Pediatrics NATIONWIDE

Advancing the Conversation on Child Health | Spring/Summer 2023

Micro-dystrophin: A Small Gene With Big Promise

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Our cover story this issue takes a look inside the creation of SRP-9001, a gene therapy approach for Duchenne muscular dystrophy that is currently being reviewed by the Food and Drug Administration for approval. The approach uses an adeno-associated vector, fitted with the SRP-9001 dystrophin transgene.

4. Once inside the nucleus, the viral capsid dissolves, releasing the single-stranded transgene.

3. The membrane of the endosome dissolves and the vector enters the nucleus.

2. It forms an endosome and travels through the cell to the nucleus.

1. The vector enters through the membrane of the muscle cell.

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> *When we implement AI in health care settings, we have to be extremely diligent… Even after we have a model that we think is good enough, we implement it in the background and monitor it another 6 months to make sure it does what we want it to do.*
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> – Christopher Bartlett, PhD, principal investigator in genomic medicine

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> *In medicine, it's not always 'if you build it, they will come.' … It can take years for there to be broad adoption and use of a new tool or change in care.*
>
> – Bimal Chaudhari, MD, MPH, neonatologist and medical geneticist

Implementation of a COVID-19 Monoclonal Antibody Program

Researchers provide guidance on risk stratification and offer subspecialists and community practitioners a streamlined approach to treating patients at greatest risk for severe COVID-19.

The COVID-19 pandemic necessitated the development of therapeutic approaches to combat the SARS-CoV-2 virus. In late 2020, monoclonal antibody therapies were among the first COVID-19 therapeutics to receive emergency use authorization from the U.S. Food and Drug Administration. In January 2021, a panel of pediatric experts released a consensus statement recommending against routine use of COVID-19 monoclonal antibody therapies in children and adolescents due to limited efficacy or safety data and in support of individualized risk assessments when considering use of these therapies.

"When the first monoclonal antibody treatment was developed, it was not clear how this new therapy, which was still considered investigational, would impact pediatric patients with COVID-19, and it was a scarce resource. So, we felt it was important to set up a program to offer outpatient treatment for children who had the highest risk of developing severe disease," says Joshua Watson, MD, pediatric infectious disease specialist at Nationwide Children's Hospital.

"Procurement of the drug was difficult, and we were often told how many doses the hospital would receive only a week in advance. This required us to be very nimble, and the program was a success because of the commitment and effort of the provider team and many other key personnel, including those in nursing and pharmacy," adds Jill Blind, PharmD, CCRP, pharmacy manager of Investigational Drug Service & Controlled Substances at Nationwide Children's.

Drs. Watson and Blind worked closely with a multidisciplinary team to establish a COVID-19 monoclonal antibody referral process that worked fluidly as doses became available and new therapies were developed. They recently published a report in the *Journal of the Pediatric Infectious Diseases Society* describing the process and clinical outcomes of patients who received a SARS-CoV-2 neutralizing monoclonal antibody infusion at the hospital.

Their standardized COVID-19 monoclonal antibody referral and approval process incorporated a tiered allocation system based on patients' underlying medical conditions.

Between Nov. 27, 2020, and Jan. 26, 2022, 182 patients received a COVID-19 monoclonal antibody infusion at Nationwide Children's. The patients were between 10 months and 21 years of age. Overall, 7 patients (4%) experienced suspected adverse reactions during the infusion, and 15 (8%) patients required a COVID-19-related visit (primary care provider, emergency department, or hospitalization) within 30 days of the monoclonal antibody infusion.

"Although the current SARS-CoV-2 variants are showing resistance to the available monoclonal antibodies, other outpatient therapies have been developed for COVID-19. Thus, this program continues to provide a valuable framework within our hospital and for other hospitals that may want to establish such a program," says Dr. Watson.

Blind JE, Sapko M, Killough A, Thornton H, Watson JR. Implementation and patient outcomes of a pediatric COVID-19 monoclonal antibody program. *Journal of the Pediatric Infectious Diseases Society*. 2022 Dec 28;11(12):565-574.

— Lauren Dembeck, PhD

TIER 1	highest-risk conditions such as severe obesity, a neurodevelopmental, genetic or metabolic disorder conferring medical complexity, dependence on respiratory technology and severe immunosuppression
TIER 2	higher-risk cardiac disease, higher-risk pulmonary disease, type 1 diabetes mellitus and obesity in addition to at least one other higher-risk condition
TIER 3	any other high-risk condition

Role of Myeloid-Derived Suppressor Cells in Septic Shock Immunoparalysis

New study is the first to describe increased myeloid-derived suppressor cells in children with septic shock.

In children with septic shock, the immune system initiates a systemic inflammatory response and a nearly concurrent compensatory anti-inflammatory response. When severe, this anti-inflammatory response is termed "immunoparalysis" and is associated with increased risk of infections and death.

Researchers recently identified a population of cells called myeloid-derived suppressor cells (MDSCs) that may perpetuate immunoparalysis.

"These cells have been extensively studied in adults with cancer and were found to cause immune suppression that contributes to worse tumor burdens and increased mortality," says Katherine Bline, MD, a critical care medicine physician at Nationwide Children's Hospital and a principal investigator in the Center for Vaccines and Immunity at the Abigail Wexner Research Institute (AWRI). "We wondered if MDSCs also played a role in mediating immune suppression in children with septic shock."

In a new study, Dr. Bline and colleagues investigated MDSCs and immune function in children admitted to Nationwide Children's Intensive Care Unit with septic shock.

"We found that MDSCs were significantly increased in the first 48 hours in children with septic shock compared to healthy controls," says senior study author Mark Hall, MD, FCCM, chief of the Division of Critical Care Medicine at Nationwide Children's and director of the Immune Surveillance Laboratory at AWRI. "And in agreement with previous studies, we found kids with septic shock had an underactive immune response and evidence of immunoparalysis."

The researchers say it remains unclear if MDSCs play a causative role in sepsis-induced immunoparalysis in children and more research is needed to establish these cells as a potential therapeutic target in this population.

A better understanding of the role of MDSCs in septic shock could have important implications for the treatment of these patients.

Currently, there are over 20 clinical trials investigating MDSC inhibitors as adjunct therapy in cancer treatment.

"If we find that these cells are clinically meaningful and contributing to immunoparalysis, we may be able to implement these therapies that are already available," says Dr. Hall, who is also a professor of pediatrics at The Ohio State University College of Medicine (OSUCOM).

In addition to investigating the timing of MDSC activity in immunoparalysis, Dr. Hall and colleagues are determining which subsets of MDSCs are most important in different patient populations.

"Like any single-center finding, it needs to be replicated in a larger cohort across multiple centers," says Dr. Bline, who is also an assistant professor of pediatrics at OSUCOM. "The good news is that we are well positioned to do that here at Nationwide Children's because we are very engaged with multiple national research networks that focus on the study of critically ill and injured children."

Bline KE, Muszynski JA, Guess AJ, Menocha S, Moore-Clingenpeel MD, Popelka JK, Hensley JM, Steele LM, Goldthwaite IC, Jedreski KJ, Hall MW. Novel identification of myeloid-derived suppressor cells in children with septic shock. *Pediatric Critical Care Medicine*. 2022 Dec 1;23(12):e555-e563.

— Mary Bates, PhD

Myopericarditis After COVID-19 Vaccination

A meta-analysis of international studies offers more detailed insight into the severity and outcomes of vaccine-related myopericarditis in the adolescent and young adult population.

Concerns over myopericarditis and other cardiovascular complications after COVID-19 vaccination in teens and young adults have gained considerable media attention. While myopericarditis-related data have been well characterized in adults with and without vaccination, the severity and outcomes of myopericarditis in adolescents and young adults had not been explored in detail in multi-institutional studies or international populations until the release of a recent systematic review and meta-analysis in *JAMA Pediatrics*.

"Vaccine-associated myocarditis is a rare adverse event, but it can be a lethal and severe complication of vaccination," says Jun Yasuhara, MD, who worked as a post-doctoral scientist in the Center for Cardiovascular Research at Nationwide Children's Hospital at the time of the research. He now serves as a cardiology fellow at the Royal Children's Hospital in Australia. "We wanted to assess and investigate the clinical picture of what was happening in this younger age group to see if it could inform decision-making about vaccinating this age group."

The analysis included 23 studies and 854 individuals ages 12 to 20 with COVID-19 vaccine-associated myopericarditis. It revealed that 90.3% were male and that incidence of myopericarditis was more common after the second vaccine dose than the first (74.4% vs 25.6%).

Nearly 93% of the patients with myopericarditis were admitted to the hospital for testing, with an average length of stay of 2.8 days and no deaths or mechanical support required. Most patients had preserved left ventricular (LV) function, but 15.6% had LV dysfunction — 14.1% were mild cases and 1.3% were considered severe. Late gadolinium enhancement was observed in 87.2% of patients, which could indicate more problematic cardiac effects despite their otherwise good outcomes.

Physiologically, the reasons behind increased incidence after vaccination (compared to a non-infected and unvaccinated baseline) — particularly after a second dose — and among males are unknown. The authors stress that other publications indicate a higher risk of myopericarditis caused by COVID-19 infection than by the vaccines.

"Now there is a big focus on figuring out what the long-term outcomes are among kids with vaccine-associated myocarditis, especially among those with late gadolinium enhancement," says Simon Lee, MD, director of the Coronary Anomaly Program in The Heart Center at Nationwide Children's and a co-author of the study. "Our research showed that at least in the short term, they usually have no major issues."

Dr. Lee, Dr. Yasuhara and their team have also published several other meta-analyses on COVID-19- or vaccine-related health complications in children, including a recent *JAMA Pediatrics* article on the topic of efficacy and safety of vaccination among children aged 5-11 years in preventing symptomatic COVID-19, hospitalizations and multisystem inflammatory syndrome in children (MIS-C).

Yasuhara J, Masuda K, Aikawa T, Shirasu T, Takagi H, Lee S, Kuno T. Myopericarditis after COVID-19 mRNA vaccination among adolescents and young adults: A systematic review and meta-analysis. *JAMA Pediatrics*. 2023;177(1):42–52.

Watanabe A, Kani R, Iwagami M, Takagi H, Yasuhara J, Kuno T. Assessment of efficacy and safety of mRNA COVID-19 vaccines in children aged 5 to 11 Years: A systematic review and meta-analysis. *JAMA Pediatrics*. 2023 Jan 23;e226243.

— Katie Brind'Amour, PhD

Preterm Birth Increases Health Vulnerabilities of Babies With Down Syndrome

Babies with Down syndrome who are born preterm have higher prenatal morbidity and mortality rates than those in babies with Down syndrome born at term, suggesting pediatricians can lower their risk threshold for certain screenings or interventions.

Compared with age-matched neonates without Down syndrome, babies with Down syndrome are more likely to experience developmental delay, gastrointestinal disorders and poor growth, among other challenges.

Neonates with Down syndrome who are born prematurely face an even steeper uphill health battle.

In a study published in the *Journal of Perinatology*, researchers reported that morbidity and mortality rates were significantly higher in neonates with Down syndrome born before 34 weeks of gestation than in those born later.

"Studies of babies with Down syndrome have not reported health outcomes according to gestational age," says Emily Messick, DO, pediatrician at Nationwide Children's Hospital and lead author of the study. "We began this project to address this gap in the literature."

For their single-center retrospective study, the team analyzed the medical records of 314 neonates with Down syndrome who were treated at Nationwide Children's NICU from 2010 to 2020.

Neonates were grouped according to gestational age: <34 weeks (n=31), 34 to 36 weeks (n=68), 37 to 38 weeks (n=127) and ≥39 weeks (n=88).

Data collected included prenatal and neonatal characteristics and morbidities experienced during the first year of life, such as necrotizing enterocolitis (NEC) and congenital abnormalities.

Morbidity rates were highest in neonates born before 34 weeks of gestation.

For example, three of the six neonates in the study who developed NEC were born before 34 weeks. The rates of oxygen supplementation and gastrostomy tube placement were greatest for the <34-week group than the other groups. Also, the use of nitric oxide, commonly used to treat respiratory failure associated with persistent pulmonary hypertension of the newborn, was highest for neonates born before 34 weeks.

The overall mortality rate in the study was 4.5%, with in-hospital mortality rates being highest (19%) in those born before 34 weeks. The most recent data for infant mortality in the US indicate a <1% mortality rate for infants born at 34 to 36 weeks.

"Awareness of these neonates' higher morbidity risks can drop the threshold for certain screening tests and prompt the early involvement of other sub-specialists to help improve long term outcomes," says Dr. Messick.

A multidisciplinary approach that is comprehensive and individualized is integral to improving outcomes for neonates with Down syndrome. For example, "A team of dietitians, speech therapists and gastroenterologists can help optimize growth for patients with feeding difficulties and poor growth," notes Dr. Messick.

Keeping a patient's family informed while the baby is in the NICU is key. "It is also helpful to look at the big picture and assess what goals need to be met for the baby to be discharged home with the family," she adds.

Messick EA, Backes CH, Jackson K, Conroy S, Hart SA, Cua CL. Morbidity and mortality in neonates with Down Syndrome based on gestational age. *Journal of Perinatology*. 2022 Sep 21. Online ahead of print.

Ely DM, Driscoll AK. Infant mortality in the United States, 2017: data from the period linked birth/infant death file. *National Vital Statistics Reports*. 2019;68:1–20.

— JoAnna Pendergrass, DVM

Going Viral: The AAV Approach to Curing Cancer

Written by Emily Siebenmorgen

According to Timothy Cripe, MD, PhD, chief of the Division of Hematology and Oncology at Nationwide Children's Hospital, it's an incredible time to be working on cancer treatment — and now, targeted cancer prevention.

"There's so much going on in the cancer world these days," says Dr. Cripe, who is also a principal investigator in the Abigail Wexner Research Institute at Nationwide Children's. "It's a horrible disease, but it's really an exciting time to be doing research with new knowledge, collaborations and an explosion of technology."

Dr. Cripe's team had their own breakthrough last summer when they reported proof-of-principle results for adeno-associated virus (AAV) gene therapy, a novel therapeutic approach that could improve the efficacy of cancer treatments.

Using mice that were injected with human immune cells, they created recombinant AAV vectors that expressed a therapeutic protein that attacked malignant B cells in the bloodstream. The key, Dr. Cripe says, is that this treatment only requires a single intravenous injection to administer.

"We're so excited about this AAV development because it's a single shot that gives you long-term, therapeutic effects," says Dr. Cripe, who's discovery has been licensed by Nationwide Children's to a startup biotech company. "I think that's the magic. Most drugs are episodic – you take a dose, or have an IV, or do a cycle of chemotherapy – and then you need to wait and recover. Even if you take a pill every day, the levels of the drug go up and down in your bloodstream until you take your next pill."

Cripe emphasizes that these "low" periods of medication are what give cancer cells opportunities to thrive.

"During those troughs of treatment, that's when the cancer can figure out how to escape the medicine," Dr. Cripe explains. "That's one of the charms of AAV technology: you get steady levels of medicine for long periods of time. It puts pressure on the tumor in a way that really hasn't been seen before."

The question is: will this technology work in patients?

Scaling Results to Trials in Humans

In their proof-of-principle results, Dr. Cripe's team designed a recombinant AAV vector they termed CD19 TransJoin, which showed reduction of CD19 flank lymphoma volume in mouse models. CD19 is a biomarker for B lymphocyte development – and since it's present on all B cells, it makes a great target for immunotherapies for conditions such as acute lymphoblastic leukemia (ALL).

"Most drugs are episodic ... Even if you take a pill every day, the levels of the drug go up and down in your bloodstream ... That's one of the charms of AAV technology: you get steady levels of medicine for long periods of time.

– Timothy Cripe, MD, PhD, chief of the Division of Hematology and Oncology at Nationwide Children's Hospital

"We are working hard to complete all of the tasks needed to be able to launch a clinical trial for patients with relapsed or refractory ALL. We need to make a clinical-grade version and develop a number of tests we will need for the trial," says Dr. Cripe, who is also a member of the Translational Therapeutics Program at The Ohio State University Comprehensive Cancer Center – James.

Following their results published in *Science Advances*, Dr. Cripe explains that they plan to bring a different version of this therapy into the clinic.

"We made a few changes to make the construct safer and more effective, which took some time."

Beyond safety and efficacy modifications, creating new versions of recombinant AAV therapies is no small feat.

"AAV vectors are complicated to make," Dr. Cripe says. "There are two major steps: making large productions of three different plasmids that contain instructions for making a virus, and then putting them together in cells to actually assemble into a virus. Both steps require expensive, large-scale manufacturing."

Dr. Cripe's team is currently preparing materials to launch a clinical trial.

Developing Targeted Therapies for a Myriad of Blood-Borne Cancers and Solid Tumors

Dr. Cripe's team is also exploring applying their therapies to targeting primary tumor masses, such as neuroblastoma and various sarcomas. Thanks to their tricky defense mechanisms, most tumors require complex immunotherapy regimens beyond the scope of AAV gene therapy alone.

"Solid tumors create problems by creating their own environments," Dr. Cripe says. "Sometimes we think of a tumor's environment as a city, with a lot of different components or buildings. The tumor co-ops other 'normal' cells, recruits them, and turns them into 'bad actors.' It's through commandeering these cells that tumors set themselves up to grow and resist therapy."

So, if solid tumors are like a black hole, sucking in helpful immune cells from the bloodstream for rogue purposes, what if recombinant AAV therapies could target the "bad actors" helping the tumor grow?

"When co-opted by the tumor, macrophages start expressing molecules that suppress T cells and immune responses, helping the tumor grow," Dr. Cripe says. "We are also testing ways we might counteract those effects and enable our therapy to work even better."

Moreover, the sustained, circulating nature of this therapy also makes it ideal for targeting cancers that are found in the bloodstream.

"Beyond leukemias, we are also testing the utility of our therapy for adult blood borne cancers such as multiple myeloma, which we picked because others have identified target proteins we could use for our therapy," Dr. Cripe explains. "The only way we've been able to get this far is by building off of work done by my colleagues using AAV for neuromuscular disorders, and other scientists developing related immune therapies for cancer. My research team and I are standing on the shoulders of those giants."

Cripe TP, Hutzen B, Currier MA, Chen CY, Glaspell AM, Sullivan GC, Hurley JM, Deighen MR, Venkataramany AS, Mo X, Stanek JR, Miller AR, Wijeratne S, Magrini VJ, Mardis ER, Mendell JR, Chandler DS, Wang PY. Leveraging gene therapy to achieve long-term continuous or controllable expression of biotherapeutics. *Science Advances*. 2022 Jul 15;8(28):eabm1890.

Beyond the Wow Factor:
Artificial Intelligence in Pediatrics

What promise do AI and machine learning hold for pediatrics, and how can their potential flourish while still safeguarding children's health and privacy?

Written by Katie Brind'Amour, PhD

Machine learning (ML) and artificial intelligence (AI) have exploded across the worlds of marketing and commerce in recent years. Streaming services track what you watch and suggest other content you may enjoy. Sales algorithms identify your shopping patterns and make age-appropriate toy recommendations for your kids over time. There's also a good chance you've read a sales letter or blog post and never suspected its author was a computer.

As ML and AI enter the world of health care and biomedical research, what are the most promising applications of computer-assisted decision-making, and how far are we from bringing these tools to daily clinical care? Where does the utility of AI end and the threat to human privacy or wellbeing begin? And what issues arise specific to pediatric applications of this technology?

A BRAVE NEW WORLD FOR MEDICINE

Proponents of AI in medicine often refer to the world of computer-based insights as "augmented" intelligence — something supplemental and human-managed that can help improve decision-making, not an entity that operates independently or overrules a physician's decision for patient care. In short, they view it as just another tool in the clinician's tool belt.

This concept of AI is both reassuring and cautionary. It asserts that computer programs are not meant to replace physician judgment in clinical care, while requiring that its users understand AI's findings, their reliability and the best way to utilize them.

At its present best, AI can accurately review a database of histology images and linked clinical data to formulate new prognostic criteria or stratify cancer by subtypes, all by detecting subtle details or drawing big data-based connections not feasible for humans to do manually.

In many other settings, application of this technology is in its nascent stages. At Nationwide Children's Hospital, for example, clinicians and researchers are using ML to figure out how early, subtle changes in coronary blood flow patterns can predict the eventual development of coronary microvascular disease. The idea is that potentially valuable information may be present outside of what physicians can observe in echocardiograms and clinical data to indicate early, potentially modifiable physiological risk factors for future disease.

To this end, Aaron Trask, PhD, FAHA, FCVS, principal investigator in the Center for Cardiovascular Research at Nationwide Children's, and experts including Christopher Bartlett, PhD, principal investigator in the Steve and Cindy Rasmussen Institute for Genomic Medicine at Nationwide Children's collaborate to "train" their imaging-based ML model. This involves adjustments to the model so that it doesn't rely purely on known risk factors for microvascular disease (such as diagnosed diabetes in the clinical file) but goes beyond, to data that humans may not be able to identify. It requires a large data set — gathered meticulously over several years and hundreds of imaging studies — and a lot of patience as the model learns to ignore things, such as the black space in the background of an echocardiogram image.

"Everything had to be analyzed in the traditional way and then fed into the data system, and then there has been a lot of back and forth to make sure the model has what it needs to learn something useful," says Dr. Trask, who has been working with Dr. Bartlett and William Ray, PhD, an expert in data visualization at Nationwide Children's, for several years to optimize the model. The latest improvements are described in *Scientific Reports*.

"At the end of the day, clinicians need to understand what factors the model is using to make its predictions," says Dr. Trask. "It can't be a black box to them, or physicians won't be able to rely on it for their own decision-making."

Beyond the contribution to accurate, informed decisions via better image processing and predictive profiling, ML and AI offer the opportunity to reduce clinician workloads and even enhance the care experience for patients.

Through a technique called natural language processing (NLP), advanced ML and AI applications are being trained to identify key details from in-office conversations for consolidated inclusion in medical records. According to Emre Sezgin, PhD, principal investigator in the Center for Biobehavioral Health at Nationwide Children's, NLP techniques could not only save physicians and medical assistants hours each day in note-taking, they may also be used to identify and call to attention historical notes that could be relevant to an in-progress or upcoming consultation.

NLP exploration of notes in medical records can also reveal valuable community- or population-level insights: patterns in pre-diagnostic symptoms for a particular disease, implicit bias on behalf of providers and even age-, gender- or ethnicity-based trends in describing certain symptoms that can be used to help physicians identify problems earlier in the disease course.

Beyond these applications, ML and AI are exploding in niche areas of medical science, from genomic analysis to truly personalized oncology therapy. What remains to be seen is which of the many forms of these technologies will end up in the clinic once factors of infrastructure, cost, patient acceptability, regulatory approval and clinical utility are defined.

PRACTICAL ADOPTION OF AI IN PEDIATRICS

As with most technologies, AI and ML have pros and cons. For example, ML requires many more data points than might be expected in order to come up with valid insights.

"I could train a 7-year-old to identify new things with three or four images," says Dr. Bartlett. "But it can take tens of thousands of images or data points to train a machine learning model to reach the same conclusion, because it looks at absolutely everything and has to learn the hard way what is important and what isn't."

For adult cancers with common mutations, large data sets are relatively easy to obtain. But for children, who rarely get cancer and who tend to have unusual mutations, there may be very few samples or data points with which to train a model. This necessitates collaboration, and collaboration necessitates a common framework for structuring the data.

Enter the Bridge2AI Program, an initiative funded by the National Institutes of Health Common Fund to advance the infrastructure and processes by which AI can usher in the future of biomedical research. Top among the program's goals are the generation of data sets that are appropriately set up for AI applications and the development of best practices for the application of ML and AI.

"We are building standards across broad segments of the biomedical domain to make data sets interpretable for computerized learning," says Alex Wagner, PhD, principal investigator in the Institute for Genomic Medicine at Nationwide Children's and a co-lead of the Bridge2AI coordination center standards core.

His efforts involve development of standards to structure and annotate data sets so that, from institution to institution, certain key structures or elements remain

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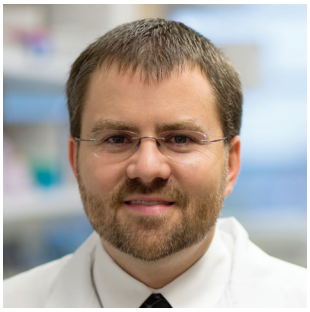
>
> – **Aaron Trask, PhD, FAHA, principal investigator in the Center for Cardiovascular Research at Nationwide Children's Hospital**



> When we implement AI in health care settings, we have to be extremely diligent. We need to know the weaknesses up front, watch it at every step, and build in complete transparency. Even after we have a model that we think is good enough, we implement it in the background and monitor it another 6 months to make sure it does what we want it to do."
>
> – **Christopher Bartlett, PhD, principal investigator in the Steve and Cindy Rasmussen Institute for Genomic Medicine at Nationwide Children's Hospital**

the same and can be used by ML or AI to navigate and interpret the data.

"It's an enormous undertaking to invest in AI from the ground up, not just in the data standards we are working on in the Global Alliance for Genomics and Health," Dr. Wagner says. "Bridge2AI also has experts working to create foundations for AI's ethical use, the ability to identify bias in data sets, accessibility for research, and much more. I think it bodes very well for our ability to mine these data for insightful, AI-based discovery down the road."

Even seemingly basic applications of AI require carefully designed infrastructure and data features. And of course, they must be highly accurate and fit for purpose in order to be ethical and useful.

"When we implement AI in health care settings, we have to be extremely diligent," says Dr. Bartlett, who has painstakingly worked to design and deploy Nationwide Children's electronic health record (EHR) ML program. "We need to know the weaknesses up front, watch it at every step, and build in complete transparency. Even after we have a model that we think is good enough, we implement it in the background and monitor it another 6 months to make sure it does what we want it to do."

Only after thorough, prospective trial periods does his team release ML-based features in the EHR system. Examples of successful efforts already in practice include early prediction of sepsis, which tripled the average number of days between sepsis-related emergent transfers to the pediatric intensive care unit, and automation of predictive assessments for cardiac arrest, which matched predictive accuracy of a manual early warning tool 2 hours before a cardiac event.

These improvements, published in *Pediatric Quality & Safety*, are in good company; ML has also improved prediction of families at high risk for no-shows in a neurology clinic (published in the *Journal of Child Neurology*) and dramatically reduced in-hospital deterioration events at Nationwide Children's (published in *Pediatric Critical Care Medicine*).

These applications are just the tip of the iceberg, though. Drs. Trask, Bartlett and Ray are also collaborating on work that could hit the clinic relatively soon: ML-based analysis of blood flow imaging to predict fetal growth restriction (FGR) before symptoms emerge.

"In prenatal ultrasounds, clinicians already look at blood flow through the umbilical cord," explains Dr. Trask, who has joined forces with Mark Santillan, MD, PhD, an obstetrician at the University of Iowa with about 63,000 ultrasound files. "If by clicking a button during a routine ultrasound an obstetrician can find out whether this pregnancy is at heightened risk for complications due to FGR, that's a no-brainer addition to practice. It would immediately change that pregnancy's management."

Other potential applications to clinical practice may also become available sooner rather than later.

"ML models are already helping us classify tumors from epigenomic assays, but soon it could feasibly offer decision support for variant interpretation as well," Dr. Wagner suggests. "It could predict how patients will respond to therapeutics and prompt data requests to help improve its prognostic ability, perhaps by suggesting what other test results it needs to be more useful for a patient."

This type of interactive, personalized medicine comes at a price, of course, and has some specific hurdles to overcome before its widespread implementation in the world of pediatrics compared to adult medicine.

A CHILD-FOCUSED APPROACH TO AI

Three key factors distinguish AI in pediatrics from its use elsewhere in health care: reconsenting as children age so that data may continue to be used ethically; aging and its implications for ML modeling accuracy; and the complexity of source data.

Consent

When working with pediatric data that was obtained via parental consent, it is important to note that approval for use of their data is re-obtained when children reach the age of consent. This potentially limits its use — or at the very least requires strict monitoring of consent status — over time.

For applications of ML in EHRs, long-term access to files will also dictate how well programs can train language processors and track how kids' health indicators change with age. The concept of change over time is critical for a variety of pediatric-specific conditions and opens another, more nuanced area of difference from adults: the importance of growth.

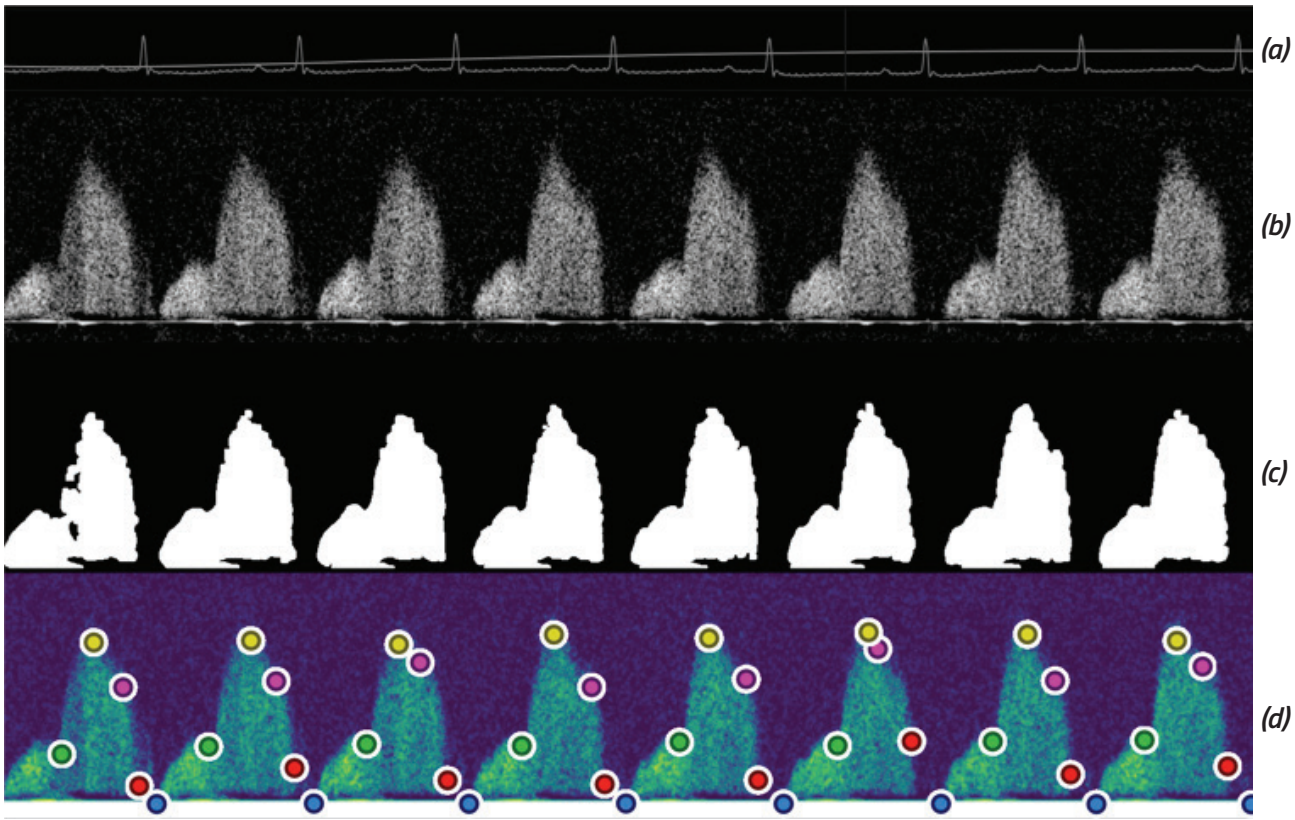
Growth and Aging

"For kids, three years is the difference between no head control at all and running all over the place, whereas adult health is usually fairly stable within that same amount of time," says Dr. Bartlett.

This growth factor adds a layer of complexity to any analysis done in children: how does their data change as they age, and what does that mean for the models being developed?

Data Complexity

These challenges are compounded by extra inputs into medical records and more frequent changes in providers. In most adult records, for instance, files include notes only from the patient and the clinician. With children, there may be notes from parents or other caregivers,



These electrocardiogram (ECG) and Doppler echocardiogram images were collected and analyzed as part of Dr. Trask's collaborative and ongoing ML-based analysis of blood flow in order to predict microvascular disease. Details on the study's findings were published in Bossenbroek et al, Scientific Reports, 2022 May 6;12(1):7490. ***(a)*** *ECG tracing output from mouse studies* ***(b)*** *Raw Doppler echocardiogram output of mouse coronary blood flow* ***(c)*** *Automated Doppler envelope extraction by the team's software program* ***(d)*** *Inflection points of the Doppler that the automated ML program uses to extract data regarding the "envelope," or mountain-shaped patterns, indicating blood flow*

> We are failing to serve vulnerable populations in the health system, and this problem doesn't go away when we apply AI downstream. These technologies will only reflect the quality of the data they receive — they won't serve everyone unless the health care system does a better job of creating fair, equitable, representative medical data first."
>
> – Emre Sezgin, PhD, principal investigator in the Center for Biobehavioral Health at Nationwide Children's Hospital

clinicians, the children themselves, numerous subspecialists and even teachers or social workers.

"When we merge all of these data sources together, it is harder to come up with accurate predictions," says Dr. Sezgin, who specializes in analyzing the health care applications of AI and recently published in *The Lancet Child & Adolescent Health* on its ethical use in pediatrics. "Many applications of ML and AI employ models that were trained using publicly available adult data sets, since pediatric data sets are less accessible due to higher standards for privacy and security. These higher thresholds for protection are appropriate, but they mean that translating those models for accurate predictions in pediatric care is challenging."

As children age, they frequently transition among facilities and, eventually, to adult providers. This can result in gaps in records or a large volume of notes to examine for insights. The result of all of these factors is a dramatic increase in data diversity and availability challenges, as well as much greater burden for NLP applications, making it difficult to tease out what weight to give the different inputs and what to do if certain inputs are missing.

A PRODUCTIVE, ETHICAL AND EQUITABLE FUTURE FOR AI

Regardless of the data source, Dr. Sezgin urges caution.

"Using AI is like teaching a little kid: you need to show them how to behave correctly, like stopping at a red light," he says. "If you don't train them properly, it could be dangerous for the child and everyone else. Likewise, these tools have great potential for pediatric settings — if they are employed with a careful team to guide them in the right direction."

This guidance involves placement of safety and privacy parameters on accessible data as well as understanding the inherent limits of AI. After all, it can only be as accurate as the data it has on hand.

Just as prediction models trained by adult data sets fall short for predictions in pediatrics without new data to improve the model, data sets with limited information about minority populations have been shown to be less effective at predictions for those populations. Unfortunately, pediatrics faces the same challenge as adult medicine in this regard: inequities in care access and research participation result in fewer data sets available for minorities.

"We are failing to serve vulnerable populations in the health system, and this problem doesn't go away when we apply AI downstream," says Dr. Sezgin. "These technologies will only reflect the quality of the data they receive — they won't serve everyone unless the health care system does a better job of creating fair, equitable, representative medical data first."

That said, Dr. Sezgin does believe AI can help improve the health system itself if applied strategically. His Chatbot for Social Needs project, funded by the Health Resources and Services Administration, uses conversational AI to address families' social needs, able to contribute to medical records with patients' self-reported health information and communicate with providers. The project aims to address social determinants of health, improve shared clinical decision-making and advance preventive medicine.

While experts in biomedical ML and AI projects temper their enthusiasm with caution, one thing is consistent across the board: an expectation that computer-based algorithms will revolutionize the way clinicians spend their work day, the way that pediatric patients experience their care, and the way improved outcomes and new discoveries are achieved.

At Nationwide Children's, the commitment to meeting challenges and surpassing expectations in the AI frontier is evidenced by the appointment of Peter White, PhD, as the inaugural chief data science officer at AWRI.

As a member of the AWRI senior leadership team, Dr. White will be responsible for building and executing a comprehensive data science strategy across AWRI, including the integration and analysis of disparate big data sources such as genomic and electronic health record data as well as using artificial intelligence and machine learning techniques to derive insights for the diagnosis and treatment of pediatric diseases. He will oversee a team of data scientists, software developers, cloud engineers, data architects, analysts and other professionals to support these efforts.

"In his new role as CDSO, he will work to empower our research community with cutting-edge data science capabilities and promote a culture that values making data accessible, removing barriers to access, and promoting transparency, collaboration and information sharing," says Dennis Durbin, MD, MSCE, president of AWRI. "His leadership in biomedical data science will substantially support Nationwide Children's mission as a leader in pediatric health care innovation."

As the infrastructure and data sources fall into place, the time is right for well-informed, collaborative experts to begin harnessing the potential of these tremendous resources, while keeping pediatric-specific considerations in mind. With patience and due diligence, it's not a matter of whether these tools will transform the practice of medicine, but when.

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Visit **PediatricsNationwide.org/NLP-GPT-3** to find out how investigators at Nationwide Children's are advancing the latest in NLP, GPT-3 and other exciting health care uses of AI.

Talking Through ML and AI

Understanding the terminology used for the field of computer-based learning and its solutions is essential to interpreting the latest advances and how medical applications of these technologies differ from (and overlap with) common uses of AI in the commercial world.

ARTIFICIAL INTELLIGENCE (AI)

Machine- or computer-based analysis of data to synthesize information and draw inferences in a way that simulates human intelligence, but with volume processing and pattern perception capacity beyond human capabilities

CONVERSATIONAL AI

These interfaces exist at the intersection of ML, AI and NLP. They enable computer-generated, interactive conversations with human users. Familiar examples include website chat-based support services, Apple iPhone's Siri and Chatbots, which respond to a wide variety of natural language inputs and can be customized for different applications, including health services.

NLP WITH A PURPOSE

More complex applications of NLP include DeepSuggest — developed by researchers at Nationwide Children's—and Generative Pretrained Transformer (GPT) models.

DeepSuggest is an AI-driven, neural network-type language mining assistant used to interactively explore clinical data and improve its utility by generating queries and offering suggestions to improve keyword searches.

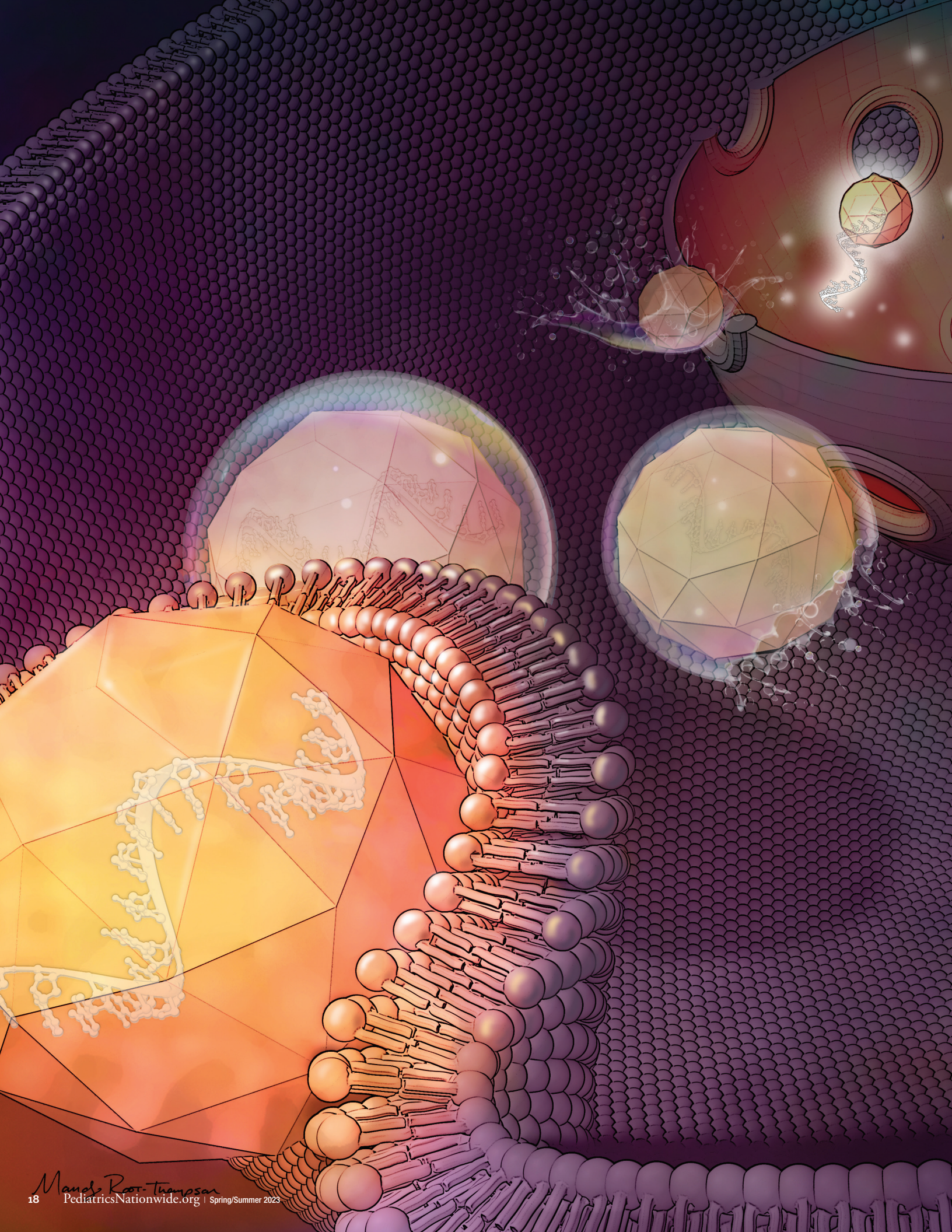
GPT models use AI and NLP to construct text that appears to be written by a human; the latest model is GPT-4, which can write essays and answer questions with little training.

MACHINE LEARNING (ML)

Computer use of data, statistics and algorithms to find patterns in data, analyze them and draw inferences from them; a simple form of AI

NATURAL LANGUAGE PROCESSING (NLP)

Use of ML or AI to study written or spoken human communications (conversation, notes, social media posts, publications) for patterns and insights



Micro-dystrophin: A Small Gene With BIG PROMISE

SRP-9001 FOR DUCHENNE MUSCULAR DYSTROPHY SUPPLIES A FUNCTIONAL DYSTROPHIN GENE VIA AAVRH74 GENE THERAPY.

Written by Abbie Miller

In 1969, Jerry Mendell, MD, was working at the National Institute of Neurological Disorders and Stroke (NINDS) when he saw his first patient with Duchenne muscular dystrophy (DMD).

DMD, a severe form of muscular dystrophy caused by a mutation in the DMD gene and resulting in a lack of the dystrophin protein, leads to muscle weakness and atrophy. DMD is an X-linked condition and, as such, typically affects boys.

Since that day, Dr. Mendell has been on a mission to develop new treatments for patients with DMD and other neuromuscular diseases. His track record is impressive, with advances in understanding how corticosteroids can improve outcomes for children with DMD and pioneering work in adeno-associated virus (AAV)-mediated gene therapy. He led the team behind the first systemically delivered AAV gene therapy to be approved by the U.S. Food and Drug Administration (FDA) — Zolgensma®, which offers life-changing outcomes for children with spinal muscular atrophy (SMA).

His next achievement may bring him full circle — back to offering a potentially life-changing therapy for children with DMD.

"Since I began investigating gene therapy as a potential treatment for children with neuromuscular disorders, it's been my dream to develop a gene therapy for DMD," says Dr. Mendell, neurologist and principal investigator in the Center for Gene Therapy in the Abigail Wexner Research Institute at Nationwide Children's Hospital. "To this point, we've had very little to offer these families. Until recently, our only approved treatment for Duchenne muscular dystrophy has been glucocorticoids, such as prednisone. Our research aims to see if gene therapy is a safe and effective option for these patients and others with rare neuromuscular diseases in the future."

Delandistrogene moxeparvovec, known as SRP-9001, which Dr. Mendell co-invented with Louise Rodino-Klapac, PhD, formerly at Nationwide Children's and presently the executive vice president, head of R&D and chief scientific officer at Sarepta Therapeutics, is a novel DMD gene-replacement therapy currently in

clinical trials. Sarepta Therapeutics licensed this gene therapy program from Nationwide Children's in 2018, and recently filed a Biologics License Application (BLA) with the FDA in the fall of 2022.

Building the Therapy That Would Become SRP-9001

Gene therapy for DMD has been a long time coming. Dr. Mendell always begins his talks with a history lesson.

Gene therapy was first proposed by Theodore Friedman about 50 years ago, with the first clinical trials beginning in the 1990s. Gene therapy research nearly ground to a halt in 1999 after the tragic and high-profile death of a patient named Jesse Gelsinger and a rash of leukemia cases linked to insertional mutations caused by retrovirus vectors. Gelsinger was treated with an adenoviral gene therapy and died because of a massive inflammatory response. In light of these setbacks, the future of gene therapy looked bleak.

Hope for gene therapy was renewed when researchers began using adeno-associated virus (AAV), instead of adenovirus or retrovirus, vectors as the vehicle of choice for systemic gene therapy. AVV is a small virus, about 25 nm, made of a nonenveloped protein shell and containing a linear single-stranded DNA genome of about 4.7 kb (kilobase, a measure of length equal to 1,000 base pairs).

One of the challenges of developing an AAV-mediated gene therapy for DMD is the sheer size of the DMD gene. The DMD gene's cDNA is about 11.5 kb. That's more than twice as large as the vector's capacity. With the required promoter that activates the gene, the transgene is 14 kb.

Drs. Mendell and Rodino-Klapac developed a shortened functional dystrophin gene, a micro-dystrophin, that would fit inside the AAV vector and produce a dystrophin protein that contains functional components of wild-type dystrophin in order to provide clinical benefit.

Their proposed therapy would work like this: when delivered via AAV vector, the micro-dystrophin gene would enter the muscle cells and be translated into a functional protein, which was missing from the DMD muscle cells.

To determine if the idea would work, preclinical studies were done to show if administering the therapy intravenously would change the amount of dystrophin in the muscle cells. If they administered the therapy and the muscle cells did not show increased dystrophin — they would be back to the drawing board.

Dr. Rodino-Klapac has been working on this therapy for nearly two decades. She says one of the first moments that stands out in her memory of working on the therapy was the first time she observed SRP-9001 protein expression localized to the membrane of muscle fibers.

"I recall running to bring Dr. Mendell to the microscope room to share in the moment," she says.

The therapy they developed uses AAVrh74 as the vector, MHCK7 as the promoter, and a shortened functional SRP-9001-dystrophin gene. The shortened functional gene was inspired by a 2002 *Nature* publication by Scott Harper, PhD, and team reporting on internal truncated dystrophin genes found in Becker muscular dystrophy patients. Dr. Harper's work eventually led him to other areas of science — specifically studying RNA interference as a therapy for dominantly inherited genetic disorders — but his early research on various small dystrophins has persisted.

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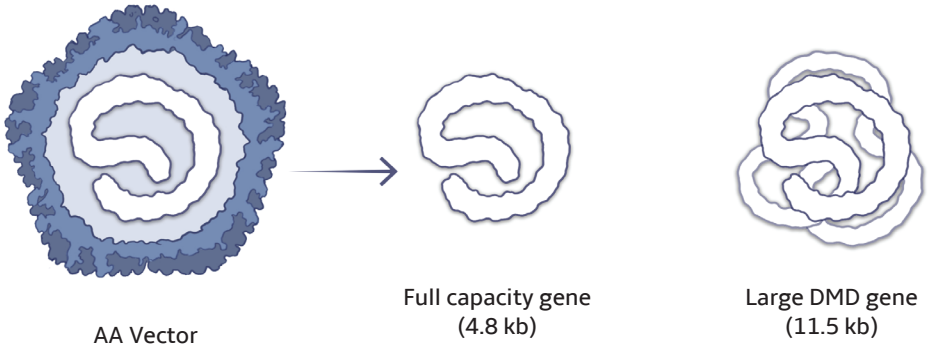
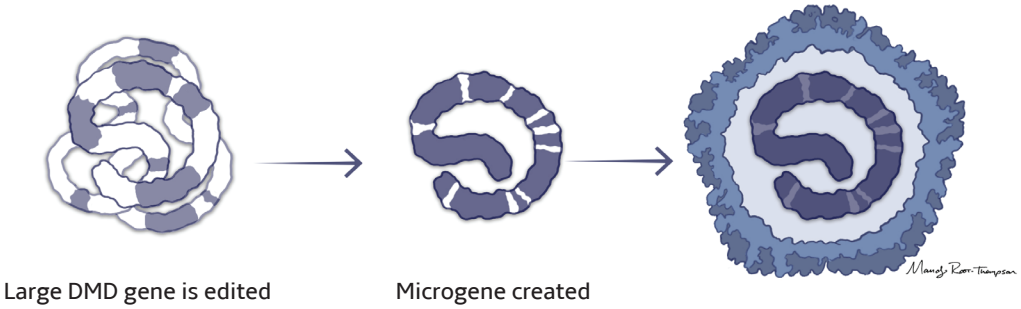
>
> – Jerry Mendell, MD, neurologist and principal investigator in the Center for Gene Therapy in the Abigail Wexner Research Institute at Nationwide Children's Hospital

Making Gene Therapy Work for a Large Gene

Small Vector, Large Genes
AAV vectors have a capacity of 4.87 kb. In contrast, the coding DNA for the DMD gene is roughly 11.5 kb - about twice the capacity



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



"It's a fun fact that I like to share," says Dr. Mendell. "Dr. Harper works at Nationwide Children's now, and though we never collaborated on this gene therapy product, and our research focuses on very different diseases and approaches, there's this connection."

"We used AAVrh74 for a few reasons," says Dr. Mendell. "First, we had isolated it here at Nationwide Children's, so it was accessible. Second, it had very good distribution into all types of muscle, including skeletal, heart and diaphragm. Third, as an AAV derived from non-human primates, the percentage of the population with pre-existing antibodies is low."

In an early safety study of a mini-dystrophin gene therapy at Nationwide Children's, the team discovered an unexpected wrinkle that could thwart their hopes for gene therapy success.

The discovery was published in 2010 in the *New England Journal of Medicine*. A patient participating in the gene therapy trial had a large DMD gene mutation with deletion of exons 3-17. The mini-gene used in this trial was delivered to the patient's arm muscle. When the gene expressed the mini-dystrophin protein, an immune response was elicited. An important lesson for future trials: do not transfer a gene that can express a novel protein and cause an immune response from the patient. For investigational DMD gene therapies, patients with exon 3-17 deletions were frequently excluded from clinical trials.

Bringing SRP-9001 to Clinical Trial

SRP-9001-101 was the first phase 1 study of a systemic gene therapy for DMD. It began in 2018, and the first-year results were published in *JAMA Neurology* in 2020. The rationale for the study used evidence from preclinical studies as well as learnings from the then newly approved Zolgensma®.

Dosing was set at 2×10^{14} vg/kg (vector genomes per kilogram of bodyweight) for the first trial. This is the

INFUSION DAY

Infusion protocols for gene therapies have evolved as the trials have proceeded. While the first SRP-9001 infusions at Nationwide Children's were done in the pediatric intensive care unit, they are now performed as an outpatient procedure. The infusion process typically takes under two hours. Continuous monitoring and supportive care helps ensure safe and successful delivery.

At Nationwide Children's, the clinical research team has administered more doses of systemic gene therapy than perhaps anywhere else. As a result, they have a system that has been refined by experience and expertise.

When a child comes in for gene therapy at Nationwide Children's, they have an IV placed in each hand. One is used for saline to maintain hydration, since participants are typically told not to eat or drink for four hours before the infusion. The other IV is for the infusion. The added bonus of the second IV is that if one fails, the infusion can be moved over to the second without disrupting the infusion time.

The infusion at Nationwide Children's typically takes 60-90 minutes. Slower infusions typically produce more optimal results, according to Dr. Mendell.

The team at Nationwide Children's also has a protocol for their patients that includes exercising the extremities during the infusion. By gently moving the shoulders, elbows, hips, knees and ankles every 10 minutes in rotation during the infusion, the team enhances by increasing the blood flow to the exercising muscles, says Dr. Mendell.

"Our center's results have been excellent, and we hope to be able to share our experience so that our protocols and techniques can help children receiving their infusions elsewhere," says Dr. Mendell.

> These families so desperately want to find significant treatments for their boys with Duchenne muscular dystrophy and give them a longer life with better quality of life. SRP-9001 appears to be significant, based on study results published so far. Providers can help to manage expectations of what the potential is for the individual child and continue to manage their overall care needs."
>
> – Kelly Lehman, MSN, CRN, at Nationwide Children's Hospital

same dosing as used in Zolgensma, but Zolgensma is only approved in infants and children up to 2 years of age. Using this dosing for older children required a lot more vector and potentially increased the risk of toxicity.

"This is a huge amount of vector," says Dr. Mendell. "Groups that are still using AAV9 are experiencing trouble with toxicity at this level. Our choice to use AAVrh74 has turned out to be a big piece of our ability to minimize toxicity."

The first trial targeted children aged 4 to 7 years. This is the age range when DMD symptoms really start showing. While the evidence points to "the earlier the better" for gene therapy for SMA, treating infants with DMD would have required nearly a decade of observation to find out if it worked. By treating children who were not yet or just beginning to show symptoms and following them for five years, the research team would have the fastest, safest and most efficient way to test the effect of the therapy on clinical outcomes.

Finally, because of a potenial risk for transgene immunity, participants with mutations exclusively in exons 18-58 were included.

"Our first trial showed robust micro-dystrophin in the muscle fibers of the calf muscle in all participants," says Dr. Mendell. "And even more exciting, they experienced no toxicity!"

"When we saw the first signs of clinical functional benefit in patients with Duchenne, it was a truly rewarding, humbling experience," adds Dr. Rodino-Klapac.

After the initial success of the 101 clinical trial, the researchers were excited to expand their work.

Expanding Clinical Studies and Gathering Results

Additional studies of SRP-9001, including SRP-9001-102, SRP-9001-103 (ENDEAVOR), and SRP-9001-301 (EMBARK), are underway. EMBARK is a global, randomized double-blind placebo-controlled study with results expected at the end of 2023. An additional study in older and non-ambulant individuals with Duchenne, Study SRP-9001-303 (ENVISION), is planned to start later in 2023.

"Through our clinical development program for SRP-9001, Sarepta has dosed over 140 individuals with Duchenne across a wide range of disease progression," says Dr. Rodino-Klapac. "As a result, we have a comprehensive data package with biologic and clinical data from multiple studies of SRP-9001. The data shows a compelling story of the safety, efficacy and durability of SRP-9001."

Across all the clinical studies to date, the safety profile of SRP-9001 has remained consistent and manageable, she adds.

After validating the expression of the micro-dystrophin in the muscle tissue, the researchers have also monitored functional improvements.

One tool that is the established best practice for measuring motor function is the North Star Ambulatory Assessment (NSAA). The 17-item rating scale evaluates how well a child can perform a range of functions, including walking, running and getting up from a reclined or lying position.

Across three independent SRP-9001 studies, the team saw meaningful and statistically significant improvements in NSAA, ranging from a 3.8-point improvement at 1-year

post-dose to a 9.9-point improvement, when compared to the propensity-score-weighted external control, at 4 years post-dose, according to Dr. Rodino-Klapac.

The 3.8-point improvement was observed in study SRP-9001-103, an open-label clinical trial, and among a cohort comprised of patients ages 4 to 7 who are ambulatory. The nearly 10-point improvement was observed in study SRP-9001-101, the initial single-center study.

"This data is especially meaningful to me because Duchenne is a disease that gets progressively worse," says Dr. Rodino-Klapac. "Around age 9, these boys would typically be in the steep decline phase of their disease, losing skills and declining about three NSAA points per year. But instead of declining, the data showed the boys in that study not only increased their function but maintained the higher score over the course of the 4-year observation."

"I have been with all of these trials from the start. It has been very exciting to see the progression as we have moved through the studies. We started with boys ages 4-7 with select mutations. Since then, we have been able to include in clinical trials younger and older boys with a wider variety of mutations, as well as ambulatory and non-ambulatory boys. We have worked with so many wonderful families and it has been a truly gratifying experience," says Kelly Lehman, MSN, CRN, a research nurse practitioner in the Center for Gene Therapy.

Next Steps

Study SRP-9001-303 will have boys older than 8 years old who are both ambulatory and non-ambulatory.

"While most of the SRP-9001 trials have focused on younger boys, we are exploring the safety and effectiveness of the therapy in patients who are older or non-ambulatory," says Dr. Rodino-Klapac. "Our aim is to expand the availability of SRP-9001 to a larger percentage of the Duchenne population."

To even further expand the number of patients who could potentially benefit from the therapy, finding a way to narrow the early-exon mutation exclusions is a logical next step. According to Dr. Rodino-Klapac, Sarepta has already begun a study to do just that.

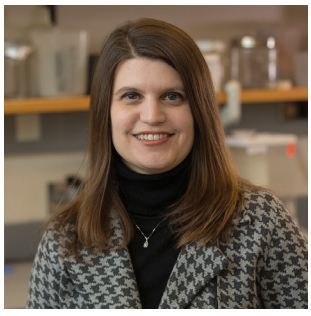
"We are investigating what our research informs us are low-risk mutations in the currently excluded range," she says.

Additional work is focused on expanding access to the therapy for people who have pre-existing antibodies to the viral vector used in the gene therapy.

"SRP-9001 uses AAV to deliver missing or corrected genes to cells. Patients who have pre-existing IgG antibodies are not currently eligible for treatment because the antibodies interfere with the therapy's ability to reach the target cells and work as designed," Dr. Rodino-Klapac says.

According to Dr. Rodino-Klapac, approximately 14% of patients with DMD have pre-existing AAV antibodies

> "This data is especially meaningful to me because Duchenne is a disease that gets progressively worse, these boys would typically be in the steep decline phase of their disease, losing skills and declining about three NSAA points per year. But instead of declining, the data showed the boys in that study not only increased their function but maintained the higher score over the course of the 4-year observation."
>
> – Louise Rodino-Klapac, PhD, formerly at Nationwide Children's and presently the executive vice president, head of R&D and chief scientific officer at Sarepta



> At the end of the day, where we are in this field is something I'm incredibly proud of. We've accomplished a lot in gene therapy in the last few years, and while there's still work to do — expanding newborn screening for DMD, addressing treatment options for patients with preexisting antibodies and eliminating the exon exclusions — we're on our way,"
>
> – Jerry Mendell, MD, neurologist and principal investigator in the Center for Gene Therapy in the Abigail Wexner Research Institute at Nationwide Children's Hospital

directed against the AAV used in SRP-9001. To meet this population's needs, her team is studying a potential pre-treatment that could inhibit the reaction of those IgG antibodies.

If this pretreatment is successful, it could offer a way to expand the accessibility of other AAV-based gene therapies to patients for whom the promise of gene therapy remains out of reach.

Waiting for the FDA

The FDA decision, which could mark the first approved gene therapy for the treatment of DMD, is expected in late May. While families await news of approval and what restrictions will be set around the therapy's use, Lehman says that health care providers can offer important insight and communication with families interested in participating in trials or getting a (hopefully) commercially available therapy in the future.

"These families so desperately want to find significant treatments for their boys with Duchenne muscular dystrophy and give them a longer life with better quality of life," says Lehman. "SRP-9001 appears to be significant, based on study results published so far. Providers can help to manage expectations of what the potential is for the individual child and continue to manage their overall care needs."

Dr. Mendell is looking forward to a brighter future for children and families with DMD.

"At the end of the day, where we are in this field is something I'm incredibly proud of. We've accomplished a lot in gene therapy in the last few years, and while there's still work to do — expanding newborn screening for DMD, addressing treatment options for patients with preexisting antibodies and eliminating the exon exclusions — we're on our way," says Dr. Mendell. "I think the future looks bright. We're very excited to see what happens next."

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Placing **Value** on a Pediatric Surgeons' Academic Work

The addition of an academic RVU system to an existing work RVU-based incentivization plan boosted academic productivity in the Department of Pediatric Surgery at Nationwide Children's Hospital.

Written by Mary Bates, PhD

At many institutions, physicians and surgeons are compensated using a productivity formula based on work relative value units (wRVUs). wRVUs commonly quantify clinical work, practice expenses and professional liability costs.

However, physicians and surgeons conduct many valuable activities in addition to clinical work, including scientific discovery and education of future generations. While physicians are reimbursed for wRVU productivity, such academic work is typically not incentivized.

In the Department of Pediatric Surgery at Nationwide Children's Hospital, bonuses were mainly linked to clinical wRVUs until 2012. That year, Gail Besner, MD, assumed the role of chief of Pediatric Surgery and redesigned the incentivization process to also include academic RVUs (aRVUs). These additional aRVUs incentivize activities including grant submissions and funding, peer-reviewed publications, national presentations, National Institutes of Health (NIH) Study Section participation, education and mentoring activities, research awards, patents filed, national committee member participation and chairing, national site visits conducted, and faculty and trainee research awards. The weighting of wRVUs and aRVUs for each faculty member is based on the individual's clinical full-time equivalent (cFTE), such that every faculty member has a personalized ratio of both work and academic RVUs.

"The way that a surgeon or any physician is going to be able to impact patients for generations to come is through research, whether it is basic science, clinical, translational, or quality improvement research," says Dr. Besner. "For that, they need protected research time — some time when they are not in the clinic or operating room where they can think about their research and academic goals. And that won't happen if one's whole entire incentive is based on wRVUs."

Recently, Dr. Besner led an effort to evaluate the Department's academic progress since the inception of the aRVU system. In a study published in the *Journal of Pediatric Surgery*, she and student coauthor Nicole

Brigstock analyzed how adding an aRVU scoring system to the existing wRVU-based incentivization plan impacted academic productivity among faculty members.

"One of my goals was to make Nationwide Children's Department of Pediatric Surgery into a nationally and internationally recognized powerhouse of pediatric surgery," says Dr. Besner, who is also a professor of surgery and pediatrics at The Ohio State University College of Medicine. "One way to do that is to build your research programs."

The results confirmed Dr. Besner's hopes. During the study period, academic productivity soared: External federal funding increased sevenfold. Annual number of publications increased from 24 to 140, and annual national presentations nearly doubled. Faculty members and their trainees received more competitive research awards; 41 at the time of publication.

What's more, the increase in academic productivity did not adversely impact clinical work productivity. During the same study period, wRVUs increased by 8%.

Along with the new emphasis on academic productivity came new hires, such as Peter Minneci, MD, MHSc, co-director for the Center for Surgical Outcomes Research at Nationwide Children's. He joined Nationwide Children's in 2011 to help build a clinical research focus. He says the aRVU system was not only supportive of his research goals, it also elevated the academic productivity of all of the pediatric surgeons, not just the researchers.

"Even a full-time clinical surgeon has some academic components to their incentive matrix, though it may represent a smaller percentage of it than mine," says Dr. Minneci. "But there is still an academic component, which suggests to the entire division that academics is valued and worthwhile. It motivated everyone in the Department to become more academic."

Dr. Minneci says the strength of the aRVU system is in the way it values academic work.

"The system uses actual quantitative methods to value academic contributions to the mission of the Department in a way that is objective and clearly defined," he says. "This helps make sure that faculty members realize that both clinical and academic work are valued, and it allows for people to quantitatively see their productivity in different realms of their work."

The Department's aRVU system is attracting attention from surgeons across the country. According to Dr. Minneci, other institutions with academic missions can learn from Nationwide Children's example and implement similar systems.

"For other university-affiliated, academic, children's hospitals, this is a great way to value the research being done and encourage your surgeons to be more academically productive," he says.

Dr. Besner agrees.

"A lesson to learn is that it is really important to pay attention to what a faculty member's goals and aspirations are, and to create an environment that optimizes their ability to reach those goals," she says.

"With this system, you not only get incentivization for your clinical output but for your academic output as well. That's important in helping faculty members avoid burnout, feel recognized, and understand that their research work is as important as what they do in the operating room."

Brigstock NM, Besner GE. Development of an academic RVU (aRVU) system to promote pediatric surgical academic productivity. *Journal of Pediatric Surgery*. 2022 Jan;57(1):93-99.

"The way that a surgeon or any physician is going to be able to impact patients for generations to come is through research, whether it is basic science, clinical, translational, or quality improvement research. For that, they need protected research time — some time when they are not in the clinic or operating room where they can think about their research and academic goals. And that won't happen if one's whole entire incentive is based on wRVUs."

– Gail Besner, MD, chief of Pediatric Surgery at Nationwide Children's Hospital

Advancing Genomics-Driven Precision Medicine in the NICU

Written by Natalie Wilson

According to the Children's Hospitals Neonatal Consortium, as many as half of newborns hospitalized in level IV neonatal intensive care units (NICUs) due to critical illness have an underlying genetic condition. Most don't get their diagnosis for months or even years. However, clinical assays, new testing modalities and clinical trials are improving their care.

Advanced Technology Speeds Diagnosis

Thanks to technological advancements in sequencing technologies over recent decades, the genetic basis for a growing number of rare, monogenic diseases has been discovered and genetic conditions can now be diagnosed much more quickly and cost effectively.

Bimal P. Chaudhari, MD, MPH, a neonatologist and medical geneticist, was recruited to Nationwide Children's to collaborate with other investigators to develop a clinical assay for in-house, rapid-turnaround genome sequencing (rGS) without relying on shipping samples to a commercial lab. The goal was to transform acute and critical care pediatrics by making rapid identification of disease-causing genetic variants part of routine care.

Even when providers are unable to find the cause of these patients' symptoms through routine clinical tests, most are not diagnosed with genetic conditions while admitted to the NICU. However, knowing a child has a specific diagnosis allows their providers to select the best treatment options and may even open doors to clinical trials or emergency, compassionate use of experimental drugs. While adverse drug reactions are a leading cause of morbidity and mortality during routine medical care, genomic information could help clinicians, including those in the NICU, predict those reactions and avoid medications that might cause them in a particular patient. Genomic information can also provide key insight into a child's prognosis, which allows for better definition of care goals.

"While receiving a diagnosis at any point is extremely valuable for families and providers, time is of the essence when waiting on results that impact care," says Dr. Chaudhari.

After spending two years developing the rGS test, according to Dr. Chaudhari, feasibility studies showed the in-house assay provided diagnostic performance

> For years, you really couldn't make a genetic diagnosis in the first week or so of a child's NICU admission. ... Now, you have a technology that can return a result in three to four days in 30-40% of neonates that are tested."
>
> – Bimal P. Chaudhari, MD, MPH, principal investigator in the Steve and Cindy Rasmussen Institute for Genomic Medicine at Nationwide Children's Hospital

indistinguishable from commercial labs while returning results to clinicians sooner. Interviews and surveys of patients, families and clinicians confirmed that there were impacts on care and that there were no discernable harms from the accelerated approach to molecular genetic testing.

The clinical laboratory at the Steve and Cindy Rasmussen Institute for Genomic Medicine at Nationwide Children's is validating this assay while Dr. Chaudhari, who is also a principal investigator in the Institute, works with partners across the hospital to accelerate the use of rGS for all patients.

But Shifting Paradigms Takes Time

"We've gotten to a point where we can do the testing and analysis in 36 hours, but we have identified other challenges," says Dr. Chaudhari. "In medicine, it's not always, 'If you build it, they will come.' We like to think that if you design this shiny new technology and drug, all the right people will realize how great it is and use it, but that's not necessarily the case. It can take years for there to be broad adoption and use of a new tool and a change in care."

A study from Dr. Chaudhari's lab presented at the 2022 Pediatric Academic Societies Meeting showed that while the age at which patients admitted to a Nationwide Children's NICU received a diagnosis has decreased, it can still take months for children with rare genetic diseases to obtain a definitive diagnosis.

In the retrospective study of 22,212 infants admitted to a Nationwide Children's Neonatal Network NICU from 2010 to 2020 and followed post-discharge, one or more genetic tests were ordered for 7.4% of patients, and 17.9% of those tested received a genetic diagnosis. Children born in 2010 received a diagnosis at an average age of 993 days, while children born in 2020 were able to receive a diagnosis at an average age of 93 days. While this represents a 90% decrease over a decade, most diagnoses were still made after patients were discharged.

Dr. Chaudhari says it's important to help physicians understand how and when genomic testing can be helpful and build the infrastructure to make testing more widespread.

"For years, you really couldn't make a genetic diagnosis in the first week or so of a child's NICU admission. Neonatologists have been trained for generations that you need to provide critical care services first, and you could talk to a medical geneticist after a kid was stable. Now, you have a technology that can return a result in three to four days in 30-40% of neonates that are tested, and those results inform care in the majority of cases," says Dr. Chaudhari. "Then the problem becomes, how do you help neonatologists recognize this kind of paradigm shift in how they deliver care?"

Nationwide Children's has made this paradigm shift — integrating genomic medicine into multiple domains of pediatric research and clinical care — a key strategic goal. To that end, Dr. Chaudhari and his team continue working to improve genomic testing, they also aim to document benefits to make genomics salient to non-geneticist health care providers.

Dr. Chaudhari leads multiple studies related to the development, implementation and evaluation of delivery strategies for rapid genome sequencing in acute and critical care settings and medically complex neonatal and pediatric populations. He also chairs the Genomics Focus Group of the Children's Hospitals Neonatal Consortium, which unites over 40 Level IV NICUs across the United States and Canada, and is involved with efforts by the American College for Medical Genetics and Genomics to create evidence-based practice guidelines for rGS in intensive care units.

Metzler M, Antoniou AA, Chaudhari BP. Ten year genetic testing utilization and outcomes trends within a large neonatal network. Pediatric Academic Societies Meeting Poster Presentation. 2022 Apr 22.

More Than a Building: Why Our Expanded Research Facilities Matter for Kids Everywhere

Dennis Durbin, MD, MSCE, President, Abigail Wexner Research Institute

At Nationwide Children's Hospital, we proudly acknowledge the significant role research has in improving patient care and overall child heath. The integration of research and clinical care is at the heart of the hospital's strategic plan — a $3.3 billion investment over the next several years in our commitment to transform health outcomes for all children.

The Abigail Wexner Research Institute at Nationwide Children's is a dynamic, collaborative, state-of-the-art environment for world-class research. More than 200 scientists, 100 trainees and 1,400 employees work together to advance the field of pediatric medicine. We have been a top-10 National Institutes of Health-funded freestanding pediatric research institute for more than a decade and have doubled our NIH funding over the past 5 years.

To do top-tier research, and attract high-quality talent, our teams need access to advanced facilities that support their work. Our facilities are on par with the best in the world, bringing technology, functionality and aesthetics together in a way that supports the work that drives our mission.

Historically, we have made bold investments in our research infrastructure that have resulted in paradigm-shifting work. We were one of the first children's hospitals to build a Good Manufacturing Practices clinical manufacturing facility to develop viral vectors and cell therapy products for preclinical and clinical research. These early efforts contributed to the major advances in gene therapy that we've seen in the past 5 years, most notably with the FDA approval of Zolgensma®, which was developed in these spaces. Now, we're on the brink of even more success. You can see more of our historical commitment to facilities and infrastructure in the timeline on the next page.

This year, our research enterprise has grown to four dedicated buildings, totaling 800,000 square feet, as well as spaces for clinical research in the main hospital. Research Building IV, opening in May 2023, marks the next step in our evolution.

It is fully connected with Research Building III, operating as a single complex. Across the (soon-to-be) green space is a sophisticated, modern conference center. Collaboration is the heart of scientific progress, and our teams work with experts around the world. Our conference facilities open the door for more collaboration and knowledge sharing, ultimately driving pediatric research forward.

Occupants of the Research Building III/IV complex include:

- Center for Injury Research and Policy
- Center for Gene Therapy
- Center for Childhood Cancer Research
- Institute for Genomic Medicine
- Center for Regenerative Medicine
- Center for Perinatal Research
- Center for Cardiovascular Research

Our buildings are full of the brightest minds in their fields, driven by the mission to advance cures and better health for children in our community and those who never walk through our doors. While our researchers are undeniably brilliant, they are also some of the most compassionate people you will meet. A beautiful building is to be celebrated, but our team is our greatest success.

Research Infrastructure Milestones

SELECTED HIGHLIGHTS FROM NATIONWIDE CHILDREN'S RICH RESEARCH HISTORY

1958:
National Institutes of Health awards hospital $180,000 for a research building; a matching contribution from Ross Laboratories sets the stage for the first dedicated research building

1962:
First medical research building on campus, Ross Hall, opens

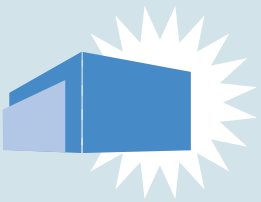
1984:
Children's launches a capital campaign to raise $7.5 million for a new research facility

1987:
The Wexner Center for Pediatric Research opens

1996:
Philip Johnson, MD, named president of Children's Research Institute

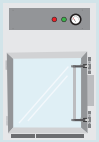
2002:
First Centers of Emphasis named, including Vaccines and Immunity, Cell and Vascular Biology, Injury Research and Policy, Molecular and Human Genetics, Gene Therapy, Developmental Pharmacology and Toxicology, Biopathology, Childhood Cancer

2004:
Research Building II opens



2005:
John Barnard, MD, becomes president of the Children's Research Institute

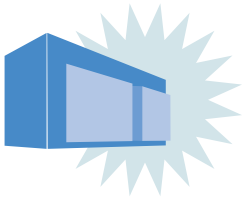
2006:
First Good Manufacturing Practice Clinical Manufacturing Facility (cGMP) opens.



2007:
Columbus Children's Hospital becomes Nationwide Children's Hospital

2008:
Office of Technology Commercialization is established

2012:
Research Building III opens

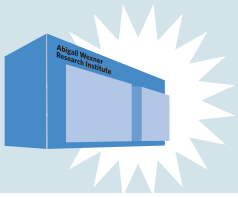


2016:
Institute for Genomic Medicine (IGM) is established

2017:
New 7,500 square foot cGMP facility increases capacity for viral vector and cell therapy manufacturing

2019:
FDA approves first ever systemically delivered gene therapy — Zolgensma® — for the treatment of spinal muscular atrophy

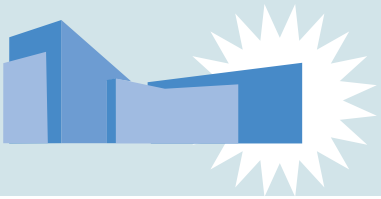
2019:
Research institute rededicated as the Abigail Wexner Research Institute



2020:
Big Lots Biobehavioral Health Pavilion opens with dedicated research space

2022:
Dr. Barnard retires, Dr. Durbin becomes president.

2023:
Research Building IV opens



Get an inside look at our facilities and learn more about our research programs: PediatricsNationwide.org/Research-Building-IV

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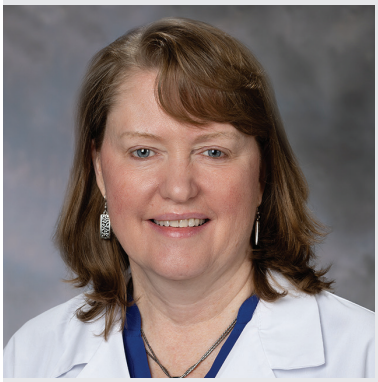
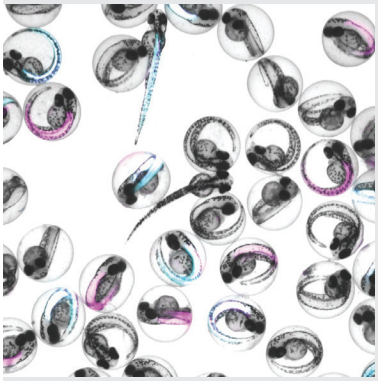


5 Things to Know About Prune Belly Syndrome

Linda Baker, MD, urologist, principal investigator, and one of the world's foremost experts on prune belly syndrome, recently joined Nationwide Children's Hospital as the co-director of the Kidney and Urinary Tract Center. She shares some important things to know about this rare disease.

PediatricsNationwide.org/5-Things-Prune-Belly



Cancer-Causing Gene and Treatment Target for Ultra-Rare Rhabdomyosarcoma Confirmed Via Multiple Models

An international team has validated a cancer-causing gene fusion — and therapeutic targets — for an unusual presentation of muscle cancer in infants. Their work, published in *Cell Reports*, reveals that the mutated fusion gene, VGLL2-NCOA2, is capable of causing muscle cancer in both transgenic zebrafish and mouse allograft models. Additionally, tumors in these models and in human patients over-express a gene called ARF6 that helps the fusion oncogene produce tumors that have characteristics of immature skeletal muscle.

PediatricsNationwide.org/Rhabdomyosarcoma-Multiple-Models

Proteins as Antibiotic Alternatives for UTIs

With the rise of antibiotic resistant infections, finding treatment alternatives is more important than ever — especially for a kind of bacteria that causes urinary tract infections (UTIs), called uropathogenic *E. coli*. In a new study published in *Proceedings of the National Academy of Sciences (PNAS)*, researchers demonstrate a way to boost the body's production of antimicrobial peptides, which may provide an alternative to antibiotic use.

PediatricsNationwide.org/AMP-UTI-PNAS

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