poverty, with its concentration in very specific geography, is a permanent sentence against our most vulnerable children.

**Kelly Kelleher, MD, MPH**

Director, Center for Innovation in Pediatric Practice  
Vice President, Community Health Services  
Nationwide Children's Hospital



Poverty brings with it a host of social determinants of health that do not often accompany children outside of poverty in the same constellations or amounts. We are challenged with dealing with organic disease that, in many cases, is the easy part of care. Managing the socioeconomic factors that support disease and impede care as comorbidities is the real challenge, and one that is often grossly underestimated.

The greatest challenge is not only offering comprehensive care that encompasses the medically sound approaches to addressing disease, but also those elements of lifestyle that can impact prognosis, recurrence and compliance. In terms of oral health, we often deal with low health literacy, advanced disease at an early age, limited resources that affect diet and dental fatalism as a result of generational poverty or cultural influences. For clinicians working with families in poverty, it is important that we understand its impact in each individual situation and not prejudice and categorize them.

**Paul Casamassimo, DDS, MS**

Chief, Dentistry  
Nationwide Children's Hospital  
Director, Pediatric Oral Health Research and Policy Center  
American Academy of Pediatric Dentistry



This year marks the 50th anniversary of the launch of President Lyndon B. Johnson's “War on Poverty.” In your opinion, what health issue related to child poverty should pediatricians and pediatric specialists focus on most to have a positive impact?



It would be easy for me as a pediatric pulmonologist to focus on asthma risk factors or the outrageous cost of preventative medications as key issues for impoverished children, but I think obesity remains our greatest challenge going forward.

The food options in the United States that most low-income families can easily access and afford are often not the same ones we advocate for every day, such as fresh fruits and vegetables. I believe the lack of access to adequate nutrition is spurring on the obesity epidemic we are facing, leading to a multitude of downstream health effects. Long-term health issues related to obesity can include social stigma, diabetes, heart disease and worsened asthma control, so this health issue directly affects every pediatrician and sub-specialist. Therefore, it is an issue that everyone can address.

The war on poverty is about access: access to care, counseling, medical monitoring and affordable foods and medications. One of the important aspects of poverty-related obesity is the impact that early interventions can have on preventing obesity. With a keen eye on targeting obesity prevention in young children in low-income families, we might have a shot at ending this war before the casualties of escalating obesity continue to rise.

**Benjamin T. Kopp, MD**

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The most important health issue related to child poverty that we see in a pediatric specialty clinic may be access to appropriate medical care, whether that means finding a primary care physician who is conveniently located to the family and accepts Medicaid; having reliable transportation to make it to health care appointments; or finding specialists in underserved areas who will see patients for medical and/or dental issues.

While we live in a wealthy country with a very advanced health care system, often your ability to receive adequate and convenient health care depends directly on your ability to pay. While the various government assistance or charitable programs that are available can bridge this gap to some degree, they can be overused, misused or, conversely, offer bureaucratically limited care such that the general public may only hear about the negatives of these programs rather than the many positives.

Unfortunately, child poverty is a multi-factorial, socioeconomic condition for which there are no simple fixes, but hopefully both individuals and society as a whole can continue to seek the complex roots of the problem and work toward its solution.

**Seth Alpert, MD**

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Join the conversation about child poverty.  
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WELCOME TO

# Pediatrics NATIONWIDE

Advancing the Conversation on Child Health

This publication, along with its accompanying website, **PediatricsNationwide.org**, is designed to advance the conversation on child health.

How many times have you simply appreciated the opportunity to talk with your colleagues, especially those who may practice in different specialties? Our goal is for *Pediatrics Nationwide* to be a forum for knowledge exchange — by sparking conversation among you and your colleagues, posing questions that allow you to share your expertise and presenting the opinions and ideas of your peers.

As a one-way communication tool, a magazine may seem an unusual channel for conversation. However, our plan is to bring you in-depth features on global issues affecting pediatrics and to explore novel research and clinical care practices. The conversation then continues on the website through commentary, blogs and imagery that offer new information and ideas.

We believe that by facilitating discussion on topics that matter to pediatric clinicians and scientists, we can collectively generate ideas that will shape the future of child health across the nation and around the world.

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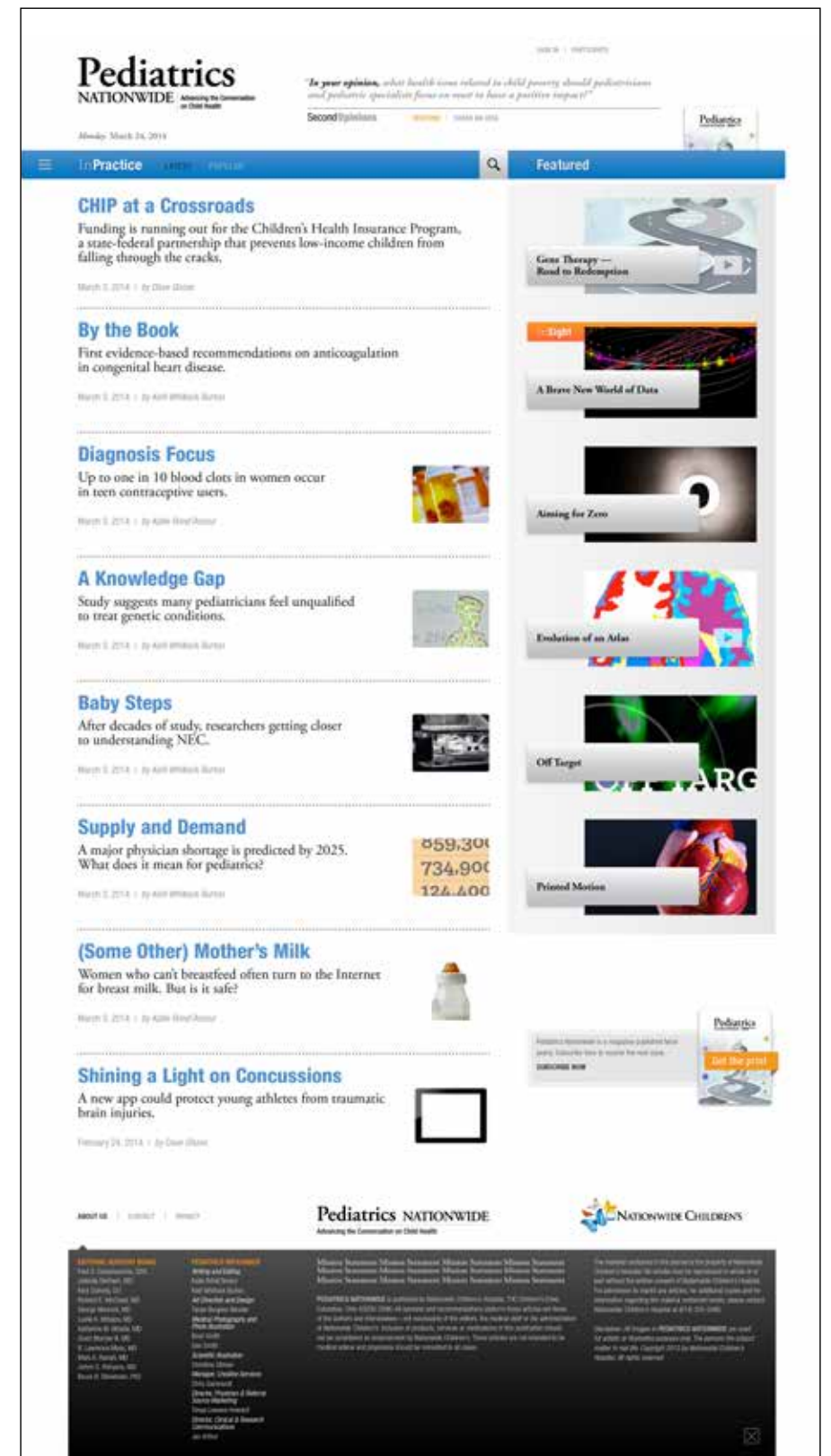
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“Whenever you find yourself on the side of the majority, it is time to pause and reflect.”

— Mark Twain





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## Printed Motion

The advent of 3-D printers enabled the handling and study of precise physical models of proteins and cells. Now, researchers are combining the idea of digital time-lapse motion prediction with an actual printed model of that motion — allowing researchers to study the molecule's movement by working with a handheld model. This use of 3-D printing technology could yield new insights about molecular motion involved in disease processes and cellular function.

The long, thin lines in this example show the paths traced by part of a protein as it rearranges from an inactive state (in blue) to an active state (in yellow). Learn more about the design and see the 3-D printing process of this molecular motion by visiting [PediatricsNationwide.org](http://PediatricsNationwide.org).

