

Spring/Summer 2015

Pediatrics

NATIONWIDE

Advancing the Conversation
on Child Health

FIGHTING FIBROSIS

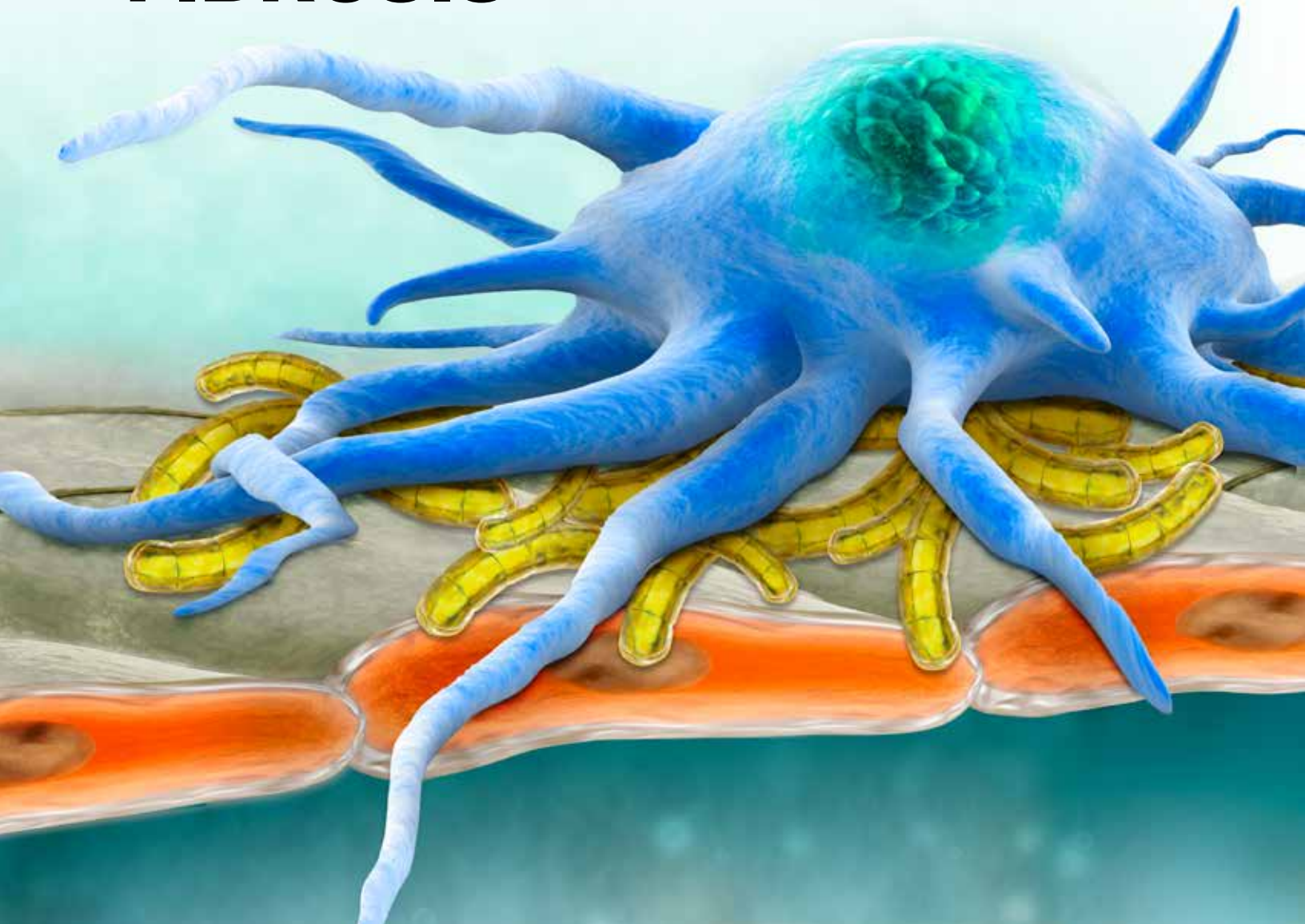


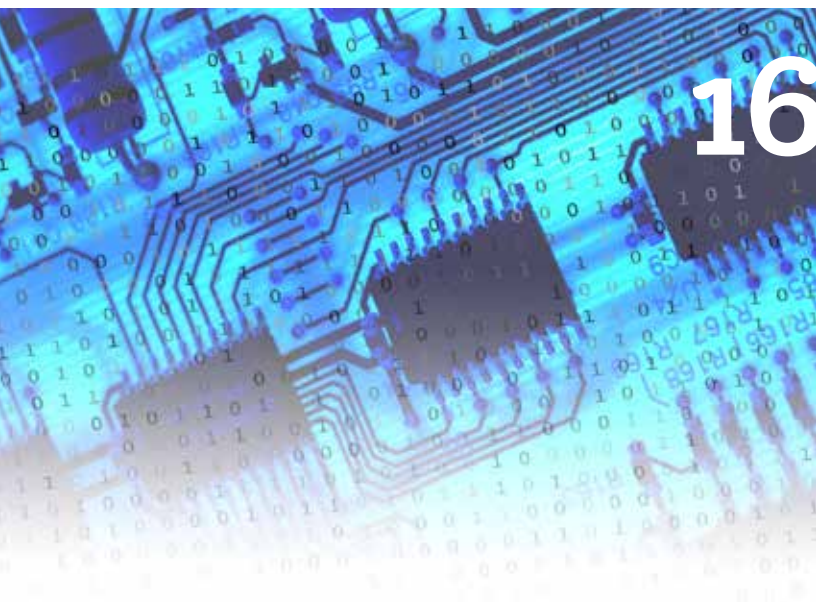
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FIGHTING FIBROSIS

Fibrosis is an unmet medical challenge with no satisfactory test and insufficient therapy. Now, one naturally occurring cellular component could simultaneously diagnose and heal patients.





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“Reversing the research-to-practice paradigm requires a variety of system-level changes.”

– Simon M. Lin, MD, MBA
Chief Research Information Officer
Nationwide Children’s Hospital
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“Our ability to advance targeted new drugs and to improve outcomes is directly dependent on our ability to do leading-edge research on specimens from our biorepositories. If we were to lose the biobanks, the impact would be devastating for childhood cancer.”

– Peter C. Adamson, MD, Chair, Children’s Oncology Group (page 29)

Patients Without Borders

Immigrant children represent the fastest growing segment of the U.S. population. What can pediatricians do to help these vulnerable patients?



James Duffee, MD, MPH, watched the immigrant population change dramatically during his 15 years as a community health pediatrician and child psychiatrist in Springfield, Ohio. When he founded the Rocking Horse Community Health Center in 1999, he treated patients at migrant camps in the surrounding rural areas. By the time he left the federally qualified center in 2014, the immigrant population was more permanent and four times as big, creating a number of unique health care challenges.

“One of the most heart-wrenching situations in community practice is to have a child born in the United States who has health care, but the older siblings do not,” says Dr. Duffee, who now works for The Center for Family Safety and Healing at Nationwide Children’s Hospital.

Dr. Duffee’s experience mirrors what is happening across the country. Immigrant children (defined as foreign-born or living with at least one parent born outside the United States) represent the fastest-growing segment of the U.S. population. They tend to be poorer (30 percent below the federal poverty line, compared to 19 percent of children with U.S.-born parents), nearly twice as likely to be uninsured and are dispersed throughout the country, with the largest growth in percentage occurring in North Carolina, Nevada, Georgia and Arkansas, according to a 2013 policy statement of the American Academy of Pediatrics.

They’re also a diverse group. They include the well-to-do offspring of accomplished foreign-born professionals and the tens of thousands of unaccompanied minors from Central America who drew international headlines when they crossed the Texas border last year. Nearly 90 percent of immigrant children are U.S. citizens, making them eligible for public programs such as Medicaid and the Children’s Health Insurance Program, or CHIP. Yet many don’t take advantage of the opportunities. Waiting periods, lack of awareness and fear of deportation may contribute to the phenomenon.

How can pediatricians break down these barriers? In its 2013 policy statement, the American Academy of Pediatrics called for extending public insurance to undocumented children.

“At the Academy, we’ve become very bold in our position that all children in the United States deserve health insurance, regardless of their immigration status,” says Ricky Choi, MD, MPH, an Oakland, California pediatrician who chairs the AAP’s Immigrant Health Special Interest Group. He also calls for expanding access to interpreters to help reduce language barriers.

“It’s expensive to get interpreters,” Dr. Choi says. “It’s time-consuming, and there need to be provisions where physicians can get reimbursements for interpreter services.”

Bold policy reforms aren’t likely in gridlocked Washington, D.C., at the moment. But Dr. Duffee says pediatricians still can improve their immigrant care by becoming more culturally informed through resources such as the AAP’s Immigrant Child Health Toolkit.

“Understanding the cultural values of the family and providing skilled interpreters are essential elements of high quality care for children in immigrant families,” he says.

— Dave Ghose



Join the conversation. What challenges have you faced related to serving immigrant children in your practice? Lend us your voice at

PediatricsNationwide.org/Patients-Without-Borders.

To Rest or Not To Rest?

Emerging research suggests prolonged postconcussion rest yields no benefit for most patients.

A decade ago, children who suffered a concussion had to be kept from running and playing too soon after the injury. Now, too many rest in bed too long.

The shift was driven by an unproven idea that spread through the medical community: If a little rest helps recovery, more must be better. News shows reinforced the notion, reporting lost memory, decreased cognitive function and personality changes in professional athletes who played despite head injuries.

But a study published by researchers from the Medical College of Wisconsin in the journal *Pediatrics* early this year provides ammunition that concussion specialists can use to return patients to normal life more quickly. For 80 to 85 percent of concussions — head strikes with no loss of consciousness — keeping a child on strict rest for more than a day or two provides no benefit.

“Some of the patients I see have already seen a sports doctor or their primary physician and they’re miserable because they’ve been sitting in bed for three months,” says Geoffrey L. Heyer, MD, director of the Complex Concussion Clinic at Nationwide Children’s Hospital. “It’s hard to say to a pediatrician, ‘Why would you recommend this?’ without a paper like this.”

The study’s finding reflects what he and other concussion experts see in practice. “For a simple concussion, we

expect rapid recovery,” Dr. Heyer says. “Symptoms should abate in a week, a few days or, in some cases, 24 hours.”

After a day or two at home, ease kids back into school with a lighter load and breaks as needed. “That’s probably the best way to get back on the horse,” says Danny G. Thomas, MD, MPH, an emergency medicine physician at the Children’s Hospital of Wisconsin and lead author of the study. He suggests patients ease into physical activities after managing a few full days of class and homework.

“The primary goal of treating patients who suffer a concussion is to prevent a second concussion before the first has a chance to heal,” Dr. Thomas says.

But exactly how much downtime that requires isn’t clear. Dr. Thomas is seeking funding for a large study with a greater variety of patients, which concussion experts say is needed before they can tailor individual recovery plans for patients.

“We may see that athletes who’ve lost consciousness benefit from strict rest,” Dr. Thomas says. “But for those who haven’t lost consciousness and aren’t suffering amnesia or disorientation, bed rest is probably way too severe.”

— Kevin Mayhood



Ebola in Children Creates Ethical Quandary

Do you keep a parent in the room while the virus rages inside a child?

The Ebola outbreak in Guinea, Liberia and Sierra Leone has challenged emergency preparedness at Children's Hospitals and Clinics of Minnesota like nothing before — even more than the early days of AIDS and outbreaks of measles and H1N1 flu, says Infection Prevention and Control Director Patsy Stinchfield, MS, RN, CPNP.

Children's of Minnesota, in St. Paul, is one of the six original children's hospitals designated for Ebola management by agreement among local and state health departments, the hospital and federal agencies. The city is home to a large Liberian community.

“One of the silver linings about Ebola is we're better prepared to handle most any infections emergency, not just Ebola,” says Stinchfield, an infectious disease nurse practitioner.

Beginning at the emergency department reception desk, staff is on the lookout. They ask patients reporting a fever a series of questions to catch measles, tuberculosis and now Ebola. “You have to think of the common and uncommon causes of illness all the time,” Stinchfield says. “Keep the lens wide.”

They've developed tight response teams with members ranging from doctors to environmental services workers. They talk each other through procedures, trust each other and feel free to speak up when a superior missteps, Stinchfield says. Members trained at Emory University Hospital, which successfully treated four adult Ebola patients. In St. Paul, they drill and drill.

The teams soon found the Ebola outbreak highlights novel ethical concerns in pediatric infectious disease care that many hospitals — even those that are well prepared logistically — are hard-pressed to resolve.

“With the focus on family-centered care, the usual practice is to have a parent present during treatment. But what are the ethics with Ebola?” Stinchfield says. “It's heart-wrenching, because when the child is dying, the child needs the parent most. But that's the riskiest time to be exposed to Ebola.”

Some argue the parent is already exposed and should remain and provide comfort. “But if the parent gets sick and dies, we've done the child no favor,” she says.

The parent could look through a window into the room or video chat using a computer tablet. But the options may be agonizing for the adult and terrifying for a toddler isolated with shrouded strangers.

Until guidelines emerge, the onus is on pediatric institutions to develop clear guidance on when and how a parent may be present with a child with Ebola.

— *Kevin Mayhood*

Join the conversation. Where is the balance between compassionate and responsible health care for children with Ebola and their parents? Lend us your voice at PediatricsNationwide.org/Ebola-in-Children.

A Shift in the Antibiotic Prophylaxis Debate?

The RIVUR trial laid to rest certain questions surrounding antimicrobial prophylaxis in children with vesicoureteral reflux. But it also launched a new debate.

The Randomized Intervention for Children with Vesicoureteral Reflux (RIVUR) trial was supposed to provide clear direction for pediatric urologists. To date, it is the largest double-blind, placebo-controlled, randomized, multicenter study examining urinary tract infection and renal scarring in children with vesicoureteral reflux (VUR). Despite the study's strong design and sample size of more than 600 children, its results and recommendations continue to be met with resistance.

"If you go back a decade or so, we used to prescribe prophylaxis routinely in most children with vesicoureteral reflux," says Tej K. Mattoo, MD, a principal investigator on the RIVUR trial and chief of Pediatric Nephrology and Hypertension at Children's Hospital of Michigan, Detroit Medical Center. "Then a series of studies and guidelines — based on lower quality evidence — were released and people felt we should not use routine prophylaxis. It's not surprising there is disagreement on the topic."

Next came the RIVUR trial's results, published in 2014 in the *New England Journal of Medicine*. The study revealed antibiotic prophylaxis cut UTI recurrence nearly in half compared to children taking a placebo. A flurry of critical commentaries followed, which the trial's investigators addressed in a rebuttal in the journal *Pediatric Nephrology*.

"Not using prophylaxis for anyone is not an option. Selective prophylaxis is what we need to do," says Dr. Mattoo, lead author of the group's editorial response. "We as clinicians need to figure out which patients are going to benefit from prophylaxis."


According to Dr. Mattoo, factors including severity of the reflux, patient gender, family history of VUR, recurrence of UTI, kidney damage and parental opinion should be weighed by the clinician in the case of older children with VUR. But he defends the group's recommendation for prophylaxis in young children.

"I wouldn't take the chance of forgoing prophylaxis with children who aren't yet toilet trained," Dr. Mattoo says. "The risk of infection is higher, symptoms are not as straightforward, collecting urine samples is not easy, sepsis and need for intravenous antibiotics are more likely, and the list goes on."

He concedes that the idea of a point-of-care decision may not lend itself to clear clinical guidelines favored by groups such as the American Academy of Pediatrics. But Dr. Mattoo believes that current and future research efforts will inform clinicians in their treatment decisions by identifying patients at the highest risk of recurrent infections or scarring. In the meantime, he prefers to err on the side of prophylactic treatment in high-risk children.

"When I'm talking to parents, what matters is what will happen to that particular child, not what happens to others," Dr. Mattoo explains. "If you can lower the risk of infection for that particular patient, it's worth it."

— Katie Brind'Amour

 **Join the conversation.** Would guidelines resolve the controversy, or will the idea of prophylactic antibiotics always ruffle feathers? Lend us your voice at PediatricsNationwide.org/Antibiotic-Prophylaxis.



Telepsychiatry to the Rescue

A North Carolina telepsychiatry program is helping hospital emergency departments overcome practitioner deficits. But is this a one-size-fits-all solution?

North Carolina needs more psychiatrists, social workers and psychologists. The federal government has designated 58 out of the state's 100 counties as areas without enough mental health professionals, putting people in these communities with depression, anxiety or other behavioral issues at risk.

To address this health challenge, North Carolina public health officials launched a statewide telepsychiatry program in January 2014 to help hospital emergency departments without enough mental health care resources. With nearly 91 million Americans across the country living in federally designated mental health professional shortage areas, the North Carolina initiative could serve as a model for addressing this common problem, which, according to experts, is even more pronounced in pediatric mental health care.

"Telepsychiatry offers lots of opportunities," says Chris Collins, MSW, the director of the North Carolina Office of Rural Health and Community Care. Her office oversees the program, which has already resulted in shorter wait times in emergency departments and prevented unnecessary commitments to state psychiatric facilities, Collins says. By the end of the fiscal year 2017, she predicts the program will save about \$7 million in hospitalization costs.

Mental health professionals at four locations use secure audio and video technology to diagnose and treat individuals at the hospital emergency departments participating in the program.

"You have the provider in the emergency room, and you have the psychiatrist going through the exam, just like they would in person," Collins says. "It's all in real time, and then you have the psychiatrist providing consultation to the medical provider for whatever course of action is appropriate."

In 2013, North Carolina state officials invested \$4 million to expand a smaller pilot telepsychiatry initiative funded by the Albemarle Hospital Foundation. Since then, the program has grown to include 50 hospitals throughout the state and is projected to increase to 77 by 2017. The East Carolina University Center for Telepsychiatry and e-Behavioral Health is partnering with the state on the project.

David Axelson, MD, medical director for Behavioral Health Services at Nationwide Children's Hospital, praises the North Carolina effort.

"You often can't afford to have a trained mental health professional in an emergency room," Dr. Axelson says. "There would be a lot of downtime, and it would be very expensive. So this is a way of getting that expertise where it's needed in a more timely fashion."

When Nationwide Children's experimented with telepsychiatry in the past, Dr. Axelson says, the initiatives worked best when augmenting outpatient centers or large pediatric practices that already had established programs and therapists on site.

"It's been effective in the practices that were committed to providing a fair amount of mental health care themselves and were looking for additional assistance," Dr. Axelson says.

Still, telepsychiatry may not completely fill the mental health void.

"It's definitely worth trying and seeing where it might be helpful, but I don't think it's a substitute for getting more mental health practitioners," Dr. Axelson says.

— Dave Ghose

Primary Care Practitioners Feeling Squeezed

Possible solutions may include more technology, physician extenders and seeing children less often.

The Physicians Foundation's recent survey of practice, patterns and perspectives found 44 percent of U.S. doctors plan to cut patient access, a move that both reflects and potentially exacerbates trends troubling pediatric medicine. Eighty percent say they can handle no more patients or already have too many.

The growing number of patients with behavioral or chronic and complex conditions and a shortage of pediatric subspecialists are already shifting work onto primary care pediatricians. The additional millions insured under the Affordable Care Act and the emphasis on creating a patient-centered medical home are sources of consternation for some, but the lead authors of the 2013 American Academy of Pediatrics Pediatrician Workforce Policy see them as improvement opportunities.

"A lot of physicians feel overloaded with their practice, and that varies by where they practice," says Mary E. Rimsza, MD, chair of the AAP Committee on Pediatric Workforce. In rural areas and underserved neighborhoods, she says, "We find primary care pediatricians work longer hours and take care of more complex cases compared to areas where patients have access to subspecialists."

While nearly half of all doctors in the Physicians Foundation survey give the ACA a grade of D or F, Dr. Rimsza says the act has been positive for pediatrics. "Certainly, it's better for pediatricians that more kids are insured and Medicaid has been expanded," she said. More secure sources of funding encourage pediatricians to open and keep practices.

Dr. Rimsza and William T. Basco, MD, MS, director of the Division of General Pediatrics at the Medical University of South Carolina, are lead co-authors of the

AAP's Workforce Policy. To deal with growing caseloads affecting primary care doctors, they endorse more use of technology, but to different degrees.

"Increasing the use of telemedicine may help," Dr. Rimsza says. "It may not be financially feasible to set up a pediatric cardiology practice in a small town, but using telemedicine can make it possible for a pediatric cardiologist to assist the primary care pediatrician to provide care in the child's medical home."

Another option is to expand services provided in the medical home by a nurse practitioner or physician assistant. Either could see a healthy 6-year-old with a cough but no fever. The pediatrician would see the 6-year-old with cerebral palsy, a cough and fever, Dr. Basco says. "That's a model we're slowly evolving to now."

But Dr. Basco also sees medical homes as the place to make serious changes. "I'm not sure the AAP would endorse this," he says. "But do I really need to see every child every year?"

Instead, a practice could send an email asking the technology-literate parent of a 6-year-old to fill out online behavioral, physical and cognitive development screens, Dr. Basco suggests. The practice reviews them and if the child passes, it emails the parent saying so, scheduling a vaccine visit or eye or hearing screening if needed, and saying, "We'll do this again next year."

"That's almost heresy," Dr. Basco admits. "But I think for a huge proportion of 6-year-olds, that may be all that's needed."

— Kevin Mayhood

44%

of pediatricians say they're burned out

72%

believe there is a physician shortage

81%

of physicians say they will take no new patients or have too many

Sources: Medscape's Physician Lifestyle Report 2015 by Carol Peckham and The Physicians Foundation's 2014 Survey of America's Physicians.

Conflicting Directions for BPD Treatment

Treatment of bronchopulmonary dysplasia differs dramatically among institutions. But why does variation matter?

Recent studies report extreme variation among hospitals ordering three common medications for chronic lung disease, or bronchopulmonary dysplasia, calling into question the appropriateness of their use and the reason for their prescription.

“In the use of diuretics, inhaled bronchodilators and inhaled corticosteroids, there’s profound variation. The institution that babies are admitted to appears to have far more to do with what drugs they’re given than how sick they are,” says Jonathan L. Slaughter, MD, MPH, a neonatologist and principal investigator in the Center for Perinatal Research in The Research Institute at Nationwide Children’s Hospital. “The national picture shows that we, as neonatologists, don’t actually know what to do with these drugs.”

In 2013, Dr. Slaughter published a study in *Pediatrics* reporting diuretics were ordered for anywhere from 4 to 86 percent of BPD patients, depending on the hospital. His work published in *PLoS One* and the *Journal of Perinatology* in the next two years revealed similarly striking variations in prescriptions for corticosteroids and bronchodilators.

The inconsistencies may be due to a lack of evidence that these three medications improve long-term outcomes in infants with BPD, Dr. Slaughter theorizes. “There is a lot of research to discover new drugs, but not to evaluate the effectiveness of drugs we’re already giving.”

This knowledge gap undoubtedly affects patient health as well. At best, Dr. Slaughter explains, patients are either not receiving a drug that could help or are receiving ineffective drugs. At worst, they’re experiencing harmful side effects and footing the bill for inappropriate treatments.

“We really need to take a hard look at what we’re doing as a group and determine whether it’s evidence-based or just based on tradition,” says Dr. Slaughter, who is co-leading a brainstorming workshop on standardization and practice variation in pediatrics at the 2015 Pediatric Academic Societies annual meeting.

He advocates for comparative effectiveness studies of existing treatments and changes to standardized algorithms used in clinical practice to improve therapies in neonatology practice.

“Therapies that are well supported by evidence are used similarly across the board,” Dr. Slaughter says. “The degree of variation in BPD treatments shows the neonatal community that we have a problem we need to solve.”

— Katie Brind’Amour

RANGES OF DRUG USE BY PERCENT

DIURETICS:



HOSPITALS RANGE IN
PRESCRIPTION FROM

4% to 86%
of BPD babies
40% overall

INHALED CORTICOSTEROIDS:



HOSPITALS RANGE IN
PRESCRIPTION FROM

0% to 60%
of BPD babies
25% overall

INHALED BRONCHODILATORS:



HOSPITALS RANGE IN
PRESCRIPTION FROM

0% to 81%
of BPD babies
33% overall

Placental Transfusion Confusion

Medical professional organizations cannot reach consensus regarding delayed cord clamping and umbilical cord “milking.”

Nearly every relevant professional organization has its own recommendations for placental transfusion techniques known as delayed umbilical cord clamping and milking. But it’s unclear whether additional research will lead to consensus.

The American College of Obstetricians and Gynecologists and American Academy of Pediatrics say there’s insufficient evidence full-term infants benefit from delaying cord clamping at least 60 seconds to recommend for or against the practice. They do, however, advocate the practice for all preterm births, when feasible.

“I think it is unlikely that ACOG and AAP will change their recommendations until research strongly indicates that the short- and long-term benefits outweigh the potential risks in term babies,” says Carl H. Backes, Jr., MD, neonatologist at Nationwide Children’s Hospital and lead author of two recent studies on placental transfusion in premature infants.

The American College of Nurse-Midwives recommends delayed clamping for all babies and endorses cord milking (quickly stripping the cord toward the baby) in infants requiring resuscitation. The World Health Organization supports delayed clamping regardless of gestational age at delivery, even in certain cases requiring immediate resuscitation — highlighting another point of friction among professional organizations’ guidelines.

“There is very good data that, among preterm infants not requiring active resuscitation, delayed cord clamping or umbilical cord milking will improve outcomes, but there’s not a lot of good data to tell us how to combine resuscitation with delayed cord clamping,” explains Dr. Backes, who also is a principal investigator in the Center for Perinatal Research in The Research Institute. “At least in preterm infants, it sounds like the ideal scenario would be to delay cord clamping and provide active resuscitation at the bedside. But the logistics of that are difficult.”

He knows of several groups working to identify effective methods for delayed clamping when resuscitation is required. But that’s only one step toward resolving the controversy surrounding placental transfusion.

“We still have a lot to learn about subgroups among preterm and term infants who may respond differently to the delay, such as infants born at less than 26 weeks or those with heart disease,” says Dr. Backes, who is finalizing studies on both of these populations.

High-quality investigations should shed light on when and how to implement placental transfusion strategies, he says. “Then we have to figure out how to get clinicians from multiple disciplines to translate that evidence-based medicine into clinical practice.”

— Katie Brind’Amour

Out-of-Hospital Medication Errors

Out-of-hospital medication errors among U.S. children younger than 6 years of age were analyzed for 2002-2012 using the National Poison Database System. The first comprehensive study to examine the epidemiology of this public health issue reported alarming statistics.

696,937

total episodes in children under 6

63,358

episodes per year

1 child every **8** minutes

25 deaths

93.5%

cases managed outside of a health care facility

64.8%

errors involving analgesics, cough and cold medicines or antihistamines

59%

decrease in errors involving cough and cold preparations

765%

increase in episodes caused by dietary supplements, herbals and homeopathics

27%

errors attributed to accidentally taking medication twice

40%

deaths caused by analgesics

SOURCE:
Smith MD, Spiller HA, Casavant MJ, Chounthirath T, Brophy TJ, Xiang H.
Out-of-hospital medication errors among young children in the United States,
2002–2012. *Pediatrics*. 1 Nov 2014; 134(5):867–876.



ORPHAN DISEASE SEEKS PARENTS, FUNDING

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..... Highest standard 121 sq m near

RESEARCH ON RARE PEDIATRIC DISEASES OFTEN REMAINS UNDERFUNDED AND OBSCURE UNTIL MOTIVATED FAMILIES GIVE SCIENTISTS — AND THEIR OWN CHILDREN — A MUCH-NEEDED SHOT AT POTENTIAL THERAPIES WORTHY OF FEDERAL FUNDING.

..... *by Kevin Mayhood*

Reagan McGee’s pediatrician couldn’t figure out why she had cold after cold. Her parents, Karin and Peter McGee, took her to an ear, nose and throat specialist who discussed adenoids and ear tubes, but then said their girl didn’t quite resemble either parent.

“Coarse features, he called it,” Peter McGee says. The doctor suggested they see a geneticist.

The geneticist ordered X-rays that revealed suspicious features in Reagan’s bones. A blood test confirmed she had something they’d never heard of: Sanfilippo syndrome type A.

“We thought we had a healthy baby and then we find she has a terminal disease,” Karin McGee says.

The McGees grieved.

Then they dove into the scant Sanfilippo literature.

KNOW YOUR ENEMY

Children with Sanfilippo syndrome develop then degenerate, losing the ability to speak, walk and eat. Most die between age 10 and 20. The cause is a mutation to a gene that normally makes an enzyme that breaks down and disposes of mucopolysaccharides, long-chain sugar molecules essential to building connective tissues. When the molecules accumulate in cells, they cause progressive damage to organs and the central nervous system.

Sanfilippo syndrome is one of nearly 7,400 diseases classified as “rare” or “orphan” by the Centers for Disease Control and Prevention. They’re called rare because they afflict fewer than 200,000 people in the United States and orphan because drug companies historically found them too uncommon to invest in. Nearly 95 percent of the diseases currently have no cure.

Researchers recently compiled a list of about 130 patients with the most common two forms of Sanfilippo. They believe it includes the majority of U.S. children with the disease.

Online, the McGees found the O’Neill family in South Carolina, whose daughter Eliza was also in early stages of the disease. The O’Neills raised nearly \$2 million for clinical trials with a video of Eliza that went viral. The McGees created their own nonprofit foundation, named Reagan’s Hope: A Cure for Sanfilippo, which has raised \$30,000 in less than a year.

“You have to be out there,” Karin McGee says. “There’s no mega-foundation bringing in millions and millions of dollars.”

While Peter slept one night, Karin was on the computer and saw local Columbus, Ohio, experts were working for a Sanfilippo cure. She emailed Kevin Flanigan, MD, a neurologist and principal investigator in the Center for Gene Therapy in The Research Institute at Nationwide Children’s Hospital.

Dr. Flanigan responded within minutes. They talked about the disease, Reagan and plans to test new treatments in clinical trials.

For the first time in a long time, the McGees felt hopeful.

A DOCTOR-PATIENT ALLIANCE

“When you work with rare diseases, it can be a very small community, and we rely on each other,” Dr. Flanigan says.

Parents need experts to advise them, treat their children and seek cures, and researchers need parents and patients in order to do their work.

“We turn to their foundations to fund early research that the National Institutes of Health and pharmaceutical companies show limited or little interest in,” Dr. Flanigan continues. “We wouldn’t be here at all without the foundations.”

Dr. Flanigan and his team — which includes Kim L. McBride, MD, MS, a geneticist and principal investigator in the Center for Cardiovascular and Pulmonary Research in The Research Institute at Nationwide Children’s — will test therapies that have been more than a decade in the making.

The two gene therapy approaches were developed by Haiyan Fu, PhD, and Douglas M. McCarty, PhD, principal investigators in the Center for Gene Therapy, and will target the two most common forms of Sanfilippo syndrome: types A and B.

The experimental therapeutic uses a modified virus to cross the blood-brain barrier. They hope that with one injection, the virus will deliver corrected genes and enzyme-making supplies to cells in the central nervous system and organs throughout the body. A single injection strikingly improved the health of mouse models of Sanfilippo.

Their early work was funded through an NIH grant to Dr. Fu. But since 2003, they have received continuous generous support from the Sanfilippo community through Ben’s Dream — The Sanfilippo Research Foundation. And since 2010, The Children’s Medical Research Foundation, Inc. (A Cure for Kirby), Sanfilippo Children’s Research Foundation (A Life for Elisa), Team Sanfilippo and LivLife have provided funds to accelerate the work. The team’s successes have drawn additional NIH funding into the mix to support moving these therapies towards their planned clinical trials in children with Sanfilippo disorders.

To scale up production of therapies for a clinical trial, Nationwide Children’s Office of Technology

Commercialization reached out to an entrepreneur already commercializing another therapy developed at the hospital.

Abeona Therapeutics was formed to quickly move the therapies, called ABX-A and ABX-B, to the initial round of testing in patients. Abeona licensed the technology and is raising money; 15 Sanfilippo foundations from around the world have already invested. Drs. Fu, McCarty, McBride and Flanigan work closely in preparation for the first clinical trials, which will take place at Nationwide Children's.

This path to a new orphan drug is well worn.

“Throughout the history of the rare disease community, patients and patient groups have played an enormous role in research,” says Mary Dunkle, vice president for Educational Initiatives at the National Organization of Rare Disorders.

NORD was created to help those with orphan diseases and the organizations that serve them. Its founders were drivers behind the 1983 Orphan Drug Act. In the decade prior, 10 treatments for rare diseases were brought to market. Since then, 460 have made it. Most often, patients and their families fueled the drive for these new treatments, Dunkle says.

The Orphan Drug Act provides tax breaks and other financial incentives for drug- and device-makers to serve a smaller population of patients. Such drugs as Cerezyme® to treat Gaucher disease, Soliris® for paroxysmal nocturnal

hemoglobinuria and Elaprase® for Hunter's Syndrome cost \$300,000 to \$440,000 per patient annually and showed that orphan drugs could yield a return on investment. But by and large, big pharmaceutical companies have only recently shown interest.

VERSATILITY REQUIRED

Just as orphan diseases force parents to take on the roles of fundraiser and advocate, they require doctors to fill many needs.

Dr. Flanigan treats patients, does scientific research, oversees clinical trials, consults as a member of orphan disease advisory boards and reviews grant applications for other proposed research in the field. He's an educator who talks at parents' meetings and hosts intensive training each year for new doctors. For Duchenne muscular dystrophy, another orphan disease he studies, Dr. Flanigan's research group puts out a monthly podcast to parents and primary care doctors. He's a fundraiser who writes grants, informs foundations and parents about his work and, when the time is right, asks them to help fund the next step.

Karen McCoy, MD, chief of the Section of Pulmonary Medicine at Nationwide Children's, also wears many hats while working on a more common orphan disease.

Dr. McCoy is a principal investigator for the Cystic Fibrosis Therapeutic Development Center and the director of the Cystic Fibrosis Center at the hospital. Her work has been funded by the Cystic Fibrosis Foundation for 28 years. In her role as educator, Dr. McCoy limits her trainees to those who will continue in academic medicine.

“There's still so much to learn,” she says.

The Cystic Fibrosis Foundation is 60 years old, serves 30,000 U.S. patients and has been integral to bringing treatments to market. Like the Sanfilippo foundations, it was started by parents of patients.



Peter and Karin McGee, pictured here with daughter Reagan and dog Oscar, started a foundation to raise money and awareness when they learned their child has Sanfilippo syndrome. Such efforts by parents and patients with rare diseases have been essential to raising money needed for research.

“We turn to their foundations to fund early research that the National Institutes of Health and pharmaceutical companies show limited or little interest in. We wouldn’t be here at all without the foundations.”

– Kevin Flanigan, MD

“At the beginning of my medical career, I learned about cystic fibrosis and sickle cell disease. Both kill early and make for a very hard life,” Dr. McCoy says. “But sickle cell has not had the benefits of a powerful organization backing research. There have been improvements in care, but not to the degree seen in cystic fibrosis.”

With more patients come more helping hands and more clout. But beyond that, the Cystic Fibrosis Foundation is held up as a model organization. The foundation’s headquarters in Bethesda, Maryland, has developed and maintained strong relationships with the NIH and the Food and Drug Administration — groups the foundation relies on for grant funding and drug approvals.

The foundation created and certifies more than 110 care centers and 82 therapeutic development centers at hospitals across the United States. These provide treatment, advocate for patients and conduct clinical trials. By holding the centers to the same high standards, the centers provide strong, repeatable data needed to bring drugs to market quickly.

“It’s a group effort to make advances,” Dr. McCoy says.

COMMITMENTS TO THE FUTURE

The Cystic Fibrosis Foundation made history this year when it took in \$3.3 billion by selling royalty rights to drugs it helped develop. That’s as much money as the organization raises in a decade.

Leaders say the money will be folded back into foundation efforts to allow each successive drug to help fund the next attempt to provide cures. One of the drugs, Kalydeco®, is among the most costly on the market



*Karen McCoy, MD, and Kevin Flanigan, MD
Nationwide Children’s Hospital*

at \$300,000 annually, but the results are phenomenal, Dr. McCoy says.

Despite the cost, no insurance company has yet rejected payment for Kalydeco®, and foundation officials say parents aren’t complaining, either. They want cures.

As do the McGees. Reagan, now 3, is part of a foundations-funded study helping doctors learn the natural progression of Sanfilippo syndrome — information needed to measure whether treatments in clinical trials make a difference.

Reagan was recently fitted with hearing aids due to hearing loss.

“We feel like it’s a race against time now,” Peter McGee says. “We want to be in that window where there can be a cure.”

The couple doesn’t dwell on the other possibility.

“Other families whose children have died have kept their foundations going and continue raising money for the cause,” Peter McGee says.

His wife shares his determination. “We’ll continue fighting.”



Join the conversation. How might the increasing involvement of parents in grassroots fundraising change the future of orphan disease research? Lend us your voice at PediatricsNationwide.org/Orphan-Diseases.

FROM BEDSIDE TO BENCH

How evidence-generating medical care could revolutionize research

by *Tiasha Letostak*

Since the passage of the HITECH Act of 2009, rates of adoption for electronic health records (EHRs) have doubled for physicians and quadrupled for hospitals. As of 2013, 78 percent of office-based physicians had adopted at least a basic EHR system, and nearly half of all physicians and six in 10 hospitals had adopted an EHR system with advanced functionalities.

Since EHR implementation at Nationwide Children's Hospital, the third busiest pediatric hospital in the country, the hospital has accumulated a record 800 million patient data collection forms.

With health care effectiveness, quality and efficiency as top priorities for hospitals around the country, one important question is on the minds of researchers and clinicians.

What — if anything — can be done with all this clinical data?

In recent years, substantial federal investments and initiatives have encouraged clinical and translational research. Traditionally, the relationship between research and practice has been unidirectional: research findings influence practice to comprise evidence-based medicine.

This is the classic bench-to-bedside paradigm.

But with millions of data collection forms being created through EHR systems, experts are suggesting a shift in this paradigm to redefine the relationship between research and practice as bidirectional. Information, they argue, should go both ways.

UNDERSTANDING EVIDENCE GENERATION

Peter J. Embi, MD, MS, chief research information officer at The Ohio State University Wexner Medical Center, knows a thing or two about data.

Dr. Embi has discussed the concept known as evidence-generating medicine at national meetings, including the American Medical Informatics Association Annual Symposium and the Summit on Translational Science. He also recently co-authored a study on how a sea change involving evidence-generating medicine (EGM) could accelerate research and improve health care.

“Successful medical research depends on the ability to leverage activities at the point of care and on systems that generate knowledge through routine practice,” says Dr. Embi, who is also vice chair of the Department of Biomedical Informatics and an associate professor of biomedical informatics and of internal medicine at The Ohio State University. “Health care professionals can systematically collect relevant data during clinical practice, generate research questions informed by practice and recruit patients for clinical studies.”

But this ideal bidirectional relationship may be difficult to implement.

According to Simon M. Lin, MD, MBA, chief research information officer at Nationwide Children's Hospital, the bottleneck involves hospitals realistically utilizing the large volume of data collected by EHRs to gain insight and better inform clinical practice.

“Other industries, such as retail and hospitality, are already collecting and using data to improve

FROM BEDSIDE TO BENCH

customer service,” says Dr. Lin, who is a national expert on data-driven health care innovations. “Institutions like ours are investing in health information technology infrastructure and accumulating data at a rapid rate. The next steps are to derive value from this data by analyzing it and using it to change practice.”

The EGM movement is a foundation for what the Institute of Medicine calls the “learning health system” — ongoing adoption and meaningful use of health information technology, such as electronic health records, to continuously improve health care and accelerate research.

LEARNING FROM PATIENTS, FOR PATIENTS

Learning health care systems are a major research focus for Kelly J. Kelleher, MD, director of the Center for Innovation in Pediatric Practice and vice president of Health Services Research at The Research Institute at Nationwide Children’s.

“In pediatrics, most database studies are conducted with national surveys by federal or large insurance claims databases,” explains Dr. Kelleher, who is also a pediatrician and professor in the Department of Pediatrics at The Ohio State University College of Medicine. “One largely untapped source of data is the burgeoning EHR repositories, which can be used to

study all the patients and data routinely collected by labs and clinics to learn what works best for whom and under what circumstances.”

But according to Dr. Embi, current regulatory frameworks are often developed, implemented and interpreted with research as an afterthought. This leads to the unintended consequence of erecting barriers between research and practice, ultimately restricting access to and use of clinical information for both scientific and health services improvement endeavors.

“Reversing the research-to-practice paradigm requires a variety of system-level changes,” agrees Dr. Lin. “And it starts with an investment in health IT infrastructure to support rapid and efficient data collection and analysis.”

Use of EGM — where every patient encounter becomes an opportunity to learn — should lead to accelerated and generalizable findings, says Dr. Lin, making it more likely that evidence will exist to improve the care of future patients.

And according to Dr. Embi and colleagues, health care organizations that prioritize investments in health IT infrastructure and integration of medical research are poised to lead the way in the development and operationalization of EGM’s future — which, it seems increasingly likely, is the future of medicine as a whole.

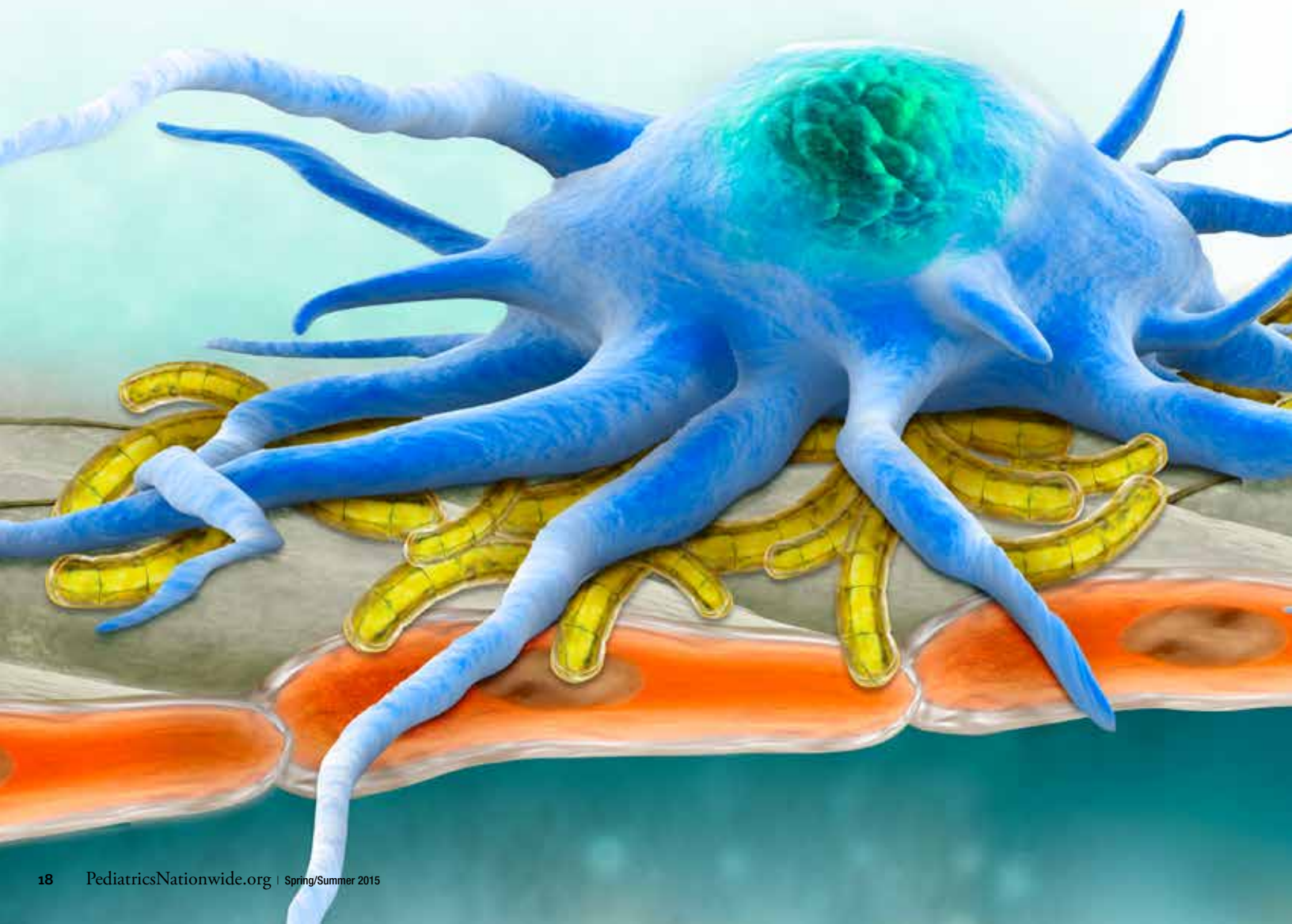


Join the conversation. How can physicians restructure their clinical practices to collect data that can facilitate research? Lend us your voice at PediatricsNationwide.org/Bedside-to-Bench.

FIGHTING FIBROSIS

FIBROSIS IS AN UNMET MEDICAL CHALLENGE WITH NO SATISFACTORY TEST AND INSUFFICIENT THERAPY. NOW, ONE NATURALLY OCCURRING CELLULAR COMPONENT COULD SIMULTANEOUSLY DIAGNOSE AND HEAL PATIENTS.

by Katie Brind'Amour



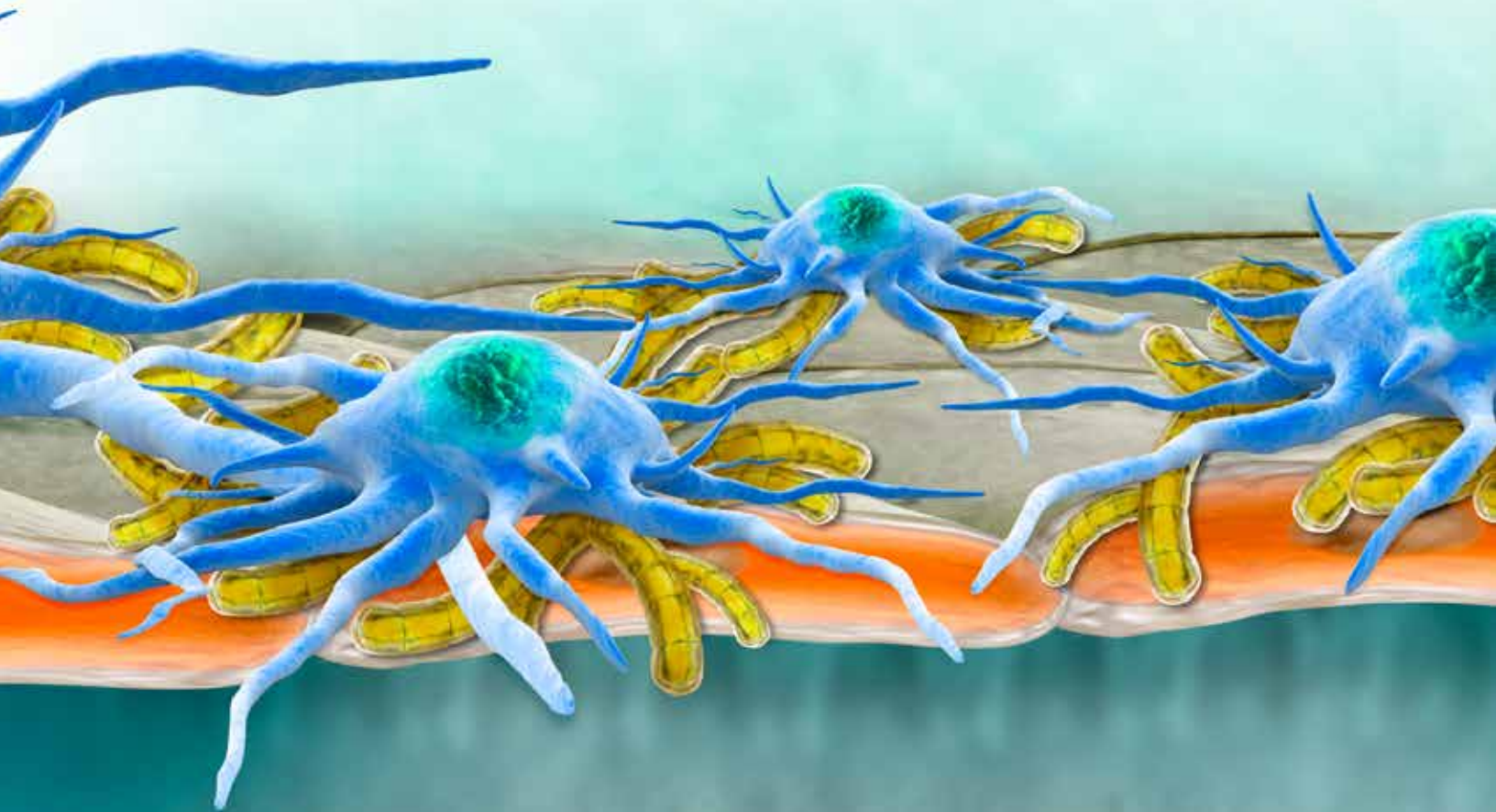
It's much more than a million-dollar idea.

The person who invents a simple blood or urine test that can accurately measure the severity of scarring in internal organs will have developed a diagnostic and clinical monitoring tool to help hundreds of thousands of people — adults and children alike — avoid risky biopsies and expensive imaging tests each year.

Even more dramatic will be the discovery of a therapy that cures fibrosis, the formation of scar tissue that, in excess, can interfere with organ function. Although this scarring may subside in some individuals after the underlying disease or problem is addressed, there are many others whose bodies cannot dissolve the fibrous tissue and replace it with healthy cells.

Bringing a cure to people who otherwise may be destined for organ transplant would make a lot of happy patients. And a much shorter organ donation wait list.

After all, scarring is a very common problem.



From the fine line that remains after a small cut to the expansive, collagen-rich matrix that is a feature of organ damage caused by long-term disease, there are few individuals who have not experienced the biological phenomenon to some degree. And in certain organ systems, the problem is a growing one.

More than 100 liver diseases and a wide variety of other medical complications can cause liver fibrosis in children. Some of these are anatomical defects, such as biliary atresia or missing bile ducts, and some are the result of chronic illness, drugs or even poor diet.

Most pediatric health professionals are no strangers to the quickly increasing rates of obesity among U.S. children. What fewer people may know is that rates of liver complications, such as nonalcoholic fatty liver disease and nonalcoholic steatohepatitis, are rising with the excess weight. These conditions result from excessive fatty deposits accumulating in the liver, which lead to inflammation and liver damage and, in some patients, fibrosis and cirrhosis.

Estimates suggest that as many as one in every 10 U.S. children have fatty livers, a major risk factor for developing future liver fibrosis.

An accurate liver fibrosis diagnostic test — and a cure — cannot come soon enough.

Now, the research of David R. Brigstock, PhD, principal investigator in the Center for Clinical and Translational Research in The Research Institute at Nationwide Children's Hospital, may have identified a striking way to resolve both diagnostic and therapeutic challenges with one molecular answer: exosomes.

BUILDING A BETTER BLOOD TEST

Although dangerous internal scarring affects millions of U.S. children and adults, there is currently no accurate, noninvasive way to assess this pathology. Biopsies are the gold standard for measuring liver fibrosis, but this approach is subject to errors in sampling and is highly invasive, carrying rare but significant risks of complications and presenting obstacles for patients who need to be tested repeatedly.

Imaging technologies, including ultrasound, elastography and MRI, are evolving rapidly and have the advantage of being noninvasive. But readings may not provide the desired discrimination and can be skewed by the presence of other liver pathologies. The

expense and time-consuming nature of such procedures accentuate the need for a simple biomarker-based blood or urine test.

But it wasn't this clinical objective that Dr. Brigstock and his three-person team initially intended to achieve.

Their past research focused on the body's mechanisms for regulating the production of connective tissue growth factor, which is instrumental in the production of scar-forming collagen. They changed course upon their discovery that exosomes are produced by the key fibrosis-inducing liver cells, called hepatic stellate cells, and have since devoted their work to understanding how exosomes package and deliver molecular information about cell activity to other liver cells.

Exosomes are tiny vesicles that carry molecular information from cell to cell, serving as communicators and, perhaps, instigators. Many human cell types pack exosomes with a complex molecular payload that is a snapshot of their own activity. Exosomes carrying micro-RNA (miRNA), messenger RNA (mRNA) and proteins are ejected from the cell and then taken up by other cells whose behavior is modified according to the molecular messages received.

Exosomes secreted by liver cells don't just take up residence in the liver. They travel, and some make their way into the bloodstream — hence Dr. Brigstock's idea for a novel blood test to indicate the presence and severity of liver fibrosis.

"If we can 'read' the molecular information being conveyed in exosomes, we may be able to filter out the molecular messages that relate to liver fibrosis and use them as biomarkers for assessing different levels of scarring," says Dr. Brigstock, who also is a member of the Department of Pediatric Surgery at Nationwide Children's and a professor of surgery at The Ohio State University College of Medicine. "Theoretically, the concept could be applied to any organ, since the process of fibrosis and collagen production is very similar throughout the body."

Dr. Brigstock believes that the molecular information carried by exosomes may include signals that can be used to track them to a specific injury site in the body. Further changes in that information could theoretically offer indicators of increasing or decreasing injury. The key is learning to read the signals.

“We are desperate to know what’s going on in the liver. David’s research is among the most exciting of its type anywhere.”

— Scott L. Friedman, MD, Icahn School of Medicine at Mount Sinai



Photo credit: Catherine Clarke

“We are desperate to know what’s going on in the liver,” says Scott L. Friedman, MD, chief of the Division of Liver Diseases and dean for Therapeutic Discovery at the Icahn School of Medicine at Mount Sinai. Dr. Friedman discovered the hepatic stellate cells that release the exosomes identified in Dr. Brigstock’s work. “David’s research is among the most exciting of its type anywhere.”

Developing accurate blood tests for fibrosis is not without its challenges, however.

Pediatric liver fibrosis expert Ronald J. Sokol, MD, section head of Gastroenterology, Hepatology and Nutrition at the University of Colorado (Denver) School of Medicine, is quick to point out that many attempts at blood tests to detect specific degrees of liver fibrosis have also looked promising — and ultimately fallen short of clinical needs.

“The study of exosomes and microparticles is a very hot area in science now,” says Dr. Sokol, who also serves as the associate medical director of UC Denver’s Pediatric Liver Center and Liver Transplantation Program. “Lots of researchers are examining it in cancer and other biologies, and it’s something that you can measure very nicely in the lab. To extrapolate that finding into a blood test for fibrosis is challenging, particularly when so many other biomarker-based blood tests have failed to pan out.”

Even so, he cannot deny the appeal of such a test and genuinely hopes Dr. Brigstock succeeds.

“It’s every doctor’s dream to have a simple blood test that tells us how much scarring is in the liver, and nothing currently on the market is completely accurate,” Dr. Sokol explains. “Many approaches in pharmaceutical

development are enormously promising in mice and then don’t pan out in humans. That doesn’t mean that this technology should not be explored — it should be explored. There are a lot of good ideas that turn out to be true as well.”

But Dr. Brigstock’s approach has a special appeal, according to Laura E. Nagy, PhD, a professor of molecular medicine at Cleveland Clinic Lerner College of Medicine and director of the Cleveland Alcohol Center. Dr. Nagy reached out to Dr. Brigstock to collaborate after hearing his invited lecture at her institution.

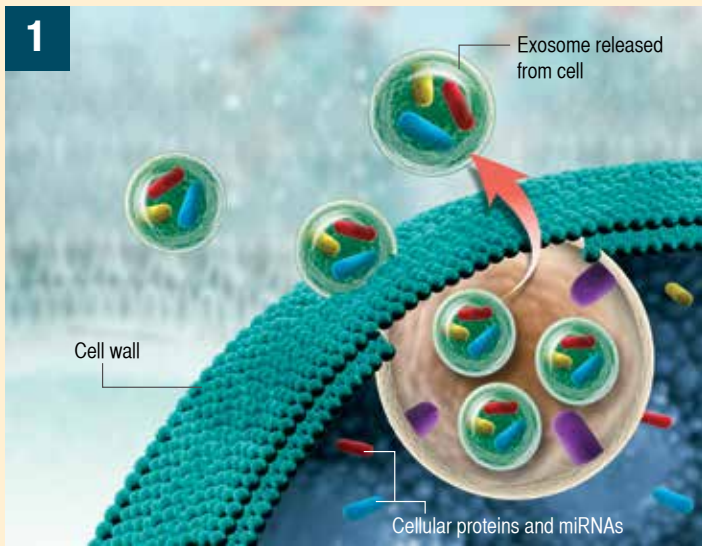
“Many other biomarker approaches focus on one or two indicators,” Dr. Nagy says. “But exosomes are packed with information, and I believe they could offer a much broader perspective on what’s going on in the body. The more information, the better.”

Later this year, Dr. Nagy’s pending project center grant from the National Institutes of Health and the National Institute on Alcohol Abuse and Alcoholism will facilitate Dr. Brigstock’s clinical research on human blood samples.

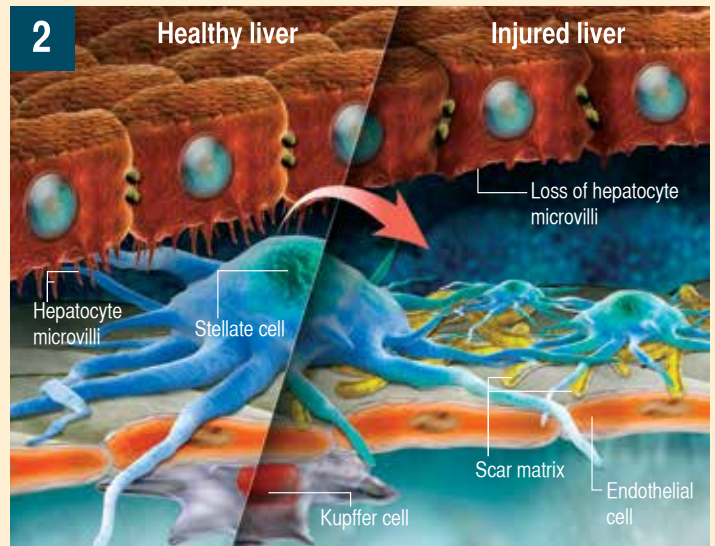
“There’s lots of work to be done,” Dr. Friedman says of Dr. Brigstock’s work. “And while it’s not ready for prime time yet, the ability to capture information circulating in the blood about the state of the liver is exactly the type of new approach we need.”

And remarkably, this new angle on fibrosis research is not limited to a potential noninvasive blood profile.

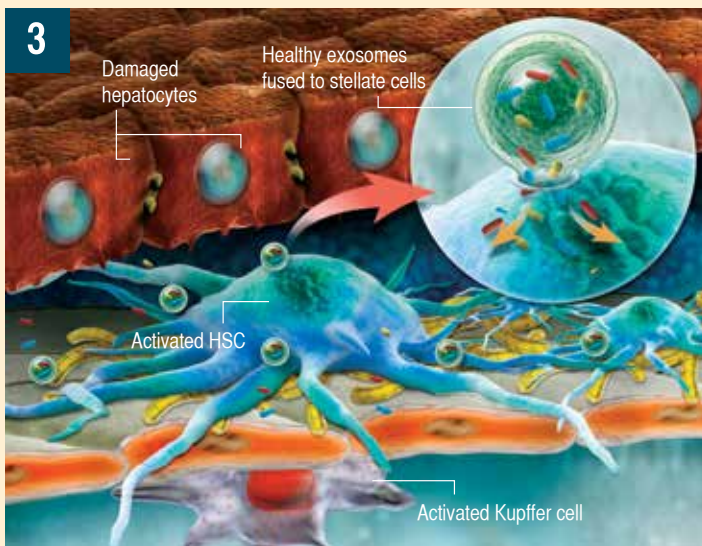
Exosome Therapy for Liver Fibrosis



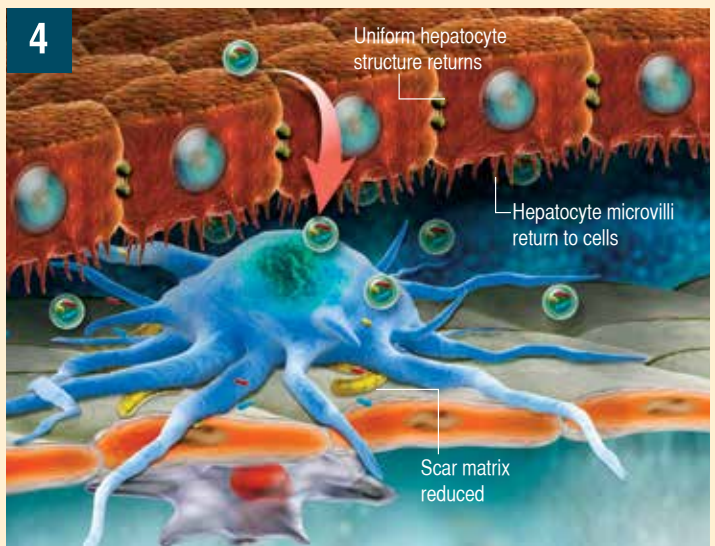
1. Exosomes are careening around the body all the time. Cells release them and they can act locally, but they can also get into body fluids. miRNAs are one of the types of molecules that get into these organelles and are important in intercellular communication.



2. The stellate cells, which drive fibrosis, produce large amounts of scar matrix during chronic injury. This affects organ architecture and can compromise liver function.



3. When exosomes from healthy subjects are administered in the circulation, they are absorbed by the liver and fuse with target cells. “Healthy” molecular information is conveyed from the exosomes to damaged cells. Stellate cells become reprogrammed to deposit less collagen.



4. After administering exosomes for a week, fibrosis is reduced or eliminated and prior damage to other liver cells is repaired.

SCRATCHING THE SURFACE

It's rare for biology to hand medical science a veritable Holy Grail with sufficient power to both diagnose and cure disease. But judging by early work in mice, Dr. Brigstock believes that exosomes may just have that sort of potential.

"Exosomes appear to be critical in telling other cells whether to increase or decrease their production of fibrosis-inducing molecules such as connective tissue growth factor," says Dr. Brigstock. His team made this discovery, which was featured as the cover article in a 2014 issue of the journal *Hepatology*. "The molecular information packaged into exosomes changes dynamically according to the status of the cell that loaded it up and sent it off into the world. In turn, this information is conveyed to neighboring cells that respond according to the exosomal messages received."

If a hepatic stellate cell is over-producing collagen, Dr. Brigstock theorizes, it's likely packaging molecular information into its exosomes, which communicate this message to neighboring cells that then follow suit.

The same goes for liver cells that have suppressed their fibrotic activity. Presumably, cargo from their exosomes could potentially reprogram other cells to stop their collagen production.

"It's a newly discovered mechanism by which fibrosis is being regulated," Dr. Brigstock says. "And whenever

you're talking about molecular mechanisms, many components in those processes are theoretical points of therapeutic intervention."

Unlike the diagnostic profile test for which Dr. Brigstock has already begun pursuing human blood samples, exosome therapies for liver fibrosis cannot readily be moved out of the realm of animal studies.

But what he's seen in animal models has not disappointed.

When Dr. Brigstock's team recognized that mice with fibrosis produced exosomes containing different information than nonfibrotic, healthy mice, they put two and two together.

"The question was whether, if we administered exosomes from healthy mice into the circulation of fibrotic mice, the liver would receive some of this information and respond by becoming less fibrotic," Dr. Brigstock says. It seemed like a long shot.

They injected exosomes from healthy mice into mice with induced liver fibrosis. Within a week, the animals' fibrosis had disappeared.

"It was stunning," Dr. Brigstock says.

While his team gathers additional data to move their exosome projects along, with the hope of securing additional NIH funding, the possibilities for exosome therapy seem wide open.



“The question was whether, if we administered exosomes from healthy mice into the circulation of fibrotic mice, the liver would receive some of this information and respond by becoming less fibrotic.”

— David R. Brigstock, PhD, Nationwide Children's Hospital

A WINNING STRATEGY

Dr. Brigstock's mouse models benefited from exosome therapy when it was delivered via a simple injection. Although he has no particular reason to assume one method will win out over any other, Dr. Brigstock does admire the simple elegance of exosomes as a directly donatable or culturable product.

He is not alone. The method is already being tested in a field quite different from liver fibrosis: oncology.

For years, the field of cancer research has been buzzing about exosomes and their role in intercellular communication — signaling other cells to produce more active immune cells, for instance.

As many as half of all cancer patients receiving stem cell transplants develop severe graft-versus-host disease, a deadly condition in which the recipient's body is at war with the donor cells. And half of these patients do not respond to the standard corticosteroid treatment.

Convinced that some of the curative capacity of the stem cells used in these transplants was derived from healthy exosomes, clinician-scientists in Germany increased the expression of exosomes in these stem cells and repeatedly injected them into a patient with severe, intractable graft-versus-host disease.

The patient's symptoms significantly improved.

Although this patient later succumbed to pneumonia, the case report demonstrated that cultured exosomes could be administered as a therapeutic. Dozens of similar therapeutic applications have since begun at

hospitals across the globe, with several therapies now in Phase II clinical trials.

Beyond direct culture and injection, alternative methods exist that offer researchers multiple avenues for exosome therapies.

According to Dr. Brigstock, techniques could include packaging a drug or replicated material from healthy donors into exosomes for targeted delivery to fibrotic liver cells. Theoretically, the same concept could work for other organ systems in the same way. And a similar "packaging and delivery" process is already therapeutically used with liposomes.

"I like the concept that you might bioengineer exosomes and package them with a molecule you would design that would turn off the fibrosis-related genes," Dr. Sokol says. He believes a targeting mechanism would improve the chance of success. "Cells could recognize another engineered molecule on the exosomes' surface and take them up to deliver the drug to a specific cell type."

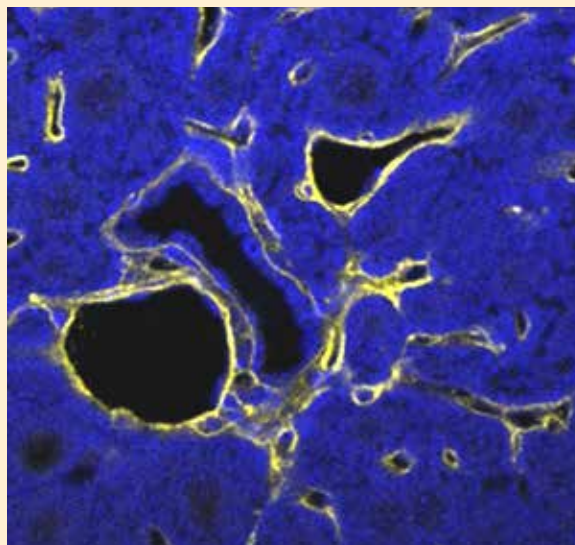
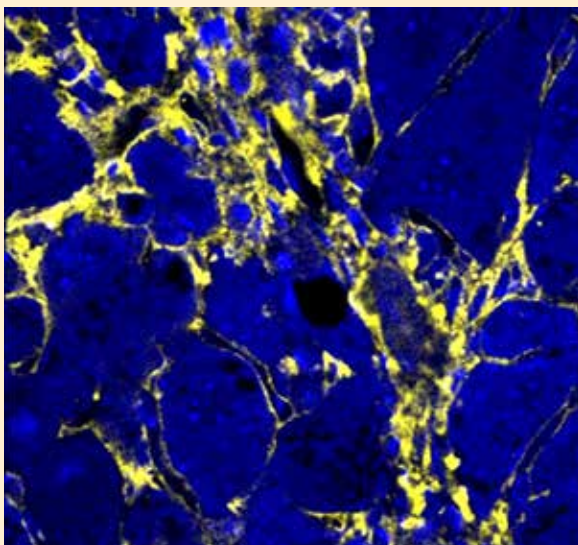
The approach has science on its side, Dr. Brigstock says.

"Exosomes are nature's own delivery vehicles. They protect their contents from adverse extracellular environments and allow molecular information to be delivered to another cell," he says. "That is what you want to do with drugs. The body wouldn't even recognize them as foreign before the drug was delivered."

Dr. Brigstock is understandably optimistic. It's not just the promise of the exosomes that makes him so, but the

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— Ronald J. Sokol, MD, University of Colorado (Denver) School of Medicine



The image on the left shows collagen detected by immunohistochemistry in mice after experimental fibrosis was induced for five weeks. During the fifth week, some mice also received intraperitoneal injections of exosomes harvested from the circulation of healthy mice. The image on the right reveals that the fibrotic interstitial collagen disappeared in the exosome-treated mice. The collagen that remains is nonpathologic and is involved in structurally supporting the hepatic blood vessels and sinusoids.

prospect for significant clinical improvements for individuals with liver fibrosis and other scarring problems.

While curing the underlying chronic disease leads to resolution of fibrosis in some patients, these responders cannot be predicted ahead of time. Those who are unlucky enough to remain heavily scarred need options.

A COMMON GOAL

Promising drugs developed by groups across the country are now in clinical trials. Some target the collagen matrix and attempt to break up the fibrous cell networks. Other approaches aim to block molecular pathways that perpetuate the production of fibrotic tissue. These and additional endeavors swell the range of biomarker-based blood tests and imaging research that could significantly improve fibrosis diagnosis and measurement in the future.

Dr. Brigstock knows his own ideas still face many obstacles before they can be clinically tested. But he remains driven by the overarching goal of targeting scar tissue to detect — and reverse — fibrosis.

“The truth of the matter is that when you test these approaches in animal models, you don’t really get a sense of whether they’ll work in people,” he says. “Ideally, I’d like to see exosomal therapy proven in other models of fibrosis and then investigated in clinical trials. It’s not a difficult path to anticipate.”

Not difficult to anticipate, perhaps, but a challenge to execute. Dr. Brigstock and his team are already collaborating with fibrosis experts from Ohio, California, New York, Canada and China to open the road to additional federal funding.

Whether or not an accurate reading of exosomal information in humans is possible, the group will continue animal studies to examine the tiny packages’ potential for fibrosis treatment.

“It may be a difficult path to tread,” Dr. Brigstock says, “But I have an innovative and resourceful team working on this project. I think it’s the most exciting work that we’ve participated in during the nearly 25 years I’ve been at Nationwide Children’s.”



Join the conversation. Initial research suggests exosome profiles can also communicate information about inflammation. How might exosome-based diagnostics impact the assessment of other pediatric diseases? Lend us your voice at [PediatricsNationwide.org/Fighting-Fibrosis](https://www.pediatricsnationwide.org/Fighting-Fibrosis).



PRESERVING BIOPRESERVATION

Funding challenges, operational complexity and poor visibility threaten the field of human tissue biobanking. How sustainable are biorepositories?

by Katie Brind'Amour

4,000,000 BIOSPECIMENS
1,000 RECEIVED DAILY
70,000 DISTRIBUTED ANNUALLY
\$15,000-\$27,500 PER FREEZER
154 FREEZERS
160 EMPLOYEES
25,000 SQUARE FEET
1 BIOBANK

The Children's Oncology Group (COG) boasts the collaboration of more than 9,000 pediatric cancer experts. They treat patients and research disease at more than 200 hospitals around the world. Nine out of every 10 U.S. children with cancer receive care from a COG professional or facility. And nearly all of those patients end up donating tissue or serum samples for preservation and storage at a single biobank.

Hundreds of COG samples arrive daily, and the bank distributes up to tens of thousands to researchers annually. And COG is just one client. Large banks often store samples for numerous federally funded projects or pharmaceutical studies.

Clinicians and researchers alike have relied on this biobank's collection to drive improvements in diagnosing childhood cancers, including rare tumors such as neuroblastoma and ultra-rare tumors such as hepatoblastoma. COG Chair, Peter C. Adamson, MD, says biobanking of specimens was, is and will continue to be crucial to the development and improvement of clinical therapies in pediatric oncology.

But what if the biobank were to go out of business?

The scenario is not hard to imagine. Facilities, such as the one at Nationwide Children's Hospital hosting the COG samples, cost a fortune to start and an even greater fortune to maintain. Cuts in federal grant money, increasing equipment and personnel expenses and difficulty disseminating samples left over from large clinical trials add to the mounting challenges.

The future of biobanking is uncertain and expensive.

IT'S A BUSINESS. OR IS IT?

Like any bank, biobanks accept deposits and safeguard them for many years, providing security and monitoring. They collect, process, store and distribute tissue, blood, serum and other human biospecimens for a wide range of clients — private individuals, large clinical trials, pharmaceutical companies, university research labs and others.

Yet the standard bank analogy is too simple. At a regular bank, one dollar is the same as another. Clients don't expect to withdraw the exact same dollar bills they deposited. Not so with biobanks, where a precise, annotated chain of custody is required for each sample.

It is the Biopathology Center (BPC) at Nationwide Children's that houses the biobank for COG, which is funded by the National Cancer Institute. The BPC also houses other NCI-funded biospecimen collections, including those of SWOG (formerly the Southwest Oncology Group), the Gynecologic Oncology Group, The Cancer Genome Atlas and the Childhood Cancer Survivor Study. Nationwide Children's internal investigators also base statewide and national grant-funded projects at the BPC, including the biospecimen collections for the Ohio Perinatal Research Network, The Cystic Fibrosis Therapeutics Development Network and the Nephrotic Syndrome Study Network.

As the federal government continues to limit and even reduce funding for research projects, scientists — as well as biobanks and other industries their grant money supports — feel the effects.

"Most of these grants are being cut consistently, at least 10 percent every year, so we're doing way more than we end up being funded for," explains Nilsa Ramirez, MD, director of the BPC of surgical pathology at Nationwide Children's. "If we lose one of these grants, it's not like losing a single customer at a regular bank. Because of their large size, we'd lose a lot of business."

Having to juggle budgets and staff is not ideal, Dr. Ramirez concedes, but it's necessary to the biobank's survival. And thankfully, the hospital provides considerable support.

"You have to have institutional support to survive, and in that sense we're very lucky," Dr. Ramirez says. "The biobanking efforts of the BPC are mainly supported by money from federal grants. However, this institution shares our vision and consistently provides us with great resources and an infrastructure that allows us to be incredibly successful."

Not all biobanks are fortunate enough to have a sponsor at the ready to cover facility costs, electricity or other expenses in a pinch. The reliance many hospital- and university-hosted biobanks have on their supporting institutions highlights the crux of the issue: biobanks struggle to be financially self-sufficient.

"Most noncommercial biobanks do not have a good idea of their operating costs," says Jim Vaught, PhD, editor-in-chief of *Biopreservation and Biobanking* and president-elect of the International Society for Biological

and Environmental Repositories (ISBER). “They are often funded by central institutional budgets and have never thought of their biobank as a business operation.”

Although commercial biobanks’ funding sources aren’t dependent to the same degree on the generosity of Congress, they face their own sustainability issues.

“Industry biospecimen collections face many of the same challenges,” says Kathi Shea, vice president of bioservices at Precision for Medicine — which runs a large commercial biorepository — and past president of ISBER. “The biobank grows and grows, and the cost to sustain the biobank increases over time.”

A PROBLEM OF VOLUME

Hundreds to thousands of samples arrive at the typical large biobank daily, but comparatively few leave. Many specimens are banked with the expectation that they’ll sit unused for upwards of a decade. It’s not a business designed for short-term profits. And most programs collect more than they need.

These study leftovers, called “legacy” samples, are available for a service fee to approved researchers who make solid, relevant proposals to use samples for related research.

“The samples that turn out to not be interesting from the scientific perspective of one researcher can often be greater than the number that end up being useful,” Shea says.

“Finding ways to make archive collections known to the broader research community to maximize the use of the biospecimens by additional researchers is a challenge faced by many institutions.”

Many federal grants now include funds for long-term storage of samples, but it is better to have them distributed and used rather than just sitting in storage.

“We could get 10 important medical questions answered instead of one by getting more researchers access to those specimens,” Shea explains.

Short of creating a website that continually updates researchers on the archive collections available for research at each biobank, there’s no way to let people know what’s up for grabs. And while profitably offloading a greater number of otherwise unproductive specimens could help some banks, this solution — like other ideas for rescuing the endangered industry — is unlikely to be one-size-fits-all.

According to Shea, the number of unused specimens

banked could also be reduced by more conservative planning, balancing the number and type of specimens collected against the likelihood the assets will ever be needed. Well-designed trials could decrease the amount of tissue or blood that needs to be collected from participants while improving cost efficiency at the biobank.

CHANGING THE MODUS OPERANDI

Solving sustainability issues in biobanking is also, in part, about running a tight ship. Dr. Ramirez and her team construct business plans, mapping the life of major grants and expected funding over three to five years.

“We usually know when a big dip in funding is coming and can try to make sure that whatever loss we envision we can complement with some other project being developed,” she says. “Things often end up evening out — we get another grant, technology improves or certain processes become cheaper. We always have to do a little bit of magic in there, but we still get everything taken care of properly.”

Designing more space-efficient storage and automating certain procedures are additional ways to drive efficiency and decrease operating costs, Shea suggests.

But redefining user expectations for the expenses associated with storing or obtaining biospecimens could be equally critical.

“Users of specimens often have the perception that they should be free or very low cost, due to their limited knowledge about how much it costs to collect, process and store samples,” Dr. Vaught explains.

At the same time, biobanks struggle to determine appropriate charges.

“Quantifying expenses is difficult when direct and indirect expenses are covered by various funding resources,” Dr. Ramirez explains. “For grant-funded biobanking efforts like ours, it is a challenge to estimate 100 percent of our costs when there are so many variables to consider. We do our best to calculate them based on prior experiences and on the contributions of our expert BPC team, but it is a challenge.”

This calculation is less difficult for commercial organizations but still requires regular evaluation and adjustments. Other potential solutions, such as reworking overarching business models, require more substantial adjustments.

“Biobanking is not an inherently good business, since it’s difficult to recover a significant fraction of the operating costs,” Dr. Vaught says. “But in general, diversifying is good. Have a mixture of government grants or contracts, pharmaceutical or biotech partners and services for fees. And if staff has the expertise, biobanks could offer consulting services as well.”

Dr. Vaught also believes that in order to achieve long-term sustainability, many noncommercial biobanking operations would have to develop comprehensive business plans and add ancillary services such as DNA extraction, private sample storage for a fee and more.

Despite a bank’s best efforts, funding and volume of stored biospecimens fluctuates. And in such a volatile environment, any given biobank’s stability could be at risk.

A FUTURE FOR BIOBANKING

Despite the beleaguering day-to-day battles with bottom lines and shifting clientele, not all experts worry for the long-term survival of the field.

“I believe that biospecimens are the future of medicine since they are a basic building block used in all scientific research, particularly as we navigate through the era of precision medicine and develop targeted approaches to improve health,” Shea says.

Broader recognition of this fact, Dr. Ramirez explains, will eventually guarantee the perpetuation of biobanking as an industry. After all, she says, the future depends on it at least as much as the past has.

“There is probably not a childhood cancer where the biorepository hasn’t impacted our understanding of disease and, in certain cases, the treatment of disease,” says COG’s Dr. Adamson, who also is a pediatric oncologist at The Children’s Hospital of Philadelphia. “What will be central for future treatments is the study of well-annotated biospecimens — having biological material linked with knowledge of a child’s diagnosis, treatment and outcome. Without that, we will be extremely limited in our ability to bring 21st-century treatments to children with cancer in this country or in other parts of the world.”



Thousands of slide drawers store hundreds of samples each at Nationwide Children’s Biopathology Center.

Studies involving the Nationwide Children’s BPC specimens have resulted in medical advances published in journals such as the *New England Journal of Medicine*, *Cancer Cell*, the *Journal of Clinical Oncology* and *Blood*.

“Our ability to advance targeted new drugs and to improve outcomes is directly dependent on our ability to do leading-edge research on specimens from our biorepositories,” Dr. Adamson says. “If we were to lose the biobanks, the impact would be devastating for childhood cancer.”

The knowledge that these biobanks have truly made a difference in the clinical world helps motivate Dr. Ramirez and her colleagues when many biobanks face discouraging financial setbacks.

“We want to make sure we are good stewards of these samples,” Dr. Ramirez says. “All those patients who were gutsy enough to donate specimens for banking 30 or 40 years ago contributed to the research that improved medical treatments, resulting in the incredible childhood cancer survival rates that you see now. If biobanks were not around, it would be catastrophic to the future of medical research and care.”



Join the conversation. How could biobanks improve awareness of and access to legacy biospecimens for researchers? Lend us your voice at PediatricsNationwide.org/Preserving-Biopreservation.

A WINDOW TO THE HEART

Cardiac magnetic resonance imaging (MRI) is transforming the clinical approach to complex surgeries in The Heart Center at Nationwide Children’s Hospital. The technology provides a radiation-free imaging option and detailed live-motion or 3D images of cardiac function, morphology and all venous and arterial anatomy.

CARDIAC MRI FOR HYPOPLASTIC LEFT HEART SYNDROME (HLHS)

HLHS is a potentially fatal congenital heart defect affecting blood flow. It requires multiple palliative surgeries, starting within the first week of life. Nationwide Children’s employs a hybrid surgical approach.

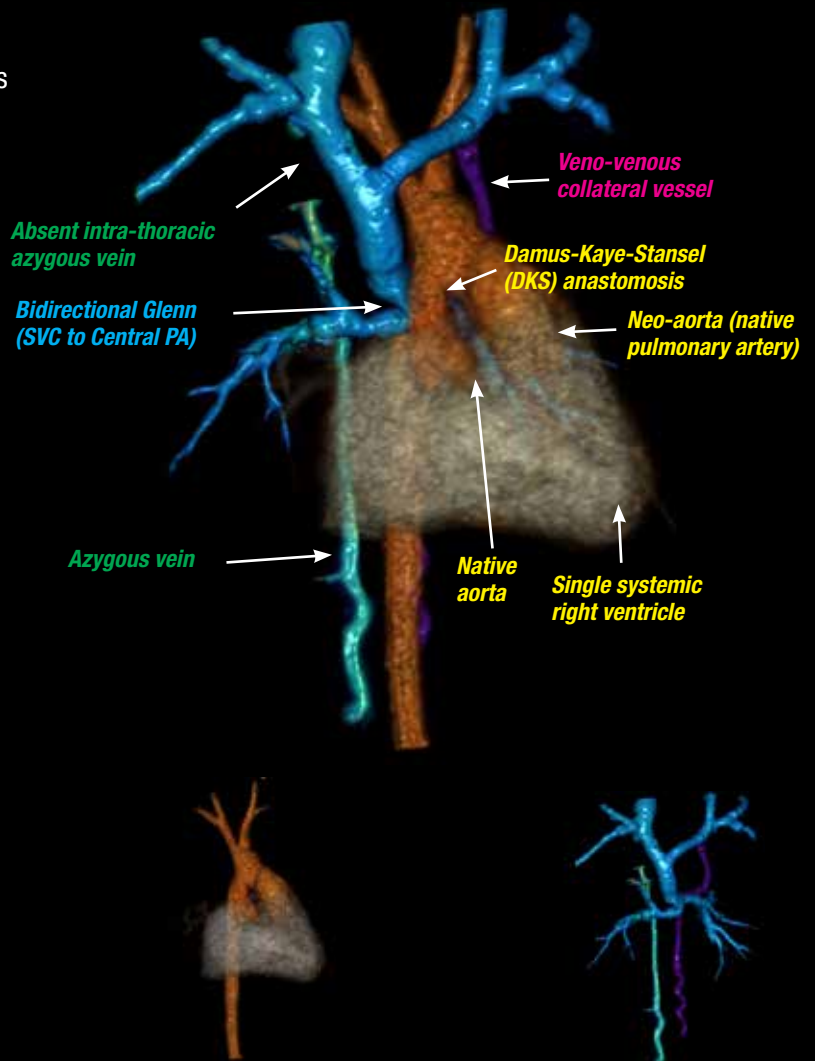
Hybrid Stage I *(not shown)*

Bilateral branch pulmonary bands are placed to restrict blood flow. A stent is placed to augment systemic blood flow, and an atrial septostomy allows improved mixing of the saturated and unsaturated blood. Unlike the standard Norwood procedure, hybrid stage I typically allows discharge within a week or two.

Comprehensive Stage II

This surgery removes the previous stent and bands and surgically enlarges the atrial defect. This stage also includes aortic arch reconstruction and connects the superior vena cava to the pulmonary artery (bidirectional Glenn).

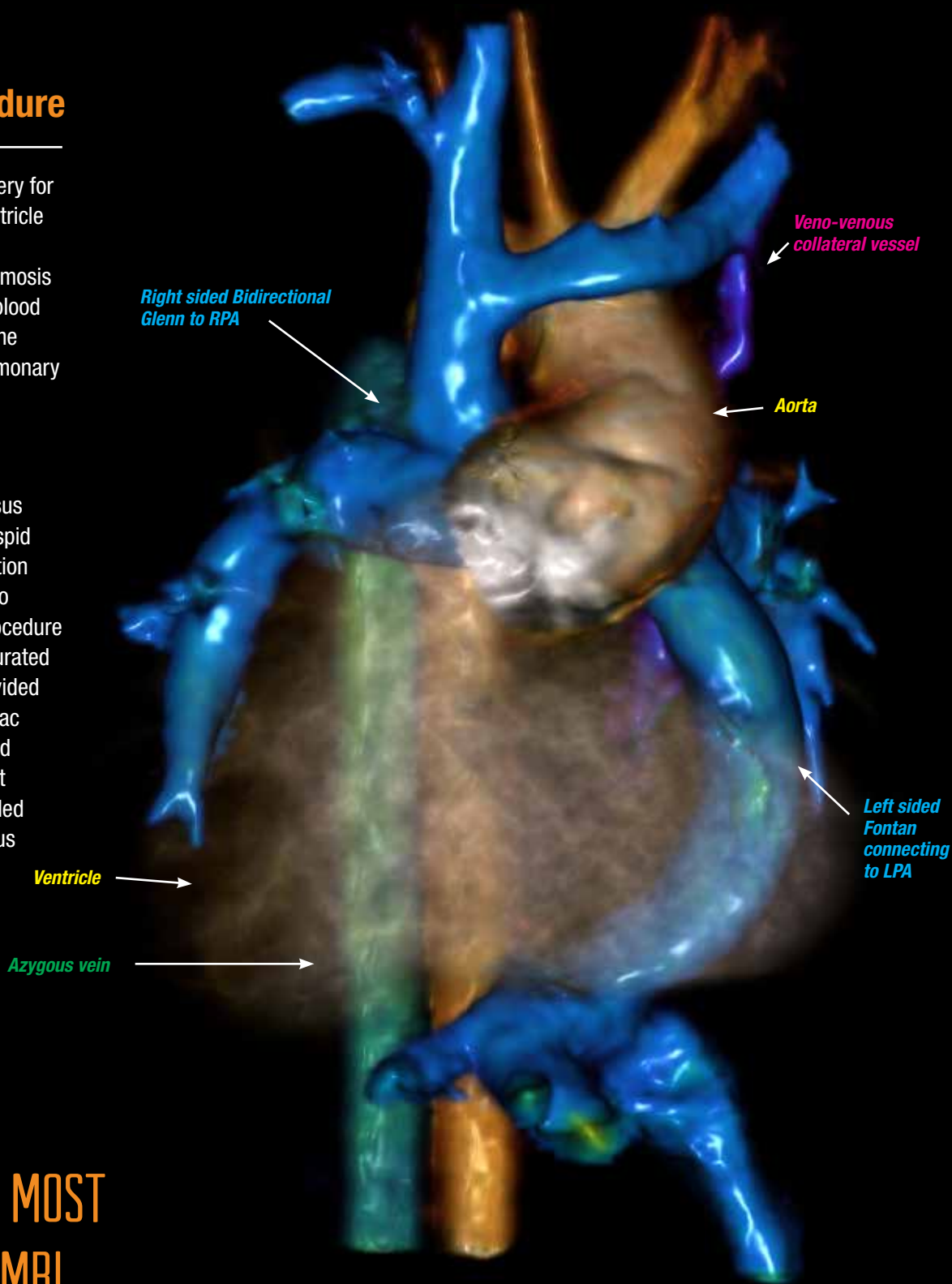
In this 6-month-old patient, cardiac MRI enabled cardiologists to identify three abnormalities: a clot in a portion of the azygous vein, a veno-venous collateral vessel and a kink or narrowing at the point of insertion of the superior vena cava into the right pulmonary artery (bidirectional Glenn), altering the patient’s treatment.



Stage III – Fontan Procedure

The final palliative surgery for patients with single ventricle defects completes the cavo-pulmonary anastomosis (Fontan), which routes blood from the lower part of the body directly to the pulmonary artery.

This image depicts the heart of a 16-year-old patient with situs inversus with dextrocardia, tricuspid atresia and L-transposition of the great arteries who underwent a Fontan procedure and is now more desaturated (blue). Cardiac MRI provided a roadmap for the cardiac catheterization team and enabled a more efficient procedure, which included occlusion of veno-venous collateral vessels and stent placement in the affected portion of the central pulmonary artery.



MAKING THE MOST OF CARDIAC MRI

According to Kan Hor, MD, director of the Cardiac MRI program at Nationwide Children's, approaching complex heart surgeries with a patient-specific, pre-surgical visual guide enables physicians to prepare for functional and anatomical abnormalities that may not be visible with standard echocardiogram. Unlike CT imaging, cardiac MRI does not involve the use of radiation, nor is it as invasive as cardiac catheterization.

To learn more about how cardiac MRI is transforming clinical care and research, visit PediatricsNationwide.org/Window-to-the-Heart.

QUESTION: How will the increasing use of patient apps and do-it-yourself health technologies impact the future of pediatric care and disease management?



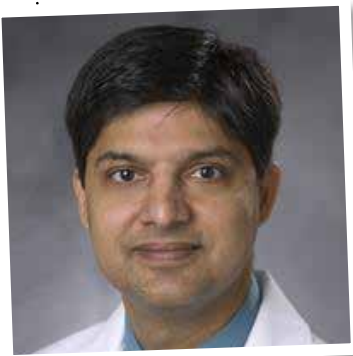
A: The use of popular technology mediums, such as interactive apps, has the potential to empower both parents and pediatric patients to take a more active role in their medical care. At the same time, it encourages health care providers to engage families in medical decision making by facilitating shared knowledge and creating alternative ways in which families can communicate with the health care team.

– **Katherine J. Deans, MD**

Principal Investigator, Center for Innovation in Pediatric Practice

Surgeon, Center for Colorectal and Pelvic Reconstruction

Nationwide Children's Hospital



A: The future of patient care apps is moving towards individualized care and improved decision making. An increasing number of families and patients have smartphones and devices to enable the use of patient care apps, which has promoted the development of apps for self-improvement and awareness. It is critical for health care teams to grow with this technology. Collecting data from these apps allows a huge opportunity to offer continued care for patients between patient visits. Importantly, the effort has started to focus on the development of patient-specific recommendations based on individual data.

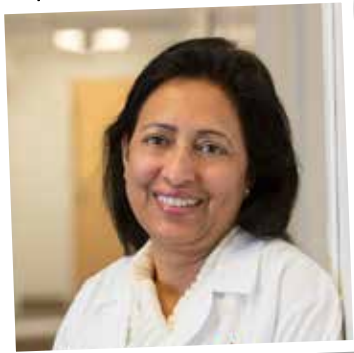
Our efforts have included the development of a mobile app for patients with sickle cell disease (Sickle cell Mobile Application to Record symptoms via Technology, SMART), which allows symptom management through patient logs, bi-directional communication and algorithms for treatment decisions. As a medical provider caring for patients with chronic diseases, I aim to improve the recognition of unique characteristics of each patient through the use of technology. Patient care apps and do-it-yourself health care technology is the impetus to advance the future of health care towards this goal.

– **Nirmish Shah, MD**

Director, Sickle Cell Transition Program

Hematologist, Division of Pediatric Hematology/Oncology

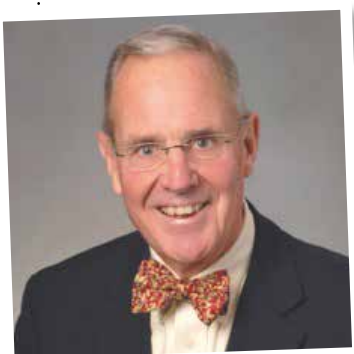
Duke University



A: We are living in the digital era. Our adolescent population thrives on apps for all their needs. Diabetes apps, such as the one built at Nationwide Children’s Hospital, facilitate many disease-specific knowledge and calculation tasks and also provide important diabetes education. Using our tool, patients and families are able to look up carbohydrate contents of many foods, log in blood glucose data, calculate an individualized insulin dose and much more.

The aim of the diabetes app is to increase interest and facilitate self-care in patients with type 1 diabetes. This concept, however, could be applied to many chronic conditions with equal success. I believe these tools will reshape how families manage long-term conditions by making self-care simpler — providing guidance for “sick days,” the ability to track health metrics, reminders for medication or check-ups and much more. Not only will such apps make our jobs easier, they may result in better treatment adherence and will likely improve children’s health outcomes, as well.

– Manmohan K. Kamboj, MD
Interim Chief, Endocrinology, Metabolism and Diabetes
Nationwide Children’s Hospital



A: Parents are increasingly sophisticated in their capacity to inform themselves on the Internet. Our young pediatricians have high expectations that electronic medical records have the capacity to interconnect with their patients, registries, schools and public health departments. And the American Academy of Pediatrics is invested and committed to continued development of resources to meet the needs of families and pediatricians. Remembering that nothing trumps the face-to-face office visit, there is no doubt the future of pediatrics will be full of information technology.

Clinicians can rely on Pediatric Care Online, an app that provides point-of-care access to clinical information. Using it is like having a full medical library in your pocket and a consultant by your side. The Academy also has had great success with HealthyChildren.org, a trusted website that parents use for answers to every aspect of childrearing. Finally, our Bright Futures Visit Planner helps providers track their patients’ well visits and get quick access to industry-standard information for pediatric preventive care, including immunizations, pre-visit questionnaires and patient handouts. These and other innovations are sure to improve the efficiency and collaborative nature of pediatrics by increasing information accessibility and patient-provider communication.

– Michael V. Severson, MD
Immediate Past District VI Chairman, American Academy of Pediatrics
Pediatric Hospitalist
St. Joseph’s Medical Center of Brainerd, Minnesota



Join the conversation. How might apps and digital personal care technologies negatively impact pediatric health? Lend us your voice at [PediatricsNationwide.org/Apps-Future-Health](https://www.PediatricsNationwide.org/Apps-Future-Health).

Help us advance the conversation on child health.



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Beyond the Basics: Enrolling Children in Research

by Katie Brind'Amour

The ethics of pediatric research include more than the concepts of autonomy and assent. According to Victoria A. Miller, PhD, director of research in the Department of Adolescent Medicine at The Children's Hospital of Philadelphia, appropriate inclusion of the child in all discussions involving his or her participation in research is crucial. Learn more about this and other emerging ethical issues in pediatric research at PediatricsNationwide.org/Child-Research.



How to Build and Lead a Successful Medical Department

By V. Rama Jayanthi, MD

Fostering an environment that supports evidence-based medicine, professional development and equal footing for clinician-researchers is a critical challenge for medical leadership. Find out how Nationwide Children's chief of urology, V. Rama Jayanthi, MD, has reinvented his department to encourage innovation, advancement and job satisfaction for his fellow physicians at PediatricsNationwide.org/Building-Success.



Second Opinions: What is Essential to Bedside Manner?

Effective, compassionate "bedside manner" means something different to every physician. Find out what your colleagues have to say on the matter — and contribute an answer yourself — at PediatricsNationwide.org/Bedside-Manner.

“To raise new questions, new possibilities, to regard old problems from a new angle, requires creative imagination and marks real advance in science.”

– Albert Einstein

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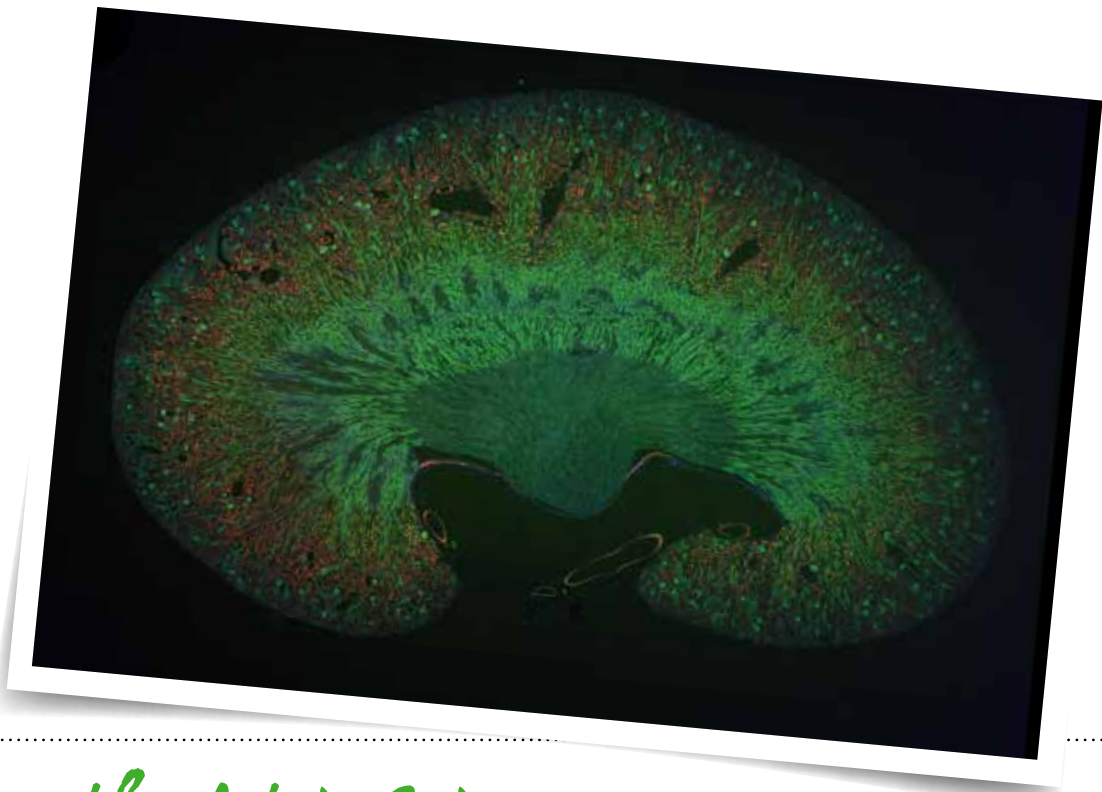


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Finding the Art in Science

Reminiscent of Van Gogh's swirled paints, this fluorescent kidney slide bridges the worlds of art and biopathology. The Biomedical Imaging Team creates scans like this for the Biopathology Center in The Research Institute at Nationwide Children's Hospital. An immunofluorescence slide scanner captured this unique picture from a removed, bisected kidney after staining with immunofluorescent antibody stains.

The green spots near the edges highlight the kidney's tight collections of capillaries that filter the blood, and the small orange and yellow dots are the convoluted tubules that filter chemicals. The green and blue lines near the center are the kidney's straight tubes and collecting ducts. The larger orange circles are vascular structures, likely veins.

View this and a gallery of other striking and quirky tissue stains — including a series of samples resembling fish, hearts and even racecars — from the Biomedical Imaging Team at [PediatricsNationwide.org/Art-in-Science](https://www.PediatricsNationwide.org/Art-in-Science).