

Spring/Summer 2020

Pediatrics

NATIONWIDE

Advancing the Conversation
on Child Health



SURVIVING
THRIVING
AFTER
SEVERE BPD

**INSIDE
THIS ISSUE**

Transforming Medical
Science Through Research
Affinity Groups

Epigenetics, Chromatin
Architecture and a
Judo Mechanism to
Attack Cancer

Why Synthetic Tracheal
Replacements Fail and
Hints for Success

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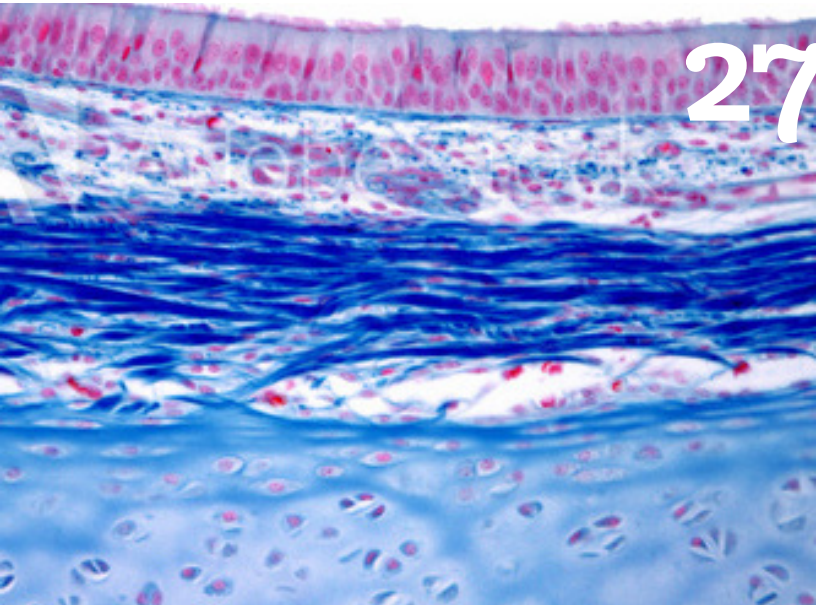


18

~~SURVIVING~~ THRIVING AFTER SEVERE BRONCHOPULMONARY DYSPLASIA

Meet Willow. She was born via emergency C-section at just 22 weeks. Doctors at the delivering hospital told Willow's mom Cortney that her baby's chances of survival were low. But after a long journey through the newborn intensive care unit (NICU) at Nationwide Children's Hospital, Willow is a vivacious 4-year-old looking forward to starting kindergarten in the fall.

Willow faced numerous challenges as a result of her extreme prematurity, but her mom says that BPD was the biggest obstacle. In this issue, learn more about the life-long implications of BPD, as well as a model of care that is changing outcomes for babies like Willow.

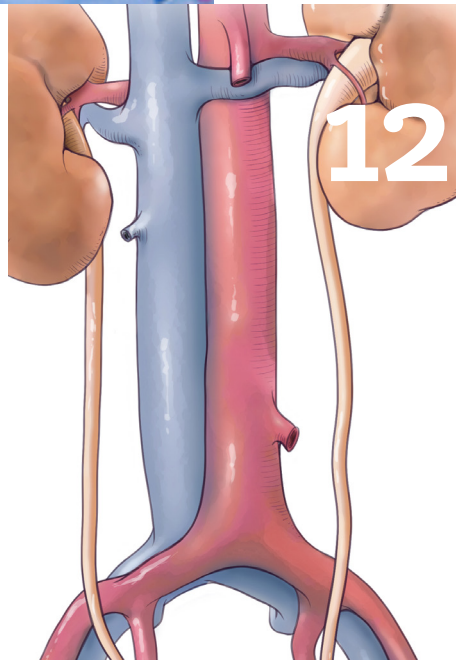


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“ Supporting each other and the next generation in the advancement of relevant, powerful research is the best legacy NURAG can leave. ”

– Christina Ching, MD, urologist and researcher at Nationwide Children’s Hospital

“ More than anything else, I want this technique to be applied to other systems and to be useful to the broader community. It is my hope that this spike-in approach will broadly enable insights into the architectural features in human disease. ”

– Benjamin Stanton, PhD, principal investigator in the Center for Childhood Cancer and Blood Diseases at Nationwide Children’s Hospital

Unlocking the Structure of Biofilms

Researchers characterize a component that stabilizes biofilms, a step toward learning ways to disrupt protection of harmful bacteria.

In the extracellular DNA lattice of bacterial biofilms, nature appears to reprise the functional equivalent of Holliday junction (HJ) intermediates — cross-shaped structures formed during the process of genetic recombination, researchers at Nationwide Children’s Hospital report in *Proceedings of the National Academy of Sciences*.

The HJ-like structures are key to a stable biofilm that protects bacteria. The protection, which includes the biofilm’s resistance to DNA-cleaving nucleases, allows the pathogens to act as a reservoir for chronic and recurrent infections, costing thousands of lives and billions of dollars in care annually.

“Bacteria in a biofilm state are 1,000-fold more resistant to antibiotics than when they are free-living,” says Steven Goodman, PhD, a principal investigator in the Center for Microbial Pathogenesis at Nationwide Children’s and senior author of the research. “There’s plenty of use for preventing biofilm formation, but for practical reasons, getting rid of an extant matrix has much more utility. Usually you don’t have a medical problem until you come to the doctor with biofilm infections.”

Dr. Goodman and colleagues are already developing a potential antibody-based therapy to disrupt biofilms but, “once we understand what the structure is, we’ll be able to find other ways to undermine it. This is a big step in a series of steps to figure that out.”

The research builds on a discovery Dr. Goodman and Lauren Bakaletz, PhD, director of the Center for Microbial Pathogenesis, made nearly a decade ago. The two identified the protein DNABII as a lynchpin contributing to the structural integrity of single-species and multispecies biofilms found on devices and in chronic infections of the ear, lung, urinary tract and more.

Due to the HJ-like shape of the lattice structures and DNABII’s affinity and specificity to HJs, the researchers suggested the structures were related to HJs. Aishwarya Devaraj, PhD, a senior research scientist in Dr. Goodman’s lab, tested the hypothesis by establishing equivalence.

On biofilms of uropathogenic *Escherichia coli*, non-typeable *Haemophilus influenzae* and *Staphylococcus epidermidis*, Dr. Devaraj added an antibody the researchers have shown removes DNABII and collapses the biofilm. At the same time, she added the protein RuvA, which binds to and stabilizes HJs.

The structures held and were as strong as before.

She then added the proteins RuvB and RuvC, which when combined with the RuvA, chop HJs and resolve them into two double-stranded DNA helices.

The biofilms collapsed.

“The only reason the RuvABC complex was able to chew up the DNA matrix is we knocked off the DNABII protein,” Dr. Goodman says. “But how these scaffolds form, what the big thick strands of fibers are, why other proteins that degrade DNA have no effect — those are things we’re currently studying.”

Devaraj A, Buzzo JR, Mashburn-Warren L, Gloag ES, Novotny LA, Stoodley P, Bakaletz LO, Goodman SD. The extracellular DNA lattice of bacterial biofilms is structurally related to Holliday Junction recombination intermediates. *Proceedings of the National Academy of Sciences*. 2019 Dec 10;116(50):25068-25077.

— Kevin Mayhoo

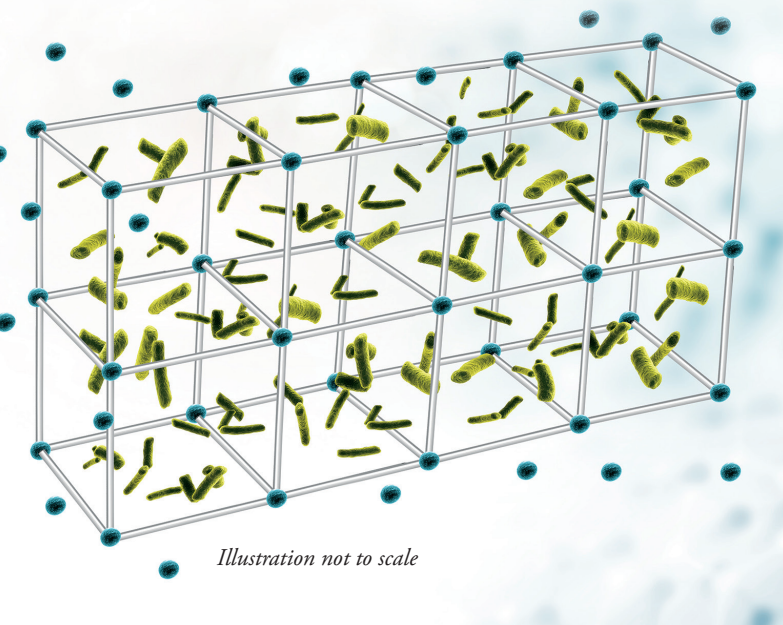
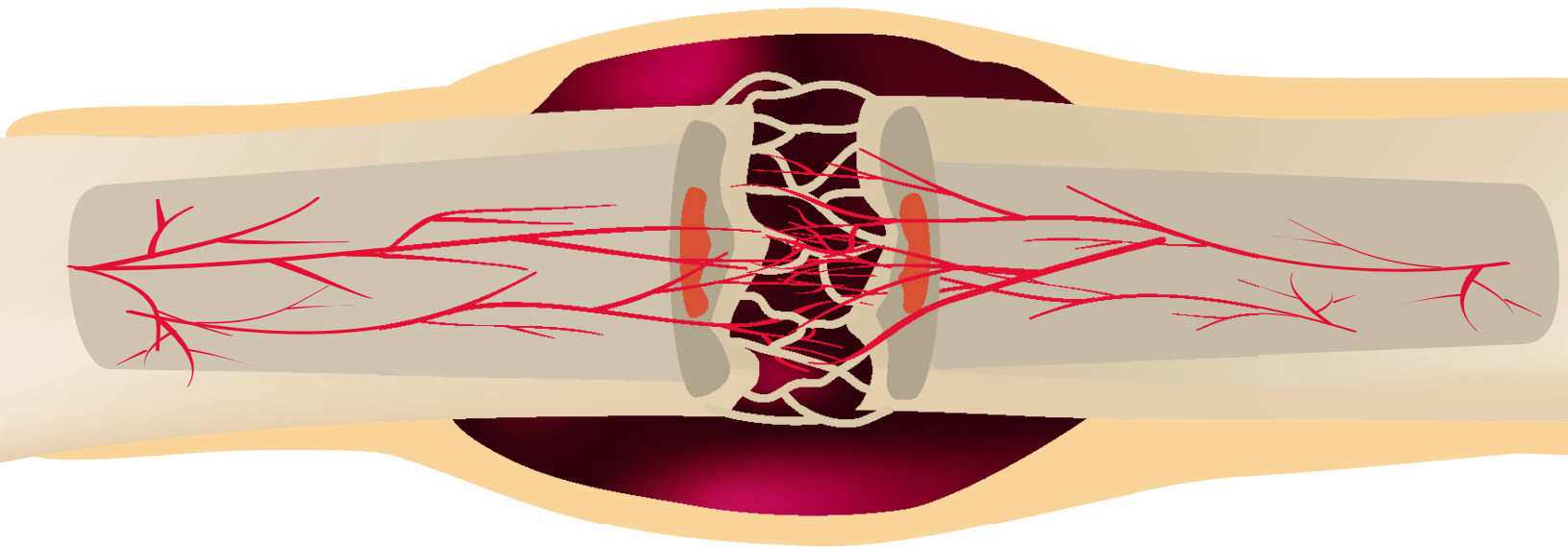


Illustration not to scale



Better Bone Healing by Reversing Current Techniques?

Bones may heal denser and stronger when given room for controlled micro-movement at first, followed by rigid stabilization — a complete flip-flop of the standard of care.

A combination of biology and mechanical influence determines how well a bone heals, for better or worse. For half a century, physicians have believed that complete bone immobilization after a fracture, followed by a gradual increase in movement and weight-bearing, is the optimal way to spur new bone growth and effective healing. Now, research in large and small animal models suggests the reverse approach (called reverse dynamization) may be more effective.

“Biologically, it makes sense that dynamization may not be the best solution, since it’s like trying to glue two pieces of wood together while you move them back and forth,” says Christopher Iobst, MD, director of the Center for Limb Lengthening and Reconstruction at Nationwide Children’s Hospital. “The glue doesn’t set well.”

The underlying concept of reverse dynamization is that, after the body begins to make new bone — a process that happens the fastest immediately after the break and when there is some mobility allowed — fixation should allow the bone to mature and fully heal. Dr. Iobst was searching for possible ways to improve bone healing and patient experience when he first discovered promising work on reverse dynamization in rats by Vaida Glatt, PhD, director of basic science research at University of Texas Health – San Antonio. Dr. Iobst and collaborators

Mikhail Samchukov, MD, and Alexander Cherkashin, MD, co-directors of the Center for Excellence in Limb Lengthening and Reconstruction at Texas Scottish Rite Hospital, reached out to Dr. Glatt to develop a study using a large animal model.

The study team used three fracture treatment models: complete immobilization, dynamization (micromovement the entire time), and reverse dynamization (micromovement for 3 weeks, followed by 5 weeks of rigid fixation). The fracture sites were examined for bone callus, bone volume, bone density — a better indicator of quality than volume — and strength under stress.

Fractures undergoing reverse dynamization healed stronger and with greater bone density than either other treatment method, and the differences were statistically significant. Dr. Iobst presented the group’s research at the 2019 Limb Lengthening and Reconstruction Society’s Annual Meeting, where it received the award for Best Basic Science Research.

“If these results in animals are confirmed by early human studies, it could really change the fields of limb reconstruction and orthopedic trauma,” says Dr. Iobst.

Glatt V, Samchukov M, Cherkashin A, Singh S, Iobst C. “Reverse dynamization accelerated bone healing in a large animal osteotomy model.” Presentation at the Limb Lengthening and Reconstruction Society 28th Annual Scientific Meeting; Jun 2019. Boston, MA.

— Katie Brind’Amour, PhD

Helping Children With Sickle Cell Disease Adhere to Their Medication

Mobile intervention increases medication adherence in the children who engage with it.



A study published in *JMIR mHealth uHealth* shows that an electronically delivered intervention can improve medication adherence in children with sickle cell disease.

Hydroxyurea is a life-changing medication for children with sickle cell disease (SCD). However, many patients may not consistently receive their hydroxyurea.

To overcome some of the adherence barriers, researchers at Nationwide Children's Hospital recently tested the effectiveness of Mobile Directly Observed Therapy (Mobile DOT), an electronic hydroxyurea adherence intervention for children with SCD. Mobile DOT sends daily text message reminders to patients to take their medicine. Then, patients record and send daily videos of their medication adherence to the research team, who provides them with feedback. Patients also receive small monetary incentives if they achieve high hydroxyurea adherence.

The team compared patients' hydroxyurea adherence during the six months that they received Mobile DOT to their adherence six months before and after the intervention. They also looked at the impact of the intervention on laboratory markers, including fetal hemoglobin and mean corpuscular volume.

"We found that significantly more patients improved their adherence when they were receiving the intervention than when they were not," says Susan Creary, MD, a hematologist at Nationwide Children's and the study's first author. "But that was only the case in those who actually engaged with the intervention. Patients who consistently participated throughout the six months were the ones who improved their adherence."

Additionally, engaged participants' fetal hemoglobin and mean corpuscular volume levels increased during the Mobile DOT period, suggesting that their blood was having more of a response to the medication.

"More and more patients are taking hydroxyurea, and they are starting at younger ages," says Dr. Creary, who is also assistant professor of Pediatrics at The Ohio State University College of Medicine. "Unfortunately, children with SCD tend to have more complications over time and their disease becomes more severe as they get older. Our hope is that increasing hydroxyurea adherence in childhood will have an impact both on patients in early childhood and as they age."

Dr. Creary and her colleagues are using their participants' feedback to identify ways to make this and other adherence interventions more engaging. In the future, they want to specifically look at how these interventions impact the clinical outcomes of children with SCD.

"Mobile DOT has the potential to reduce hospitalizations, which we're interested in from a health care utilization point of view, but it can also affect outcomes that have an impact on social well-being and productivity, like days of school or work missed," says Dr. Creary. "Additionally, we think that with modifications, Mobile DOT could be generalizable to improve medication adherence and outcomes among other chronically ill populations."

Creary S, Chisolm D, Stanek J, Hankins J, O'Brien SH. A multidimensional electronic hydroxyurea adherence intervention for children with sickle cell disease: Single-arm before-after study. *JMIR mHealth uHealth*. 2019;7(8):e13452.

— Mary Bates, PhD

Keeping Kids in Treatment for Opioid Use Disorder

A multifaceted quality improvement program increases patient retention in addiction treatment.

Adolescents and young adults with opioid use disorder often struggle to stay in treatment that's not designed for people at their developmental stage. The Medication-Assisted Treatment of Addiction (MATA) Program at Nationwide Children's Hospital is one of the only pediatric providers for adolescents with opioid use disorder in the country. They provide medication treatment, such as buprenorphine/naloxone or naltrexone with case management for behavioral health treatment.

"We have noted several challenges within our clinic population with coming to clinic visits and continuing to maintain sobriety," says Erin McKnight, MD, MPH, a member of the Section of Adolescent Medicine at Nationwide Children's. "Studies we had done in the past showed that coming to appointments and being active in clinic was predictive of long-term sobriety, so we were concerned about our initial dismal numbers."

To increase early engagement and 6-month retention numbers at the clinic, Dr. McKnight and her colleagues developed a multifaceted quality improvement (QI) program. The team investigated the mitigating factors causing people to not return to clinic and initiated several interventions. These included training staff on motivational interviewing techniques, providing food and transportation vouchers, and using tokens of incentive for treatment and recovery milestones to enhance patient motivation. Their results were published in the journal *Pediatric Quality and Safety*.

Following these QI interventions, Dr. McKnight and her colleagues saw a significant increase in both second visit return rate and 6-month retention rate.

"Our providers have found it wonderful to see more engagement with the program and feel like they are doing something to help mitigate barriers to treatment," says Dr. McKnight, who is also an assistant professor of Clinical Pediatrics at The Ohio State University College of Medicine.

The success of QI interventions at the clinic at Nationwide Children's can be an example to other practices, says Dr. McKnight.

"Using QI methods is a great way to see where you have problems and if there are interventions that you can put into place to help your patient population," Dr. McKnight says.

"It is also important to be re-evaluating what your patients need at different times. If they are working, continue them, and if they are not working, shift gears and see what else you can do."

Cottrill CB, Lemle S, Matson SC, Bonny AE, and McKnight ER. Multifaceted quality improvement initiative improves retention in treatment for youth with opioid use disorder. *Pediatric Quality and Safety*. 4(3):e174.

— Mary Bates, PhD

MATA CLINIC RETENTION QI RESULTS



Six month
retention rate
increased from

20% to 35%



Second visit
return rate
increased from

80% to 95%



Study Sheds Light on Causes of Phenotype Variation in IQSEC2-Related Disease

Variant type and inheritance pattern affect patient phenotypes in *IQSEC2*-related disease.

Investigators from Nationwide Children's Hospital and The Ohio State University College of Medicine recently identified additional pathogenic variants within the *IQSEC2* gene, which has previously been associated with X-linked mental retardation, in five patients. They also demonstrated that different variant types correlate with the severity of the disease in both female and male patients.

"A few years ago, we launched an exome sequencing initiative to try to diagnose undiagnosed genetic conditions in children," says Elizabeth Barrie, PhD, first author of the study, who is now an assistant professor at Virginia Commonwealth University. Dr. Barrie was a postdoctoral fellow at Nationwide Children's during the study. "This gene, *IQSEC2*, came up multiple times in our analysis, leading us to investigate it further."

The study, which was published in the *European Journal of Medical Genetics*, presented the cases of two male and three female patients. To assess potential pathogenic DNA variants, all patients had diagnostic exome sequencing. The investigators hypothesized that patient sex, *IQSEC2* variant type, and inheritance pattern interact to drive disease penetrance and expressivity.

Common among all of the patients were epilepsy, global developmental delays, intellectual disability and constipation. The team found that a *de novo*, truncating variant and nonsense variants of *IQSEC2* were associated with more severe disease in both female and male patients. For example, all of these patients were nonverbal and nonambulatory, even into the teenage years. However, when missense variants occurred, the disease phenotypes were milder in general, and when

also considering information from previous studies, these variants appeared to be more severe in males than in females.

"This [disease] doesn't really follow the classic rules for the genetic inheritance pattern," says Dr. Barrie. "It has a very complicated inheritance pattern that depends on the patient's sex but also whether they are inheriting a variant from a parent or not. Then, the type of variant also matters, so a lot of different factors are at play when trying to figure out if a variant is disease causing."

For one male patient, the investigators identified inheritance of a nonsense variant from an unaffected, mosaic mother, a finding that has implications regarding counseling for recurrence risk. This was the first confirmed case of parental mosaicism for this gene.

"While this is a relatively rare cause [of disease], it has growing importance," says Dr. Barrie. "For patients who have the phenotype of intellectual disability and seizures, a variant in this gene is a potential genetic explanation that would be important to consider. If a genetic testing panel were ordered, it would be worth making sure the *IQSEC2* gene is covered on the panel."

Dr. Barrie expanded on the importance of a multidisciplinary collaboration and team effort, including individuals with diverse knowledge bases and specialties, to diagnose rare diseases and enable much needed genotype-phenotype correlation studies such as this one.

Barrie ES, Cottrell CE, Gastier-Foster J, Hickey SE, Patel AD, Santoro SL, Alfaro MP. Genotype-phenotype correlation: Inheritance and variant-type infer pathogenicity in *IQSEC2* gene. *European Journal of Medical Genetics*. 2019 Aug 12:103735. [Epub ahead of print]

— Lauren Dembeck, PhD

Kidney Injury and Fluid Balance in Premature Newborns

A positive fluid balance is associated with acute kidney injury and worse outcomes in a new study of premature infants.



According to new research, there is an association between fluid balance and outcomes in preterm newborns, with a negative fluid balance during the first week of life emerging as a potential therapeutic target.

Premature infants can experience multi-organ dysfunction, frequently including kidney dysfunction. The international Assessment of Worldwide Acute Kidney Injury Epidemiology in Neonates (AWAKEN) study showed that acute kidney injury occurs commonly in preterm newborns and is associated with increased mortality and length of stay. Kidney injury can also affect the function of other organs through its influence on fluid balance.

The AWAKEN study captured data on acute kidney injury, fluid balance, and the impact of other kidney-related risk factors on short-term outcomes in premature infants. Researchers from institutions including Nationwide Children's Hospital used these data to investigate the changes in fluid balance in preterm newborns during the first week of life and investigate the association of fluid balance with acute kidney injury and an important short-term outcome, the need for mechanical ventilation at postnatal day 7.

"The incidence of kidney issues in this population is much higher than we appreciated," says John Mahan,

MD, director of Nationwide Children's Faculty Development and the Pediatric Nephrology Fellowship Program and one of the study's authors.

"The inability to excrete water is a significant problem in these small babies. When we looked over a large number of patients, we saw kidney involvement in many of them."

Over half the newborns had weights above birth weight in the first postnatal week, indicating a positive fluid balance in that period. Those with a positive fluid balance at postnatal day 7 were more likely to require mechanical ventilation. In addition, fluid balance was associated with acute kidney injury.

Dr. Mahan, who is also a professor of Pediatrics at The Ohio State University says kidney issues in premature infants can go unappreciated unless one is regularly testing kidney function.

"Those early signs of kidney issues, like the inability to excrete water, are easy to miss and yet these early signs of kidney issues can lead to significant and long-term problems," he says.

Elizabeth Bonachea, MD, the program director for the Neonatal-Perinatal Medicine Fellowship at Nationwide Children's and another of the study's authors, says that detecting kidney issues early is crucial.

"The next generation of studies will focus on prevention and early intervention," she says. "We are now working on developing a standard approach to detection and diagnosis of kidney injury in these babies. Looking forward, these studies will inform the institution of appropriate interventions to prevent or minimize kidney injury in premature babies."

Selewski DT, Gist KM, Nathan AT, Goldstein SL, Boohaker LJ, Akcan-Arikan A, Bonachea EM, Hanna M, Joseph C, Mahan JD, Mammen C, Nada A, Reidy K, Staples A, Wintermark P, Griffin R, Askenazi DJ, Guillet R, Neonatal Kidney Collaborative. The impact of fluid balance on outcomes in premature neonates: a report from the AWAKEN study group. *Pediatric Research*. 2020 Feb;87(3):550-557.

— Mary Bates, PhD

Epigenetics, Chromatin Architecture and a Judo Mechanism to Attack Cancer

UNDERSTANDING CHROMATIN ARCHITECTURE IN HUMAN DISEASE

..... by Abbie Roth

Epigenetics is the study of how genetic information is context-dependent: it is organized so it can be repressed, but also read, repaired and replicated. For example, transcription factors can “communicate” with each other through the chromatin-DNA interface, and work in combinations to regulate which genes are expressed. In many types of cancer, transcription factors can drive altered gene expression networks.

Transcription factors don’t bind to “flat surfaces” but rather to the hills and valleys of the epigenetic landscape. But how are these hills and valleys structured?

Chromatin is the material that packages DNA in higher organisms, and the most basic unit of chromatin is called the “nucleosome,” which behaves like a spool around which the thread (DNA) is wrapped. These nucleosome-DNA particles form the basic structures that assemble into chromosomes inside our cells. Our DNA accessibility is influenced by the occupancy, spacing and positioning of nucleosomes.

Interestingly, the “spool” [nucleosome] has protein tails (histones) that can be modified (marked), and there is growing evidence that this, in addition to DNA accessibility, can instruct epigenetic changes.

A modification to nucleosomes called acetylation is highly associated with more open chromatin states, where DNA is more accessible, and can be read more easily. Chromatin acetylation changes as different genes are activated and repressed.

Researchers who are interested in DNA’s accessibility frequently investigate how and why chromatin becomes acetylated and deacetylated.

One of the researchers investigating the relationships among chromatin structure, acetylation and transcription is Ben Stanton, PhD, principal investigator in the Center for Childhood Cancer and Blood Diseases at the Abigail Wexner Research Institute at Nationwide Children’s Hospital.

“It’s important to remember that while the genetic code is essentially linear, DNA is packaged into a three-dimensional chromatin landscape,” Dr. Stanton says. “We have been highly motivated to understand how histone marks and genome architecture are integrated, and the degree to which this interplay has network-level effects on gene expression.”

MEASURING CHROMATIN ARCHITECTURE

Researchers have been working to measure chromatin architecture for the last two decades: In 2002, Job Dekker, PhD, and colleagues reported a PCR-based method to define chromatin interactions (3C). In 2009, Erez Lieberman-Aiden, PhD, and colleagues reported 3D genome sequencing (Hi-C) and refined the method with new insights in 2014. In 2016, Howard Chang, MD, PhD, Will Greenleaf, PhD, and co-workers published a protein-centric 3D genome sequencing method (HiChIP).

These approaches enabled definition of chromatin interactions, the basis of architecture, but it has remained

challenging to address a central question: Is the chromatin structure in a cancer cell different to a healthy cell?

To address this question, Dr. Stanton — in collaboration with Berkley Gryder, PhD, and Javed Khan, MD, both at the National Cancer Institute — developed a method of absolute comparison for chromatin interactions using “spike-in” chromatin loops from another organism that can be sequenced together.

The method is called AQuA (Absolute Quantification of Chromatin Architecture)-HiChIP. And it has already been useful for defining chromatin acetylation’s architecture in rhabdomyosarcoma, as published in *Nature Genetics*.

With the AQuA-HiChIP method, defined ratios of mouse and human fixed nuclei are processed within the same experiment, enabling an internal control for chromatin interactions. The paired-end sequencing tags associated with interactions across “interacting chromatin” from the human genome are normalized to interactions within the mouse genome.

To show how AQuA-HiChIP can help researchers better understand changes in chromatin architecture in context, Dr. Stanton and his colleagues investigated how histone acetylation is associated with disruption of the chromatin architecture in rhabdomyosarcoma: chromatin interactions were altered with HDAC inhibitors, and the tumor cells lost the capacity to proliferate.

DESCRIBING HDAC INHIBITOR EFFECTIVENESS

Histone deacetylase (HDAC) inhibitors are a class of drugs that can increase the acetylation of chromatin on short timescales but can result in severe loss of acetylation on longer timescales. They have been shown to be useful in treating cancers in clinical and preclinical studies.

“We found that core regulatory transcription factors are essential to the tumor. They need certain patterns of DNA accessibility to keep the cancer going. Chromatin acetylation is associated with increased DNA accessibility and may fine-tune the binding sites for these transcription factors,” says Dr. Stanton.

HDAC inhibitors push the cell into “hyperacetylation mode” on short timescales, changing the chromatin architecture.

“HDAC inhibitors can be quite toxic to cancers,” says Dr. Stanton. “They operate through this ‘judo mechanism’ — using the chromatin’s momentum to toxify the cell. HDAC inhibitors push the tumor cells further and further in the acetylation direction, eventually causing a loss of the cell’s capacity to regulate its own gene expression.”

MOVING FORWARD WITH AQUA

Moving forward, Dr. Stanton and his colleagues plan the continued application of AQuA-HiChIP to central questions regarding transcription control, accessibility and tissue-specific epigenetic memory.

According to Dr. Stanton, the quantitative nature of the data produced through the method allows for specific comparisons of chromatin interactivity, not limited to rank-ordering interactivity, to compare between experimental conditions.

“More than anything else, I want this technique to be applied to other systems and to be useful for the broader community. It is my hope that this spike-in approach will broadly enable insights into the architectural features in human disease,” says Dr. Stanton. “There’s a lot of very exciting basic science to be done in childhood cancer research. Increasing our fundamental understanding of the epigenetic memory of architecture can lead to new insights.”

Dekker J, Rippe K, Dekker M, Kleckner N. Capturing chromosome conformation. *Science*. 2002;295:1306-1311.

Gryder BE, Pomella S, Sayers C, Wu XS, Song Y, Chiarella AM, Bagchi S, Chou H-C, Sinniah RS, Walton A, Wen X, Rota R, Hathaway NA, Zhao K, Chen J, Vakoc CR, Shern JF, Stanton BZ, Khan J. Histone hyperacetylation disrupts core gene regulatory architecture in rhabdomyosarcoma. *Nature Genetics*. 2019;51:1714-1722.

Gryder BE, Khan J, Stanton BZ. Measurement of differential chromatin interactions with absolute quantification of architecture (AQuA-HiChIP). *Nature Protocols*. 2020 Mar;15(3):1209-1236.

Mumbach MR, Ruben AJ, Flynn RA, Dai C, Khavari PA, Greenleaf WJ, Chang HY. HiChIP: efficient and sensitive analysis of protein-directed genome architecture. *Nature Methods*. 2016 Nov;13:919-922.

Lieberman-Aiden E, van Berkum NL, Williams L, Imakaev M, Ragoczy T, Telling A, Amit I, Lajoie BR, Sabo PJ, Dorschner MO, Sandstrom R, Bernstein B, Bender MA, Groudine M, Gnirke A, Stamatoyannopoulos J, Mirny LA, Lander ES, Dekker J. Comprehensive mapping of long-range interactions reveals folding principles of the human genome. *Science*. 2009;326:289-293.

Lin GL, Wilson KM, Ceribelli M, et al. Therapeutic strategies for diffuse midline glioma from high-throughput combination drug screening. *Science Translational Medicine*. 2019;11(519):eaaw0064.

Rao SS, Huntley MH, Durand NC, Stamenova EK, Bochkov ID, Robinson JT, Sanborn AL, Machol I, Omer AD, Lander ES, Aiden EL. A 3D map of the human genome at kilobase resolution reveals principles of chromatin looping. *Cell*. 2014; 159:1665-1680.

TRANSFORMING MEDICAL SCIENCE Through Research Affinity Groups

How a urology and nephrology affinity group redefined the meaning of collaborative research, propelling field-changing innovations in translational medicine

by Katie Brind'Amour, PhD

Purposeful synergy drives the most meaningful medical science. Nephrology physician-scientists require tissue samples, urologists desire tests to know which patients truly require surgery, and basic scientists must find ways to meaningfully assess new animal models to yield clinically valuable data.

If each of these professionals had a defined network of colleagues from the other disciplines — colleagues knowledgeable about their areas of interest and willing to collaborate — research and care could take a leap forward.

The scientist could study biomarkers to identify patients that most need surgery, the urologist could collect tissue samples on nephrology patients headed to the operating room, and nephrologists could teach bench scientists how to do a renal ultrasound on models to measure disease severity. Everyone would get what they need, and together, these experts would advance patient care and medical knowledge.

This interdisciplinary, communication-oriented approach to clinical and translational research is at the heart of the Nephrology and Urology Research Affinity Group (NURAG) at Nationwide Children's Hospital. The group was founded by a developmental biologist and anatomist at Nationwide Children's — Kirk McHugh, PhD, now director of the Division of Anatomy at The Ohio State University College of Medicine — eager to do something clinically useful

with his newly discovered megabladder mouse model. The original participants loved the early gatherings so much that NURAG organically evolved (over 15 years of monthly meetings) into a broad group of dozens of physician-researchers and basic scientists with an interest in the overlapping areas of urology and nephrology.

The group meetings include a planned speaker, either from within NURAG membership or invited from another institution. The presenter shares in-progress research, a manuscript planned for publication, or a talk about a less scientific area of medicine that affects members as well, such as quality improvement or advocacy. The audience gets to learn about something relevant and new, and the speaker gets thoughtful, well-rounded feedback from experts in numerous disciplines. And the whole group benefits from new insights and knowledge in their field, plus an abundance of spirited discussion and ideas for future exploration.

Best of all, members say, the atmosphere is friendly and fosters intellectual exchange and collaboration among multiple disciplines, giving birth to relationships and research projects that may otherwise not have seen the light of day.

The Brainchildren of NURAG

Members of NURAG have built some of the country's largest — and best-rated — pediatric research programs in both urology and nephrology, with research encompassing everything from mouse models to natural urinary tract

Acute Kidney Injury

Cardiology, basic science, nephrology and chemotherapy experts collaborate to identify mechanisms of AKI and therapeutic targets for repair or prevention.

Front Pediatr. 2019 Nov 26;7:492

Glomerular and Inflammatory Disease

NURAG researchers may have identified a biomarker to predict steroid resistance in children with nephrotic syndrome.

Kidney Int Rep. 2019 Sep 19;5(1):81-93

Obstruction and the Renal Urothelium

NURAG scientists have identified cells in the renal urothelium that remodel themselves in response to urinary tract obstruction and injury.

J Physiol Renal Physiol. 2019 Sep 1;317(3):F757-F766.

Am J Physiol Renal Physiol. 2018 Oct 1;315(4):F1019-F1031.

UTI Susceptibility and Therapy

NURAG collaborators identified peptides that protect the urinary tract and fight infection. Now they are working on how to use them to predict and treat UTI.

Kidney Int. 2018 Jun;93(6):1320-1329.

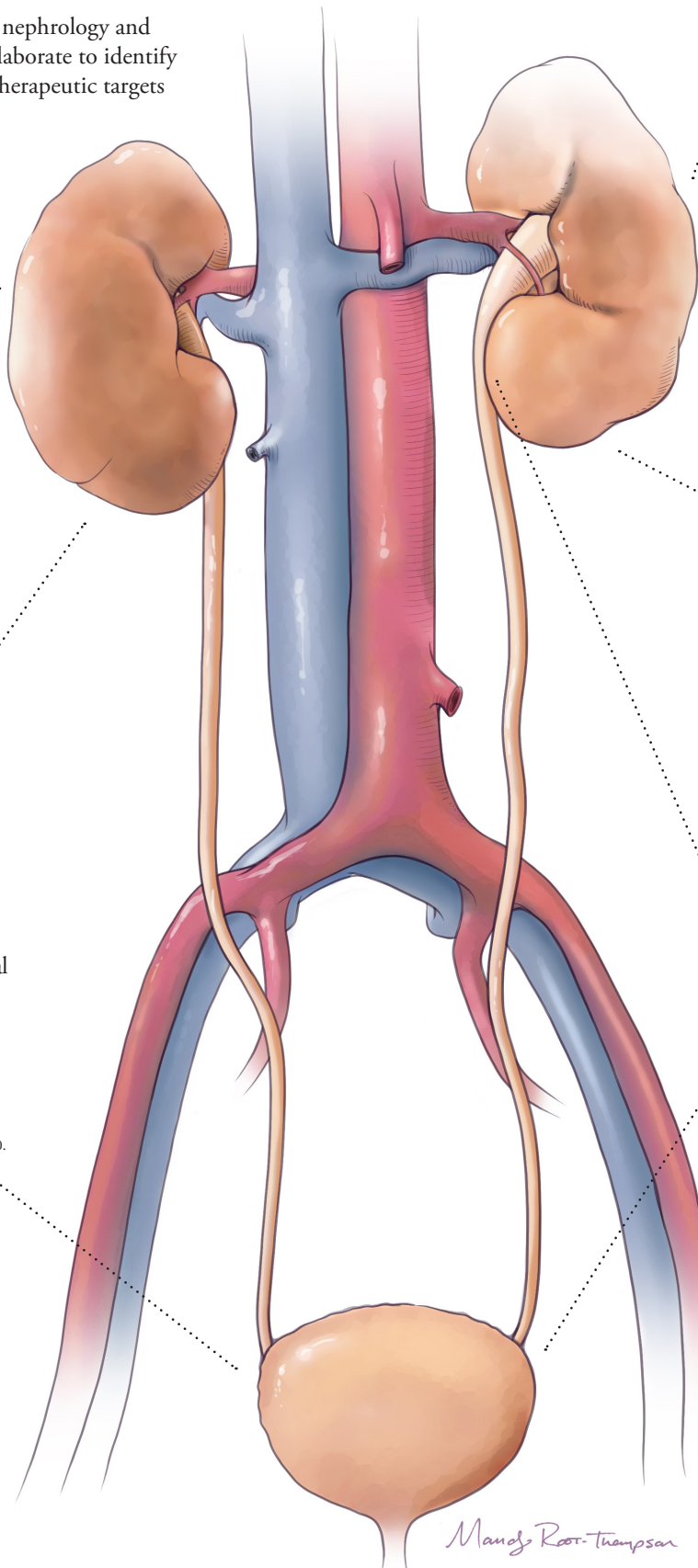
Pediatr Nephrol. 2019 Jun 13. [Epub ahead of print]

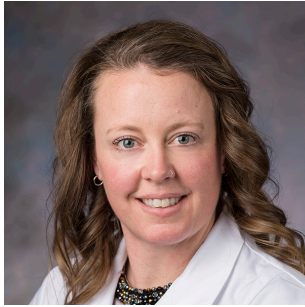
Megabladder Mouse Model

This model is the first animal model of chronic renal disease and congenital obstructive uropathy. It was recently confirmed near-identical to these problems in humans.

J Am Soc Nephrol. 2007 Feb;18(2):461-471.

J Clin Invest. 2019 Dec 2;129(2):5374-5380.





“It’s compelling to think that if we can better understand the process by which progenitor cells form the protective cells, we can maybe drive intrarenal-urothelial remodeling to protect the kidneys from obstructive disease, starting in mice but ultimately translating our work to children.”

– Ashley Jackson, PhD, postdoctoral fellow in the Center for Clinical and Translational Research at Nationwide Children’s Hospital

infection (UTI) prevention. The collaborations involve more than just lip service to the concept of translational research, and often directly influence work done both by the group’s clinical members and bench scientists on a daily basis.

Megabladder Mouse: The Original NURAG Brainchild

When Dr. McHugh first pushed to establish NURAG, he did so to unite basic science researchers like himself with curious clinicians for the advancement of pediatric urology and nephrology care. His research at the time centered around the megabladder mouse model, which became the first animal model of congenital obstructive nephropathy and chronic kidney failure. He was eager for input from colleagues in urology and nephrology to help him plan better early studies for maximum translational impact for their patients. The partnership resulted in a co-led National Institutes of Health grant with NURAG co-founder Carl Bates, MD, now chief of the Division of Pediatric Nephrology at Children’s Hospital of Pittsburgh, to investigate the mutation’s clinical implications.

The studies of Dr. McHugh and his colleagues have illuminated much about the early development and disease progression of congenital obstructive nephropathy, one of the leading causes of chronic kidney failure in children. Most recently, he had the satisfaction of validating the model; collaborators in Europe identified several human families with genetic changes and disease sequelae that directly parallel those observed in the megabladder mouse.

This watershed model has played diverse roles in numerous scientific advancements in the field and has recently had a resurgence in interest due to potential

applications in the study of urinary tract remodeling after injury — now a major area of focus for Dr. McHugh’s NURAG proteges and mentees.

Urinary Tract Obstruction and Injury

NURAG collaborators Brian Becknell, MD, PhD, a nephrologist at Nationwide Children’s and NURAG’s current director; Ashley Jackson, PhD, a postdoctoral fellow in the Center for Clinical and Translational Research in the Abigail Wexner Research Institute (AWRI) at Nationwide Children’s; Dr. McHugh and other clinician-scientists at Nationwide Children’s have long worked to understand the renal response to urinary tract obstruction in the megabladder mouse.

Their joint efforts have identified that the renal urothelium (tissue lining the drainage system of the kidneys) remodels itself to help protect the kidney during urinary tract obstruction. When obstruction occurs and urine is retained in the kidneys, these cells adapt to create a urine-proof barrier by forming a urothelial plaque, which allows expansion and provides structural support to the kidney, thus protecting it from damage. Dr. Jackson also recently identified the progenitor (cellular origin) of the protective urothelial cell.

“It’s compelling to think that if we can better understand the process by which progenitor cells form the protective cells, we can maybe drive intrarenal-urothelial remodeling to protect the kidneys from obstructive disease, starting in mice but ultimately translating our work to children,” says Dr. Jackson. The multidisciplinary team recently published their findings in the *American Journal of Physiology-Renal Physiology*.

UTI Pathogenesis and Treatment

Another key area of research for the clinicians and scientists in NURAG is urinary tract infection (UTI)

— including who may be particularly susceptible and why — as well as what these findings mean for new treatment options. The efforts of John David Spencer, MD, chief of nephrology at Nationwide Children’s, and his lab in the Center for Clinical and Translational Research in the AWRI have benefitted greatly from NURAG-facilitated collaboration with the labs of Dr. Becknell; Christina Ching, MD, a urologist and clinician-researcher at Nationwide Children’s; and Sheryl Justice, PhD, a principal investigator in the Center for Microbial Pathogenesis in AWRI.

Dr. Spencer’s lab focuses on antimicrobial peptide (AMP)-related infection responses and related downstream effects, which dovetails with Dr. Justice’s expertise in the body’s natural formation of bacterial films, Dr. Ching’s work on innate immunity and host response to infection, and immunology and physiology work done by other basic science collaborators. Together, these research teams have explored the roles of AMPs and ribonuclease “superfamilies” in the urinary tract. Fluctuation of AMPs influences the body’s susceptibility to infection and its ability to fight infection-causing bacteria, such as *E. coli*, in the urethra, bladder, ureters and kidneys.

The group is rapidly making progress toward tracking and manipulating the production of AMPs and related molecules in the urinary tract to predict, prevent and even treat UTI in the near future.

Glomerular Diseases

Glomerular diseases and inflammatory diseases of the kidneys are another area of focus for NURAG participants. Shipra Agrawal, PhD, a principal investigator in the Center for Clinical and Translational Research, has a

longstanding collaboration with nephrologist William Smoyer, MD, vice president and director for the Center for Clinical and Translational Research.

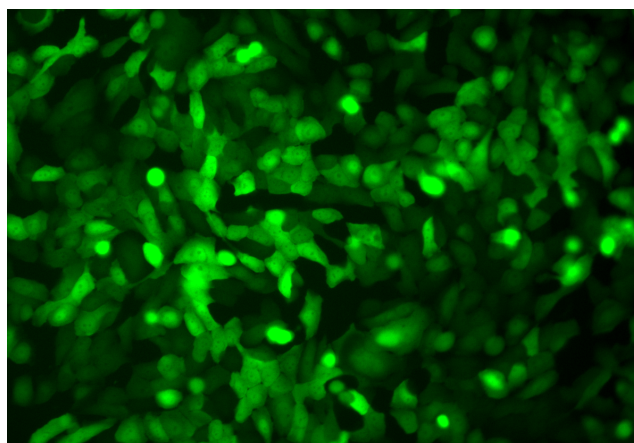
Together, they have studied molecular pathways involved in the function and injury of the kidneys’ glomerulus and podocytes, which filter toxins from the blood. By further extending their collaborations to include members of the Midwest Pediatric Nephrology Consortium, the team has recently identified potential biomarkers to predict steroid resistance in young nephrotic syndrome patients. The work appeared last fall in *Kidney International Reports*.

Mechanisms of Acute Kidney Injury

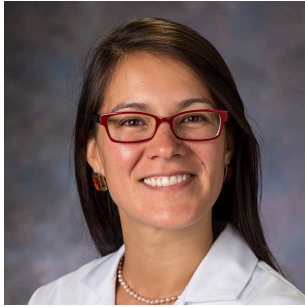
Another burgeoning area of focus for NURAG is championed by a cardiologist rather than a nephrologist or urologist. Catherine Krawczeski, MD, chief of the Division of Cardiology and co-director of The Heart Center at Nationwide Children’s, studies acute kidney injury following cardiopulmonary bypass. Now, NURAG’s acute kidney injury discussions are also expanding to include chemotherapy-induced injury and possible therapeutic targets for kidney disorders, thanks to recent additions to the group from The Ohio State University’s pharmacy program and a new physician-scientist on Nationwide Children’s nephrology team.

Future Plans and Opportunities for Growth

In addition to the key areas of research thriving under the umbrella of NURAG, collaborative opportunities continue to emerge. Unique synergies include that with Rachel Cianciolo, VMD, PhD, a veterinary pathologist in the Department of Veterinary Biosciences at The Ohio State University, and co-director of the International Veterinary Renal Pathology Service. After presenting her



Antimicrobial peptides, identified by green immunofluorescent staining, are produced by human kidney cells. Fluctuations in AMPs influence the body’s susceptibility to infection.



“Supporting each other and the next generation in the advancement of relevant, powerful research is the best legacy NURAG can leave. It truly is a breeding ground for new pediatric urology and nephrology clinicians and scientists.”

– *Christina Ching, MD, urologist and clinician-researcher at Nationwide Children’s Hospital*

own work on kidney diseases in animals to NURAG members, Dr. Cianciolo began working with NURAG researchers at Nationwide Children’s to consult on the use of animal models for various kidney disorders and to score tissue samples for glomerular disease.

Veterinary colleagues such as Dr. Cianciolo are just the tip of the affinity iceberg. Chemists, neurologists, geneticists, bacteriologists, hematologists, biostatisticians, mathematicians, immunologists, cell biologists and more all play important roles in the advancement of clinical and translational investigations at Nationwide Children’s and beyond.

Self-Propagating Translational Research

Perhaps the greatest attribute of NURAG is its potential to encourage young clinicians and investigators to consider launching a new study or to specialize in urology or nephrology — while also supporting them in their research and training. This was certainly the case for several of its current members, including the group’s director.

“I grew up with NURAG, so to speak,” says Dr. Becknell, who first experienced the group as a medical student. “It’s one of the main reasons I chose to specialize in nephrology and stay here for my residency and fellowship. I liked to see surgeons, clinicians and medical students getting together in a nonintimidating environment to share ideas. I’ve benefitted hugely from the level of support it provides.”

He’s not the only one whose career trajectory was significantly influenced by participating in NURAG. Dr. Jackson started in Dr. McHugh’s lab during her doctoral studies and enjoyed the collaborative community so much that she chose to stay for her postdoctoral work. The training environment and mentorship provided by NURAG helped her secure a National Research Service Award Individual

Postdoctoral Fellowship (F32), and she is pursuing additional NIH funding to become a principal investigator. She now serves as NURAG’s program coordinator and credits NURAG for launching her research career through early opportunities to grow and succeed, including mentorship of younger trainees.

This cultivation of the next generation of researchers is key to NURAG’s mission. The group regularly offers all participants the option to practice their presentations or submit their written work for review, ensuring that their research products are defensible, thorough and thoughtful. They also hire and provide travel funding for students, residents and fellows, and they are seeking NIH grants to begin supporting full NURAG trainee funding.

“Supporting each other and the next generation in the advancement of relevant, powerful research is the best legacy NURAG can leave,” says Dr. Ching, who credits her series of NIH grants to close relationships with her mentors, all of whom are NURAG members. “It truly is a breeding ground for new pediatric urology and nephrology clinicians and scientists.”

Building a Successful Research Affinity Group

The recipe for a successful research affinity group is probably flexible, but it is evident that it must include researchers both from the clinical world and basic science. It is also essential for participants to be curious, collegial and engaged.

Dr. Becknell believes it is the mix of new and experienced participants, as well as the relaxed but eager exchange of ideas of true scientific and clinical interest — rather than an emphasis on publication expediency or grant money competition — that creates the group’s unique appeal and, ultimately, its tremendous success.

“You feel such support knowing your colleagues are willing to help you advance your research,” Dr. Spencer agrees. “People are naturally attracted to it, and it impresses upon the next generation of physicians and scientists the value of doing collaborative work. Even those researchers who start off expecting to be independent quickly see the benefits of NURAG and fall into the fold.”

Former Nationwide Children’s clinicians have appreciated the NURAG community so much they have attempted to develop similar affinity groups at their new institutions. For others interested in doing the same, an affinity group obviously requires logistical support: space to meet, eventual financial support from grants or institutional research funds, and administrative support for the time required to meet and mentor each other.

As a group expands, so do the paperwork and planning needs. That’s why NURAG has worked to obtain institutional funding both for a biostatistician and a clinical research coordinator, who can facilitate the research done in the hospital’s Urology and Nephrology Combined Clinic and increase the support available to new investigators.

The snowball effect of knowledge generation and collaboration with the fields’ future leaders cannot be underestimated in its potential to change clinical care. Together, NURAG members publish numerous peer-reviewed papers each year — with well over 100 collaborative publications since its founding and numerous multidisciplinary, co-led NIH grants — and regularly present research at professional conferences.

NURAG participants believe this is just the beginning: new researchers join regularly, funding is growing, and subspecialty groups and collaborative grants will be priorities in 2020 and beyond.

The benefits of NURAG have been so apparent that Dennis Durbin, MD, MSCE, chief scientific officer at Nationwide Children’s, has encouraged and supported the emergence of three additional affinity groups across research and clinical staff: one to study the oral and gastrointestinal microbiome, one for neuroscience research, and one general pediatrics research affinity group. It is expected that additional groups may form as experts in other disciplines see their many benefits.

“If we can inspire young people, through an environment that supports curiosity, to consider a career in research that has something to do with the kidneys or urinary tract, that guarantees a positive future for our fields,” says Dr. Becknell. “But I think the fact that we all have a ton of fun is also a big part of what keeps this thing going.”

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~~SURVIVING~~ THRIVING AFTER SEVERE BPD

How a chronic care model for bronchopulmonary dysplasia has revolutionized outcomes

by Abbie Roth



Willow was born via emergency C-section at just 22 weeks. Doctors at the delivering hospital told Willow’s mom Cortney that her baby’s chances of survival were low. But after a long journey through the Newborn Intensive Care Unit (NICU) at Nationwide Children’s Hospital, Willow is a vivacious 4-year-old looking forward to starting kindergarten in the fall.

“Willow’s biggest obstacle during her NICU stay was her lungs, due to developing severe bronchopulmonary dysplasia,” says Cortney.

Willow isn’t alone. Each year, 10,000 to 15,000 babies born preterm are diagnosed with severe BPD, according to the National Institutes of Health. However, not everyone’s story has the same happy ending.

Babies with severe BPD are at high risk for mortality and morbidities. In fact, according to Edward Shepherd, MD, section chief of Neonatology at Nationwide Children’s Hospital, for preterm infants, in those first few days and weeks BPD and death are competing outcomes — that is, survival often comes with BPD.

“At 22 to 32 weeks gestation, babies’ lungs are underdeveloped,” he says. “Our first task is to keep them alive. The second task is to minimize the damage to the developing lungs.”

Neurodevelopmental delays, including hearing and vision impairment, cerebral palsy or delays on Bayley’s scales (developmental tests), are a common outcome for the babies with severe BPD who survive.

Willow developed what Dr. Shepherd calls “super severe BPD.” She spent 4.5 months on a ventilator before graduating to CPAP. After two months of CPAP, she graduated to a nasal cannula. Finally, at age 3 she stopped needing any oxygen support.

PREVENTING NEURODEVELOPMENTAL CONSEQUENCES OF BPD

All babies born preterm are at risk for neurodevelopmental delays and impairments. Those who develop BPD are at even higher risk.

“Historically, the medical community thought that the neurodevelopmental problems associated with BPD were caused by the lung disease,” says Dr. Shepherd, who is also associate professor of Clinical Pediatrics at The Ohio State University College of Medicine. “But other lung diseases don’t cause neurodevelopmental delays. So, we needed to look at how we’re treating the lung disease and how that could be affecting the brain.”

Traditionally, doctors have treated BPD in the same way that they tried to prevent it — by minimizing time on the vent, keeping babies sedated and using intravenous (IV) nutrition.

SEVERE BRONCHOPULMONARY DYSPLASIA DEFINED

The definitions of BPD, severe BPD and “super severe BPD” are a hot topic of conversation among experts in the field. Currently, BPD is generally defined and classified by the exposure of a preterm infant to respiratory support during the first 28 days of life and again at 36 weeks corrected.

Defining BPD at Nationwide Children’s

AGE	AIRWAY SUPPORT	DIAGNOSIS
28 days of life	Any supplemental oxygen	Some form of BPD
36 weeks adjusted	Positive pressure (supplemental oxygen or CPAP)	Severe BPD
36 weeks adjusted	Ventilator	Super severe BPD

“But 12 weeks later, when the baby is 36 weeks adjusted and officially diagnosed with severe BPD, we’re still doing that,” says Dr. Shepherd. “We need to shift away from treating it like an acute disease.”

Despite the prevalence of BPD among preterm infants, there isn’t a lot of consensus on the true cause of the disease or the best way to treat the disease after 36 weeks adjusted age.

“Once they get to 36 weeks and still need significant respiratory support, they have severe BPD. The strategies used to prevent BPD are no longer an effective approach to treatment,” says Stephen Messier, MD, medical director of Neonatology at Sanford Children’s Hospital Sioux Falls. “It takes a different way of thinking – and the acceptance that we’re now treating something that will take months to years to get better. Not days to weeks like most other things we treat in neonatology.”

Treating BPD as a chronic disease is the keystone to the care model used by the Comprehensive Center for Bronchopulmonary Dysplasia (CCBPD) at Nationwide Children’s.

“If a baby has 12 weeks of accumulated disease, they’re not going to get better today. Or tomorrow,” says Dr. Shepherd. “We have to adjust the treatment and our expectations and move at the pace of the baby. And in doing so, we improve outcomes and actually shorten average lengths of stay.”

Change Vent Settings

Have you ever held your breath for too long? It’s an uncomfortable feeling. For babies who aren’t properly oxygenated, that feeling of being “air hungry” is a powerful stress on the body.

Using different vent settings can reduce this stress. Once BPD is established, Dr. Shepherd’s team moves to a management strategy for severe BPD.

“We go from low tidal volumes, short inspiratory times and high rates to high tidal volumes, longer inspiratory times and low rates,” says Dr. Shepherd. “This shift is a different paradigm and can make some people uncomfortable. But we’re continuing to show that this approach works.”

In other words, they go from breathing fast, small breaths to breathing slower, deeper breaths.

The goal for respiratory support in the chronic care model is avoiding air hunger, keeping the babies “pink and comfortable” at all times.

Create a Joyful NICU

When you walk into the BPD Unit of Nationwide Children’s, it’s easy to forget you are in a NICU. Infants are sitting on parents’ laps, participating in music therapy while intubated or attached to a CPAP machine. In another room, a baby sits in a baby seat on the floor, CPAP tubes attaching her to the machine that helps her breath, while she plays with an array of brightly colored toys. Two doors down, a set of twins sharing a room are in their cribs, settling down for a nap, while their older sibling reads them a story.

“We are indeed a highly-skilled level 4 intensive care center,” says Dr. Shepherd. “But we apply a model of care for BPD in which we are minimizing pain and noxious stimuli and maximizing joy.”

As the only center of its kind, the BPD Unit becomes home to infants with severe BPD from around the country as they wait for their lungs to get strong enough for the outside world. The BPD Unit opened in 2005,



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Michelle Hull, a member of the Early Childhood Development Team, working with a patient on the BPD Unit and her family. The Early Childhood Development Team provides individualized developmental support for patients using a play-based model. Here, Michelle is coaching parents during a bedside play session focusing on communication and social skills.

but the team had started applying the model — including altered vent settings — as much as possible before that.

“We treat them developmentally appropriately — not waking them up. Minimizing pain and IVs. Letting parents hold them as much as they want 24/7. And relying more on physical exams and assessments to minimize blood draws and tests,” Dr. Shepherd says.

Maximizing fun can be difficult to do in the NICU, but with the support of the nursing staff, and by enlisting many different therapists — including music and occupational therapists — working with parents and educating the team, it can be done.

Participate in Research

Babies in the BPD Unit have access to all the neurodevelopmental protocols and research offered in the NICU at large. Nathalie Maitre, MD, PhD, is a neonatologist and developmental specialist at Nationwide Children’s. And she’s the leader of many research protocols aimed at supporting healthy neurodevelopment in the NICU.

“The NICU environment is very different from the home environment,” she says. “The stimuli that a baby is exposed to in the NICU can be detrimental to the

developing brain. And certain protective stimuli — such as mother’s voice and touch — are sorely missing.”

By including babies with BPD in the neurodevelopmental protocols and interventions, their brain development can be further optimized, she says.

CHANGING [MORE THAN] NEURODEVELOPMENTAL OUTCOMES

“We applied this chronic care model relentlessly over time. We thought that it would improve neurodevelopmental outcomes — and it did. But it also did so much more. Our survival rates also increased to 99% for severe BPD. Nationally, survival rates are 80-90%,” says Dr. Shepherd.

According to Dr. Shepherd, patients in the BPD Unit at Nationwide Children’s have about 10-15% risk of neurodevelopmental impairment compared to 40-50% in the national sample.

Recently, the Nationwide Children’s team published the results of a retrospective observational study following 151 consecutive patients with moderate to severe BPD who were treated in the BPD Unit at Nationwide Children’s. The study, published in *The Journal of Pediatrics*, includes data that support the concept of a comprehensive, neurodevelopmentally oriented approach.

According to the study, patients treated with this approach had better neurodevelopmental outcomes than previously reported cohorts. Additionally, the only two factors that were significantly associated with neurodevelopmental impairment at 24 months of age were lower birth weight and longer hospital stays.

“Shorter length of stay is one of the benefits to the comprehensive, chronic care approach,” says Dr. Shepherd. “This study confirms that we’re on the right track.”

As great as those results are, they are only for a single center. In order to have an even better chance at improving outcomes for babies with BPD, large, multicenter studies are needed.

“That’s exactly why we started the BPD Collaborative,” says Leif Nelin, MD, division chief of Neonatology at Nationwide Children’s and chair of the BPD Collaborative.

The BPD Collaborative was formed in 2012 to fill knowledge gaps around the care of infants with BPD by sharing data, conducting research and developing quality improvement initiatives. It started with six other centers and has more than doubled in size to include Nationwide Children’s and 17 other institutions.

18 INSTITUTIONS OF THE BPD COLLABORATIVE

- Nationwide Children’s Hospital
- Arkansas Children’s
- Boston Children’s Hospital
- Children’s Hospital of Colorado
- Children’s Hospital of Michigan
- Children’s Hospital of Philadelphia
- Children’s Mercy Hospital Kansas City
- Joe DiMaggio Children’s Hospital
- Johns Hopkins Children’s Center
- Monroe Carell Jr. Children’s Hospital at Vanderbilt
- Riley Children’s
- Seattle Children’s
- Stanford Lucile Packard Children’s
- Texas Children’s Hospital
- University Children’s Hospital (Uppsala, Sweden)
- University of Massachusetts
- University of Utah
- Women & Infants Hospital Rhode Island

“When we started, we didn’t have any funding, so we were all doing this on our own. We began having regular meetings and teleconferences and a few studies,” says Dr. Nelin, who is also professor of Pediatrics at OSUCM. “But as funding came, we began to conduct more research and submit more publications.”

In 2017 the BPD Collaborative published the “manual” on how to care for these infants, establishing the first consensus guidelines on the condition. Since then, their work has continued.

“One of the biggest challenges to BPD research is that each institution does things a little (or a lot) differently,” says Dr. Nelin. “There’s no blinded clinical trial to compare prevention and treatment approaches, so we’re focused on comparative effectiveness research.”

Part of this research is aided by a large database, supported by the BPD Collaborative member institutions. The database enables large datasets to be gathered, allowing for broader studies.

The Collaborative is also taking aim at a deeply phenotyped and genotyped study of patients with BPD by submitting a grant proposal to the NIH. The study will facilitate understanding of the causes of BPD and best treatments, by looking for genetic variations that may better predict outcomes in a large — 600 patient — cohort of infants with BPD.

“BPD is an interesting disease,” says Dr. Nelin. “If you ask a neonatal practitioner, they can tell you what BPD is, but when you ask them to define it, it’s really hard to do. We are really excited to dig deeper into ways to define the condition that are more predictive of outcomes. And hopefully, that will lead to precise medicine approaches to BPD treatment.”

LIFE AFTER THE NICU

Willow was able to finally go home after 236 days in the NICU. She came home using oxygen on a nasal cannula and a G-tube to assist with feedings. Her care plan included weekly physical therapy and months of follow-ups in the BPD Clinic.

The BPD Clinic at Nationwide Children’s operates as a “medical home model.” That is, BPD experts work closely with the child’s primary care physician to oversee the care and progress of the whole patient.

The model is fundamentally interdisciplinary.

“Interdisciplinary care teams are extremely important to support all the needs of the patient with BPD and their families,” says Susan Lynch, MD, medical director of the BPD Clinic at Nationwide Children’s. “From nutrition experts, social workers, developmental therapists and respiratory therapists to nurses, physicians and nurse practitioners — all members play a vital role in the holistic care of the infant and child with BPD.”

And the team is available 24/7.

“It is incredibly important for families of patients with BPD to be able to have access to the care team to ask questions about changes in their baby,” says Dr. Lynch, who is also an associate professor of Pediatrics at OSUCOM. “The BPD Clinic provides this access no matter the day or time. We also encourage primary care providers to work closely with the family and the BPD team to help address the family’s questions and evaluate the baby during times of change if they live far from Columbus.”

By providing round-the-clock access, the BPD team can address concerns early and often keep little ones out of the Emergency Department by seeing them in the BPD clinic, adds Dr. Lynch. It also provides the needed support to help families build confidence in their child’s care, successfully taking their child outside the hospital setting and gaining a deeper understanding of their child’s medical needs over the first three years of life.

After the implementation of the BPD program and the initiation of the BPD Clinic in 2004, one month readmission rates of patients with BPD decreased from 29% to 5%.

BPD NEURODEVELOPMENTAL FOLLOW-UP CLINIC

NICU follow-up care in the BPD clinic is divided into two subclinics: one focusing on a child’s medical needs and the other focusing on their developmental needs.

“We found that for many families, having both medical and developmental combined into the same clinic visit was just overwhelming,” says Dr. Maitre, director of NICU Follow-up Programs. “To first discuss whether or not your child was getting enough oxygen and move right on to whether he or she was meeting developmental milestones is a lot for parents to take in and process.”

By splitting the follow-up care into two clinic visits, the teams are able to spend more time with the families, give them digestible amounts of information and address their questions.

“We focus a lot on minimizing neurodevelopmental impairments in the NICU and improving neurodevelopmental outcomes,” says Dr. Maitre. “It’s important to remember that a child with a neurodevelopmental delay is not a failure, however. We give that family a good outcome by empowering them to handle whatever comes their way. An empowered family is a good outcome.”





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A BRIDGE FROM BPD CLINIC TO PULMONARY MEDICINE

Once children age out of the BPD clinic — around age 3 — they are followed by a pulmonologist.

“But not just any pulmonologist,” says Dr. Maitre.

Daniel Malleske, MD, MS, is board certified in internal medicine, pediatrics and neonatology. And he’s completing a fellowship in pulmonary medicine. For patients with BPD at Nationwide Children’s, he’s the bridge between the BPD clinic and lifelong pulmonary care.

“I think that the field could really benefit from doctors who are interested in following these patients through childhood and into adulthood — and conducting research and intervening wherever possible,” says Dr. Malleske. “I decided to be one of those doctors.”

Survivors of prematurity — with or without BPD — are at an increased risk for pulmonary complications, such as greater airway reactivity, greater air trapping and exercise limitations, in adulthood. For those with BPD, the risk is especially high.

As children with BPD age, they can present with asthma-like symptoms. In fact, those symptoms are primarily managed with asthma medications.

“We really don’t know the natural history of lung function of patients with BPD into later adulthood. Most are in their 40s at the oldest,” says Dr. Malleske. “We’re seeing examples of emphysema, or chronic obstructive pulmonary disease, in patients who were born preterm or who had BPD. They are developing COPD at earlier ages and without the common lifestyle factors.”

Once he finishes his fellowship, Dr. Malleske says he is looking forward to resuming research in long-term

airway development and pulmonary function in the surviving BPD population.

IMPROVING CARE EVERYWHERE FOR BABIES WITH BPD

As many as half of the patients at any one time in the BPD Unit may be from outside the Nationwide Children’s region. And almost all of those had a do not resuscitate order (DNR) at their previous institution.

“Parents find us online and call us asking for help. Increasingly providers are calling, too,” says Melinda Ingram, CPNP-PC. “In many cases, we can work with a willing provider at an outside NICU to help improve things for the baby at their home hospital, but sometimes transfer is the best option.”

“We begin talking with the providers, and sharing what we would do,” says Dr. Nelin. “They implement some (maybe not all) of the things, and the baby ends up improving and being more stable at time of transfer. This gets that institution thinking about the next patient, and how they can adopt some of the things we do.”

One example of how a transfer case became a lasting relationship with another institution, is a case from South Dakota nine years ago. A patient for whom the team at Sanford Children’s Hospital had done all they could was ultimately transferred to Nationwide Children’s at the parents’ request. The baby survived and is doing well to this day, says Dr. Nelin.

Dr. Shepherd shared the chronic care model used in the BPD Unit at Nationwide Children’s with the team at Sanford as he’s done for other hospitals around the country. And since then, the two institutions have continued to work together to improve care for infants with BPD.

Searching for a Predictive Biomarker of Pulmonary Hypertension in Babies With Bronchopulmonary Dysplasia

Pulmonary hypertension is high blood pressure in the lungs and is a comorbidity of bronchopulmonary dysplasia (BPD), which is the chronic lung disease of premature babies. When pulmonary hypertension is present in the context of BPD, the risk of death is significantly increased.

As neonatologists continue to define the phenotype of severe BPD, Jennifer Trittman, MD, MPH, and her colleagues in the Center for Perinatal Research at Nationwide Children's are working to identify biomarkers for pulmonary hypertension in these high-risk patients.

"My goal is to create a lab panel of biomarkers, both genetic and metabolic, that could support clinicians as they consider personalized approaches to treatment plans for patients with BPD complicated by pulmonary hypertension," she says.

In a recent publication in *Pediatric Research*, she and her team identified three novel genetic markers (*DUSP1 SNP rs322351*, *DUSP5 SNP rs1042606*, *DUSP5 SNP rs3793892*) that were statistically different in BPD patients with pulmonary hypertension compared to BPD patients without pulmonary hypertension.

The team also analyzed clinical data of the cohort.

"Analysis of the clinical data revealed that BPD patients with pulmonary hypertension were of younger gestational age, lower birthweight, received less surfactant treatment, more mechanical ventilation, and more postnatal steroids than patients with BPD and no evidence of pulmonary hypertension," says Dr. Trittman, who is also assistant professor of Pediatrics at The Ohio State University.

Ultimately, the team calculated the area under the curve (AUC), which is a standard statistical test of biomarker sensitivity and specificity. AUC was 0.76 when including both clinical and DUSP genetic data.

"Moving forward, we'll continue to identify and test biomarkers for pulmonary hypertension in babies with BPD until we reach a clinically useful AUC (0.8-1) that can be replicated in a larger independent patient cohort," Dr. Trittman says. "The goal is to have a lab test for pulmonary hypertension in BPD patients, such that depending on the patient's lab profile, treatments that are specific for known molecular targets, for example in the DUSP pathway, could be used to quickly reverse disease progression."

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"We still transport the occasional infant to Nationwide Children's," says Dr. Messier. "But we can keep a lot more of them closer to home now."

"No baby should die from BPD or have a decreased quality of life from the disease," says Dr. Shepherd. "We're excited to share what we're learning, and we look forward to learning even more together. That's why we have the BPD Collaborative. Why we publish. And why we consult with other institutions openly."

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Uncovering Why Synthetic Tracheal Replacements Fail, and Hints for Success

RESEARCHERS TAKE A SYSTEMATIC APPROACH TOWARD THEIR GOAL OF DEVELOPING AN EFFICACIOUS IMPLANT

by Kevin Mayhood

“There is no ideal replacement for the trachea,” says Tandy Chiang, MD, a pediatric otolaryngologist and a principal investigator in the Center for Regenerative Medicine in the Abigail Wexner Research Institute (AWRI) at Nationwide Children’s Hospital.

“There are many surgical techniques that can manage tracheal defects and disorders, however, for longer-segment defects, they oftentimes require replacement tissue that just isn’t available,” says Dr. Chiang, who is also an assistant professor in the Department of Otolaryngology – Head and Neck Surgery at The Ohio State University College of Medicine. “There’s no autologous substitute.”

Tissue-engineered tracheal grafts (TETGs) were thought to be a promising solution, but clinical trials in Europe were halted due to failures.

In the wake of the troubles, Dr. Chiang and colleagues, who were not involved in the European trials, have undertaken systematic investigations into why the implants fail and possible solutions.

“What happened in Europe is they went too fast,” says Susan Reynolds, PhD, a principal investigator in the Center for Perinatal Research in AWRI at Nationwide Children’s working with Dr. Chiang. Dr. Reynolds’ efforts focus on tissue stem cells that maintain the conducting airway epithelium. “We definitely know what the endgame is but solving the problem is going to take many steps.”

Bit by bit, the research team has produced three sets of data.

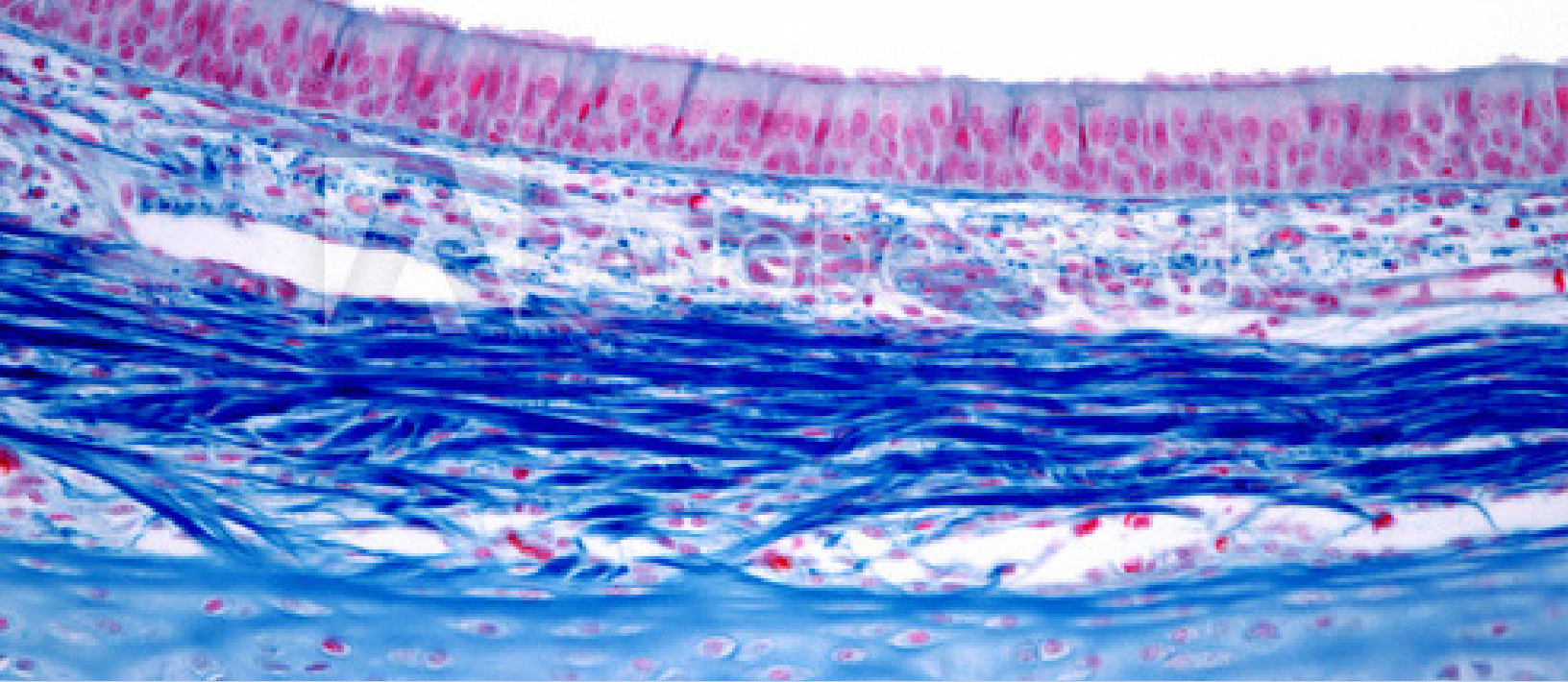
“*In vitro* data shows that the progenitor cell population is adversely affected by the scaffold,” Dr. Chiang says. “Large animal data show the synthetic implants don’t re-epithelialize well. And, data from a small animal model show that at the right scale, the implant does restore the epithelium and a functional one at that.”

In their large animal study, the researchers implanted the same type of TETGs and replicated the processes used in the trials abroad. The long-term outcomes were similarly poor. Grafts narrowed, infections occurred where synthetic and native trachea joined and no epithelialization or neovascularization occurred.

To try to understand why epithelialization did not occur, Dr. Reynolds led the effort to determine whether airway epithelial stem cells could attach to the porous scaffold and if they could attach, could they grow? Then, if the answers were “yes,” could the stem cells make a functional epithelium?

Her team made *in vitro* comparisons of electrospun polyethylene terephthalate and polyurethane (PET/PU) TETGs, like those used in the European trials, and a polystyrene control scaffold. The control lacks the biomechanical properties needed for an implant, but the cells are known to grow well on its surface.

They found native tissue-derived epithelial cells migrated poorly on the PET/PU material compared to control material and that the PET/PU scaffold failed to support basal stem/progenitor cell proliferation.



“We think the stem cells are not able to interact or attach to the PET/PU scaffold, so like grains of sand they’re just filtering through and finally getting down to the polystyrene base, and that’s a surface the stem cells can attach to,” says Dr. Reynolds, who is also an assistant professor at Ohio State. “If they grow at all, what they do is just make a column of cells.”

“It needs to be a layer and function as a barrier,” she adds.

Surprisingly, when Dr. Chiang tested a PET/PU scaffold patch on small defects in mouse models, the patch re-epithelialized quickly, he says — in two weeks.

“Not only did histology indicate the patch implant formed what appeared to be an epithelium but immunofluorescence revealed this was functional tissue,” Dr. Chiang says.

To narrow the reasons longer-segment implants may fail, the team tested whether morbidity of tracheal replacement in and of itself is contributing to failure. Avoiding detrimental immune responses, the investigators implanted genetically-identical tracheas from one mouse into another, just connecting ends of the donor trachea with the host’s.

“The grafts heal remarkably well and do not develop stenosis or collapse or show signs of respiratory distress,” Dr. Chiang says.

Because of the natural lack of blood supply to the trachea, other studies have suggested a need for staging

TETG implants by first putting them where they can create a new blood supply and then implanting them in the windpipe. But the success of the syngeneic implants suggests that with the right construct, that may not be necessary, the researchers say.

Whether or not graft seeding helps with performance of the implants has been controversial. In the mouse models, the investigators saw no differences in the degree of epithelialization or the model’s survival when using grafts seeded with bone marrow mononuclear cells versus unseeded.

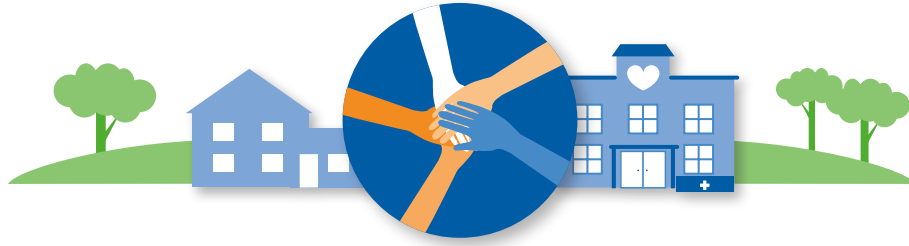
The investigators found, however, that seeded cells are rapidly cleared from the scaffold. They suggest that strategies to improve the persistence of seeded cells potentially could influence the outcome, but that remains to be seen.

The researchers are continuing their investigations, Dr. Chiang says. “The next questions are how can we accelerate the re-epithelialization process and how can we incorporate and improve compatibility of these materials with the body so that we can scale up from a patch model to something more clinically viable.”

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ACCOUNTABLE CARE AND QUALITY IMPROVEMENT

How an ACO helps community practices provide the “right care” through QI

by Jeb Phillips

An accountable care organization (ACO) should deliver “the right care at the right time,” according to the Centers for Medicare & Medicaid Services. Early, high-quality primary care helps people stay well, while coordinated specialty care can help people with chronic or complex conditions spend less time in a hospital.

ACOs are usually considered the province of Medicare, and they are usually created by large adult health care systems. But the ability of an individual community provider to deliver “the right care” is at the heart of an ACO’s success. And even though ACOs are typically concerned with adults, “right care” provided in the community can be especially important for children. When young patients receive timely immunizations, or when asthma is properly controlled in primary care, children can lead healthier lives.

That is a core tenant of the ACO created by Nationwide Children’s Hospital in 1994, called Partners For Kids®, which brings accountable care principles to a geographically distinct Medicaid pediatric population. The organization, a collaboration between Nationwide Children’s and more than 2,100 providers, is fully financially responsible for the health care of 325,000 children and adolescents covered by Medicaid in south central and southeastern Ohio.

Partners For Kids has assumed that responsibility because it can help community providers deliver “the right care” and enhance children’s health. The organization runs many programs toward that end, but the cornerstone is Quality Improvement Coaching. Partners For Kids designs QI projects that will have the largest impact on patient health, then helps community practices implement them.

“It can seem like we are making a big ask of primary care providers, when we propose projects to keep children out of the emergency department, or to reduce teen pregnancy,” says Gilbert Liu, MD, medical director of Partners For Kids. “These are longstanding, difficult problems. But we break them down into smaller parts that are easier to accomplish.”

It’s not always easy, but recent data shows this quality improvement work is having a big impact on the health of children in south central and southeastern Ohio.

PROJECTS TAILORED FOR PRIMARY CARE

Partners For Kids surveys their member providers and develops QI projects with their goals in mind. Providers are primarily motivated to want to improve care simply because they want children to be as healthy and happy as possible.

But there are increasing external motivations for quality

improvement efforts as well. The Ohio Department of Medicaid, for example, requires practices to meet certain performance measures for reimbursement and credentialing purposes – a state movement toward value-based care.

Still, there can be understandable resistance to QI projects from providers, says Heather Maciejewski, Partners For Kids' lead Quality Improvement coordinator. These projects take time, work and resources for offices that are already stretched thin. And QI requires a skill set and a learned methodology that pediatricians may not know.

“Every practice is different,” Maciejewski says. “We look at what they perceive barriers to be, and we try to overcome them.”

As a first project, Partners For Kids often suggests one that involves the simple application of a fluoride varnish to teeth, says Sean Gleeson, MD, MBA president of Partners For Kids. The American Academy of Pediatrics recommends that children first see a dentist at 1 year of age, or within six months after a first tooth appears. But many children don't, and cavities result. The regular, preventative application of fluoride in primary care can help prevent those cavities.

Partners For Kids helps educate providers about the intervention, connects providers to fluoride suppliers and facilitates reimbursement from Medicaid.

“It's often how a practice is introduced to QI, because they can quickly see the benefit both for their practice – in terms of reimbursement – and for the families they serve, in terms of better oral health,” says Dr. Gleeson. “Once they see QI at work, many come to like it.”

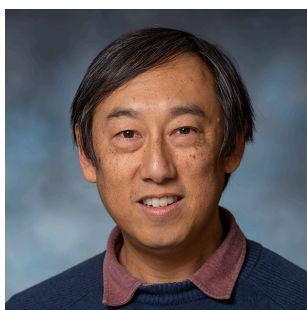
One of Partners For Kids' signature QI projects, called “Healthy Children,” can be more difficult for providers, because it appears to involve a large commitment. This effort focuses on having children and adolescents complete their recommended well-child visits, particularly children younger than 15 months; children 3 to 6 years of age; and adolescents 12 to 21 years of age.

To accomplish this on their own, a practice would need to identify patients needing well visits, to call and schedule them, to check well-visit needs when families call for prescription refills and other routine requests, and for many other purposes. Partners For Kids knows that can appear to be a huge burden. So Partners For Kids' own staff members identify patients who need a visit and make scheduling calls for the practice. Staff members can also train practices in processes such as sick-to-well visit conversion, so that patients can receive additional preventative care when they come in for treatment of an illness.

QI efforts like these have helped Partners For Kids reduce Emergency Department utilization in its region while increasing immunization rates and well visits. And individual pediatricians say those efforts make a difference in the personalized care provided.

THE TOOLS TO BE BETTER

Kate J. Krueck, MD, started her primary care career in 2002 “terrified of doing everything wrong,” and she began something of a self-education plan on her own. For example, she realized that she would need to become proficient in treating patients with attention deficit hyperactivity disorder, and so she taught herself, then worked to train her colleagues at Pediatric Associates, now one of central Ohio's largest primary care practices.



“IT CAN SEEM LIKE WE ARE MAKING A BIG ASK OF PRIMARY CARE PROVIDERS, WHEN WE PROPOSE PROJECTS TO KEEP CHILDREN OUT OF THE EMERGENCY DEPARTMENT, OR TO REDUCE TEEN PREGNANCY. THESE ARE LONGSTANDING, DIFFICULT PROBLEMS. BUT WE BREAK THEM DOWN INTO SMALLER PARTS THAT ARE EASIER TO ACCOMPLISH.”

– Gilbert Liu, MD, medical director of Partners For Kids



“I THOUGHT IT WAS JUST THE GROUP THAT HELPED US GET PAID THROUGH MEDICAID, AND NOW I UNDERSTAND THAT HELPING ME GET PAID IS NOT EVEN THE BEST THING THAT PARTNERS FOR KIDS DOES. I WOULD SAY THE MOST IMPORTANT THING IS THAT IT GIVES ME THE TOOLS TO BE THE BEST PHYSICIAN I CAN BE.”

– Kate J. Krueck, MD , chief medical officer at Pediatric Associates

That experience led to an interest in QI, which led her to QI projects through the American Academy of Pediatrics, which ultimately led to Partners For Kids. Pediatric Associates has long been part of the Partners For Kids system, and Dr. Krueck knew it as an intermediary between Medicaid managed care plans and providers.

It was only once she began taking on more administrative duties as chief medical officer at Pediatric Associates that she came to realize Partners For Kids’ QI potential.

“I thought it was just the group that helped us get paid through Medicaid,” Dr. Krueck says. “And now I understand that helping me get paid is not even the best thing that Partners For Kids does. I would say the most important thing is that it gives me the tools to be the best physician I can be.”

Dr. Krueck wants children to have a yearly visit; Partners For Kids actually provides a staff member to schedule those appointments. She wants to prescribe the medications that will be most effective and covered by insurance; Partners For Kids produces a preferred drug list and will set up educational sessions with their pharmacists. She wants patients with asthma to have better control of their conditions; Partners For Kids analyzed Pediatric Associates’ managed Medicaid claims data to see how often their patients with asthma were going to an emergency department.

“We have shared values,” Dr. Krueck says. “I practice medicine more effectively because of the resources Partners For Kids gives me.”

For more information, visit PartnersForKids.org.

PARTNERS FOR KIDS’ PROGRAMS, INCLUDING QUALITY IMPROVEMENT COACHING, HAVE LED TO SIGNIFICANT IMPROVEMENTS IN HEALTH CARE UTILIZATION RATES AND PATIENT HEALTH

EXAMPLE OF A CURRENT PROJECT

Attention Deficit Hyperactivity Disorder (ADHD)

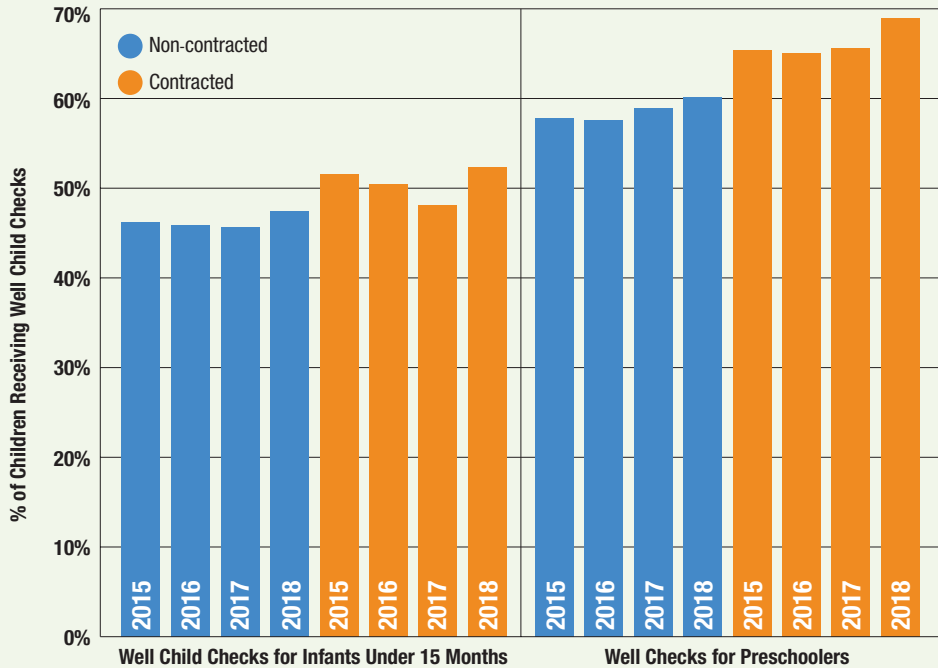
More than 25,000 children in the Partners For Kids system have been diagnosed with ADHD, and nearly 20% of the money spent on medication for Partners For Kids patients is spent on ADHD medication. This project focuses on screening and high-value prescribing for ADHD.

Partners For Kids:

- Trains practices to use evidence-based ADHD screening tools, including tools to collect information from parents and school personnel about symptoms
- Works with community providers to manage/monitor lifestyle, academic and environmental factors for patients with ADHD
- Creates and distributes prescribing guidelines that support providers in choosing the most cost-effective medications
- Develops provider-specific reports on prescription practices, so providers can benchmark their own performance and compare their practices to others

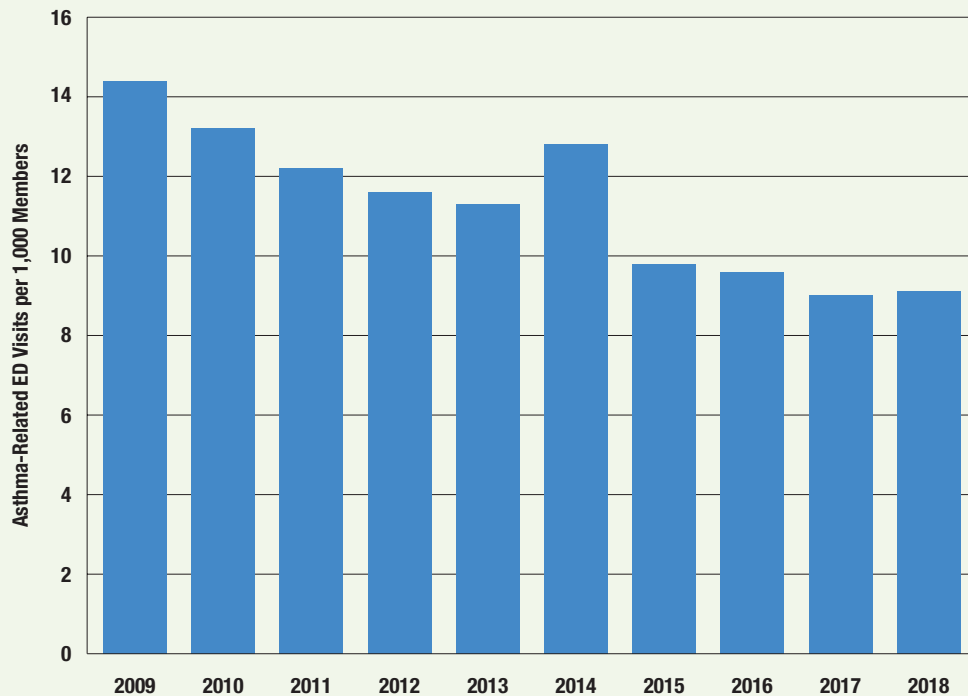
CHILDHOOD WELL-CHILD VISITS

Children attributed to Partners For Kids-contracted primary care providers have higher well-visit rates than children attributed to non-contracted providers.



COUNTY-WIDE REDUCTION IN ASTHMA-RELATED EMERGENCY DEPARTMENT VISITS

Since 2009, asthma-related Emergency Department visit rates decreased 37% at Nationwide Children's Hospital for Partners For Kids members who reside in Franklin County.



Beyond A Bigger Workforce:

ADDRESSING THE SHORTAGE OF CHILD AND ADOLESCENT PSYCHIATRISTS

How can the psychiatrists we have make the greatest impact for the most children?

..... by David Axelson, MD

The United States does not have enough child and adolescent psychiatrists. Nearly anyone who works in the field knows about the months-long wait times for new appointments that families can face, or the great distances that some must travel for those appointments.

What we have not really known, however, is the true scope and shape of the problem. A 2018 report from the U.S. Health Resources and Services Administration called “Behavioral Health Workforce Projections, 2016-2030” used a mathematical model to find that there was only a 20% greater demand for pediatric psychiatry services than the current supply – and that in a decade, supply would be greater than demand.

Nothing in my own experience substantiates this, and the significant evidence of a growing mental illness burden among young people may actually refute it. The rate of death by suicide in young people 10-19 years of age increased 86% from 2007 to 2017. Less than half of the 7.7 million children in the United States with an identifiable mental health condition are receiving services from any mental health provider, much less a psychiatrist.

A recent study in *Pediatrics* from researchers at the RAND Corporation, the University of Georgia and Harvard University gives us a better idea of where we truly stand. Some of what they found is good news. The overall number of child psychiatrists increased 21% from 2007 to 2016, and there are now 9.75 per 100,000 children aged 0 to 19.

But in a broader context, it's clear that the field isn't close to having enough child psychiatrists to meet

demand, now or in the future. The American Academy of Child and Adolescent Psychiatry estimates that the country needs 47 child psychiatrists per 100,000. That's four times the number found by the study published in *Pediatrics*. The ones we do have are heavily concentrated in metropolitan areas; 70% of American counties do not have a child psychiatrist. Massachusetts has eight times the number of child psychiatrists per 100,000 children as Iowa.

So what can be done in the face of these statistics? Many people in the field have proposed ways of increasing the numbers of child psychiatrists, including federal initiatives that would repay school loans, or offering a four-year residency program as an alternative to the typical five-year postgraduate training, or changing codes and reimbursements to better line up with the additional complexity of working with a pediatric population.

Those all have merit, and growing the workforce matters. But it probably isn't enough, especially when considering the geographical imbalance of that workforce. We should also be asking a question that is informed by a population health approach and considers the limited assets we have now instead of what we may have in the future: how can child psychiatrists have the greatest impact on the most children?

I am the chief of psychiatry and behavioral health at Nationwide Children's Hospital, and we have wrestled with this very question as we open a new center for research and treatment, the Big Lots Behavioral Health Pavilion. We have come to the realization that a better, more integrated system of care throughout our region can multiply the impact of the child psychiatrist.

“It will take time and investment, but I believe that both integrated systems of care and efforts to build the workforce are the best strategy for better outcomes. We must be open to these innovative ways of thinking to improve children’s mental health.”

– David Axelson, MD

chief of the Department of Psychiatry and Behavioral Health at Nationwide Children’s Hospital

In this concept, the psychiatrist leads a multidisciplinary team that could include advanced practice providers, psychologists, nurses, therapists and a variety of other mental health professionals. The psychiatrist treats the group of patients who need psychiatric expertise, while acting as a consultant or advisor to other team members. The psychiatrist may also work with primary care providers, school-based health care professionals and others to expand care to underserved areas. Telehealth technology can improve the quality and efficiency of this care expansion.

This model means psychiatrists, and pediatric psychiatric training, must evolve. Psychiatrists will still work with individual patients, but it’s not all they will do. They must be prepared to build and lead teams and to effectively communicate with a range of health care professionals inside their home institutions and out in their communities.

It will take time and investment, but I believe that both integrated systems of care and efforts to build the workforce are the best strategy for better outcomes. We must be open to these innovative ways of thinking to improve children’s mental health.

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Behavioral Health by the Numbers



**7.7
million**

Children in the United States with an identifiable mental health condition

49%

Percentage of those children who receive any mental health services

86%

Increase in rate of death by suicide rate in children 10-19 years of age

47

Estimated number of child psychiatrists per 100,000 children needed to meet demand

9.75

Actual number of child psychiatrists per 100,000 children

70%

The percentage of U.S. counties that have no child psychiatrists

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Oral Food Challenges: The Most Important Test in Diagnosing Food Allergy

Written by David Stukus, MD

Given the many challenges associated with food allergies, proper diagnosis is paramount. Unfortunately, readily available skin prick and blood tests have limitations. In this column, Dr. Stukus explains what the limitations of skin prick and blood tests are, why the single best test to diagnose food allergy is ingestion, and how to conduct oral food challenges safely.

[PediatricsNationwide.org/Oral-Food-Challenge](https://www.pediatricsnationwide.org/Oral-Food-Challenge)



How to Increase Continuous Glucose Monitoring Utilization in Patients With Type 1 Diabetes

by Katie Brind'Amour, PhD

Continuous glucose monitors can improve quality of life and time in range outcomes for patients. When the endocrinology team at Nationwide Children's learned that only 8% of their patients with Type 1 Diabetes were using continuous glucose monitoring (CGM), they knew they could do better. Using a comprehensive team, specific design interventions and a detailed phase approach, they launched a quality improvement initiative that multiplied CGM use almost six-fold in just two years.

[PediatricsNationwide.org/CGM](https://www.pediatricsnationwide.org/CGM)



How Does a Children's Hospital Excel in the Discovery and Development of New Therapies?

Written by Abbie Roth

Nationwide Children's has become an epicenter for gene therapy discovery and development. In this conversation with Dennis Durbin, MD, MSCE chief scientific officer at the Abigail Wexner Research Institute, we explore the role of pediatric academic centers in novel therapy development.

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