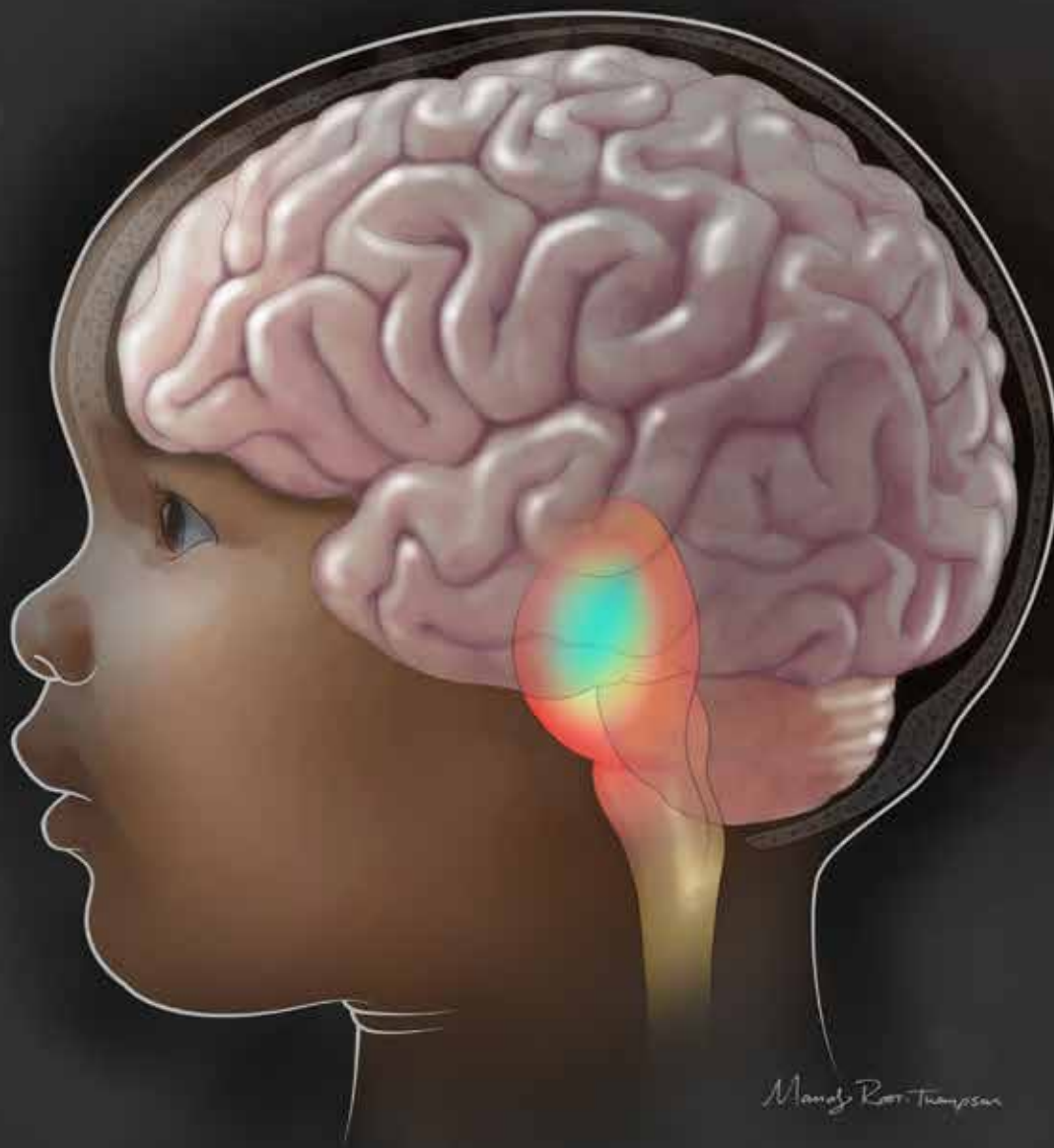


Spring/Summer 2021

Pediatrics

NATIONWIDE

Advancing the Conversation
on Child Health



Targeting DIPG: The Most Puzzling of Pediatric Brain Tumors

INSIDE
THIS ISSUE

How Can We Make
Child Health Equitable?

A Surprising Approach to
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to Build a Better Vaccine

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The past 50 years have brought story after story of success in the field of pediatric oncology. **In 1975, acute lymphoblastic leukemia had a 5-year survival rate of 57%; by 2012, it reached 92%.**

Non-Hodgkin lymphoma followed a similar trajectory, with a **5-year survival rate of only 43% in 1975, reaching 91% by 2012.**

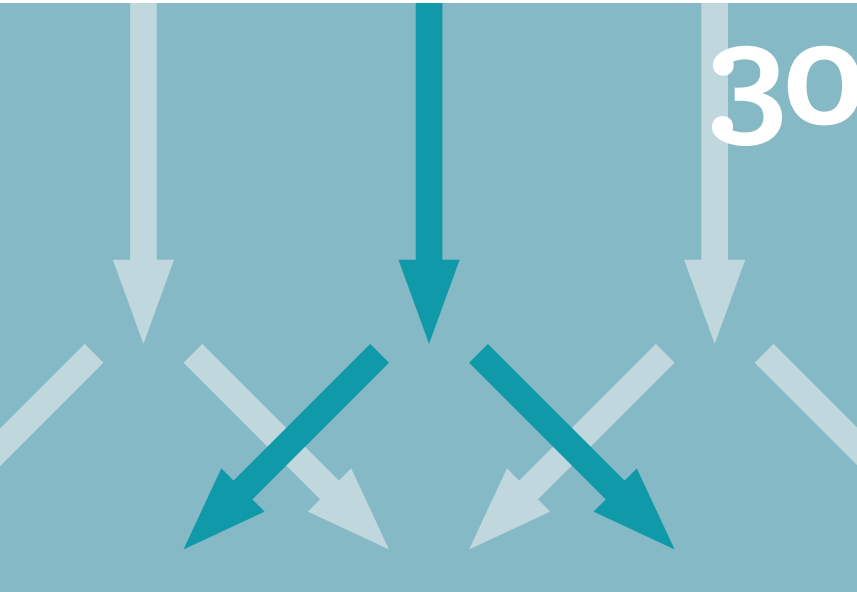
And childhood cancer in general became much less deadly during this time period, with an overall **5-year survival of 58% in the 1970s surpassing 83% by 2014.**

As the most common pediatric cancer, childhood leukemia, became increasingly curable, oncologists were left with a new main foe: brain cancers, which have supplanted leukemia as the leading cause of childhood cancer deaths.

Yet even in certain pediatric brain tumors, progress has been tremendous. **Oligodendroglioma and pilocytic astrocytoma both have 5-year survival rates of 90% or greater.**

Medulloblastoma — a historically challenging tumor despite decades of creative combination therapy studies — has offered great hope to neuro-oncologists and cancer biologists, as increased understanding of molecular subgrouping and targeted therapies have **raised survival for certain subgroups to 80-90%.**

Despite these steady and substantial improvements, **diffuse intrinsic pontine glioma (DIPG) survival remains dismal: median survival is only 8-11 months, with 5-year survival at just 2%.**



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“ You can't talk about child health equity without acknowledging the impact of racism on the health of communities, families and children. Structural racism, and the unconscious biases that accompany it, has created and enabled many of the biggest health disparities American children face. ”

– Deena Chisolm, PhD, vice president of Health Services Research at Nationwide Children's Hospital

“ You have to consider quality of life as an outcome too. The quality of life for a child who must catheterize every three hours, the quality of life for that child's family, can be difficult. Many children are unhappy needing to catheterize. Is there a way we can address that? ”

– V. Rama Jayanthi, MD, chief of Urology at Nationwide Children's

Pediatricians Offer Valuable Oral Health Services for the Very Young, Before and Throughout Pandemic

Analysis of preventive services offered by medical compared to dental professionals reinforces the importance of physician involvement in oral health care.

Medical professionals see very young children much more frequently during the first several years of life than dentists, and many states' Medicaid programs have seized the opportunity to reimburse pediatricians for preventive oral care, such as fluoride application and oral hygiene education. Despite reimbursement options and national guidelines recommending dental care begin by age 1, only about 8% of U.S. children under the age of 6 receive preventive oral care at well-child visits, and most children have no dental professional visit until the age of 3 or 4.

When COVID-19 forced many dental practices to close, Beau Meyer, DDS, MPH, a pediatric dentist at Nationwide Children's Hospital and an assistant professor in the Division of Pediatric Dentistry at The Ohio State University, sought to determine how much preventive oral care provision suffered among children ages 1-5. He and a graduate student examined data for about 335,000 Medicaid-enrolled children in North Carolina and 76,000 in Partners for Kids (an accountable care organization administering the Medicaid program in southern and southeastern Ohio) from January 2019 to June 2020.

While the rate of fluoride application at preventive dental visits and well-child visits decreased significantly during the pandemic, the proportion of well-child visits with fluoride administration remained about the same. And during the study period, the total number of children receiving oral health care from physicians actually surpassed the number receiving care from dentists among kids aged 3 years and younger.

"I was filled with gratitude when I saw that data. Even though the rates were low, physicians were still doing it — and at higher rates than dentists during the shut-down period," says Dr. Meyer, who published the research in *Frontiers in Dental Medicine* in February. "I think pediatrician-delivered oral health care makes a big difference, especially when access to a dentist is limited. Physicians become a safety net to deliver preventive oral health care to kids."

Dr. Meyer is now exploring opportunities to better quantify the impact that unique interprofessional collaborations — such as colocation of dental hygienists at medical clinics, increased referrals, improved reimbursement, supplemental physician education or identification of an oral health champion at medical offices (even among nurses or medical assistants) — could have on prevention of dental caries in young children.

"I think everything's on the table at the moment from a brainstorming perspective," says Dr. Meyer. "Pediatricians can play such an important role in preventive oral health by screening, applying fluoride varnish, referring when necessary and providing anticipatory guidance, to help build good oral health habits. The pie-in-the-sky hope is that by seeing them early, pediatricians and dentists can work together to prevent oral disease from ever developing."

Meyer BD, Danesh DO. The impact of COVID-19 on preventive oral health care during wave one. *Frontiers in Dental Medicine*, 2:636766.

— Katie Brind'Amour, PhD



The American Academy of Pediatrics offers oral health practice tools and detailed coding guidance for physicians wishing to begin providing and billing for oral health screenings and care.

Even Severe Asthma Can Improve if Guidelines Are Followed

Patients treated with adequate medications and asthma family education can significantly improve irrespective of asthma severity.

Severe asthma accounts for 5-8% of patients with asthma, but this group is more challenging to treat and is responsible for up to 40% of total asthma-care expenses. The majority of patients with severe asthma have difficult-to-treat asthma (in which poor asthma control is due to low adherence to therapy, inadequate therapy or misdiagnosis). A smaller percentage of patients with severe asthma have therapy-resistant asthma (in which asthma fails to be well controlled despite adequate treatment). Distinguishing the patients who could benefit from appropriate treatment from those who are refractory to treatment can be challenging.

In a new study, researchers from Nationwide Children's Hospital followed children with uncontrolled asthma over three years. Patients were treated according to National Asthma Education and Prevention Program (NAEPP) guidelines, which included appropriate medications and a structured family education program.

The researchers, led by Nationwide Children's pulmonologist Shahid Sheikh, MD, report improvements in asthma control as early as the first 3-month follow-up visit and persisting through the three years of the study. What's more, patients had similar outcomes irrespective of asthma severity, with even severe asthmatics showing improvements.

"This study shows that if we pay attention to patients, make sure they take their medicine, and provide them and their families with adequate education, even severe asthmatics can get better," says Dr. Sheikh, who is also a professor of clinical pediatrics at The Ohio State University College of Medicine.

In this sample, most of the children with severe asthma were not therapy-resistant asthmatics but had difficult-to-treat asthma due to inadequate therapy and/or poor adherence. Once they were receiving adequate medications and asthma education, as per NAEPP guidelines,



their asthma control improved within months. This suggests that the majority of children with uncontrolled asthma are not refractory to treatment and could improve with the right therapy.

Dr. Sheikh and his colleagues say that adherence to guidelines can also lead to savings in health care expenses. When the researchers evaluated the cost of acute asthma care in this study cohort over time, they noticed that it decreased by about 75% within a year, with cumulative savings over the three years of the study estimated to be nearly \$3 million.

"Guidelines have existed for many years. But, for some reason, in primary care settings, these guidelines are still not followed very closely," says Dr. Sheikh.

"We propose that just a little care for these patients — just gaining trust of families and patients — just following the guidelines — is all that is needed. Asthma severity is not a limitation to asthma control."

Sheikh SI, Ryan-Wenger NA, Pitts J, Nemastil CJ, Palacios S. Impact of asthma severity on long-term asthma control. *The Journal of Asthma*. 2020 Mar 23:1-10. [Epub ahead of print]

— Mary Bates, PhD

Novel Nitric Oxide-Mediated Mechanism Mediates Calcific Aortic Valve Disease

The novel pathway could be targeted to prevent or reverse aortic valve calcification in humans.

Researchers have recently described a novel nitric oxide-mediated mechanism in calcific aortic valve disease that involves the ubiquitin-proteasome pathway, and its disruption in animal models appears to cause aortic valve calcification.

The pathway could potentially be modulated to prevent or treat calcific aortic valve disease, an increasingly prevalent disease among the growing aging population and individuals born with a bicuspid aortic valve, who are predisposed to developing it in adulthood.

The findings were published in *Science Advances* by a multicenter team led by Vidu Garg, MD, director of the Center for Cardiovascular Research and the Nationwide Foundation Endowed Chair in Cardiovascular Research at Nationwide Children's Hospital.

"The proposed mechanisms are initiated by injury of the endothelial cells lining the aortic valve leaflets that ultimately drives a gene expression program within valve cells leading to calcification," says Dr. Garg.

In a series of experiments, the researchers found that post-translational S-nitrosylation of the USP9X protein stabilizes a NOTCH1 ligand found in cells of the heart valve. When the ligand is stable, it can activate

NOTCH1 signaling in neighboring cells, inhibiting calcification. When it is unstable, calcification ensues.

They first confirmed that nitric oxide and an S-nitrosylating agent can revert calcification in aortic valve cells and, via RNA sequencing, that both treatments can regulate the NOTCH1 pathway; however, no components of the cyclic GMP pathway were involved.

"Current evidence in the field demonstrates that nitric oxide prevents calcification through the cyclic GMP pathway. Our data demonstrates that the activation of NOTCH1 signaling pathway is functioning through this post-translational mechanism," explains Dr. Garg.

After identifying USP9X via a comprehensive proteomics analysis, the researchers developed a mouse model and demonstrated that USP9X deficiency leads to calcific aortic valve disease *in vivo*.

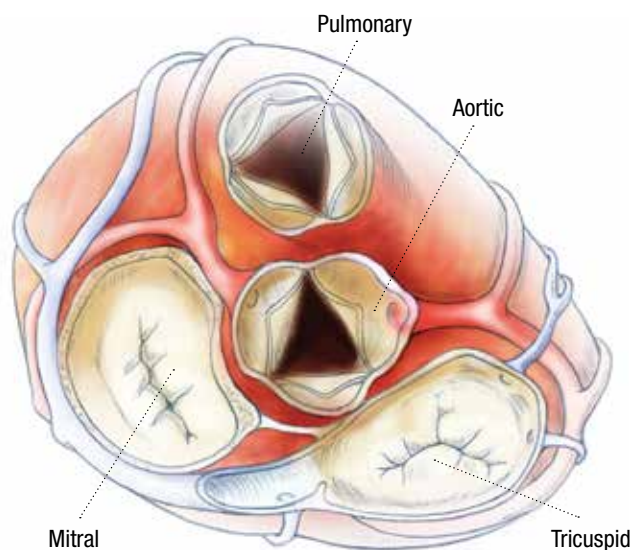
"Previously, we did not have a highly penetrant and easily reproducible mouse model to study the role of NOTCH1 signaling in calcific aortic valve disease," says Uddalak Majumdar, PhD, a postdoctoral scientist at Nationwide Children's and lead author of the study. "Now, we can study calcification *in vivo*, opening up the opportunity for preclinical testing of drug targets."

Lastly, the team showed that the amount of S-nitrosylated USP9X was inversely correlated with increasing amounts of calcification in explanted calcified aortic valve tissues from patients who had surgical valve replacement due to aortic stenosis.

"This is the first time the ubiquitin-proteasome pathway has been linked to calcific aortic valve disease. Importantly, this pathway is targetable; studies of cancer patients are already testing drug targets in this pathway, which with further investigation may ultimately be applicable in calcific aortic valve disease," says Dr. Majumdar.

Majumdar U, Manivannan S, Basu M, et al. Nitric oxide prevents aortic valve calcification by S-nitrosylation of USP9X to activate NOTCH signaling. *Sci Adv.* 2021;7(6):eabe3706. Published 2021 Feb 5. doi:10.1126/sciadv.abe3706

— Lauren Dembeck, PhD



Global Study Highlights Antibiotic Overuse in the NICU

Antimicrobial stewardship programs were associated with lower antibiotic use, regardless of the country's income level.

Excessive antibiotic use among infants born preterm in the newborn intensive care unit (NICU) is associated with poor patient outcomes, such as sepsis, necrotizing enterocolitis, bronchopulmonary dysplasia and others, and contributes to the emergence of multi-drug resistant microbes.

A new study, published in *EClinicalMedicine*, looked at an international cross section of antibiotic use in NICUs to quantify the prevalence of all antimicrobial use on a single day, to identify the clinical diagnoses used to support antibiotic use and to evaluate whether antibiotics were being used empirically, in a specific, targeted way, empiric, or as prophylaxis. The study team was led by Pavel Prusakov, PharmD, a NICU clinical pharmacist and Pablo Sanchez, MD, a neonatologist and an infectious disease physician at Nationwide Children's Hospital as well as Debra Goff, PharmD, an infectious diseases specialist The Ohio State University Wexner Medical Center.

The team sampled 84 NICUs from 29 countries (14 high-income and 15 low-to-middle income) on July 1, 2019. Antibiotics were the most frequently used antimicrobials (in 92% of patients), while antifungal (in 19%) and antiviral (in 4%) agents were also used.

Antimicrobial utilization per NICU was significantly higher in low-to-middle income countries. But centers that had a NICU-specific antimicrobial stewardship program had lower antibiotic utilization rates regardless of the nation's income level.

"There is a concerning lack of robust international or even national guidance on how to manage neonatal infections. Resources exist, but most of it is considered low quality evidence," Dr. Prusakov says. "Therefore, a lot of decision-making is based on clinical symptomatology and clinician's personal experience. Even hospital-specific guidelines are rare."

The majority of infants received antibiotic therapy as an empiric treatment for possible or culture-negative



sepsis/meningitis. Only a minority were treated for culture-confirmed infections. Infants were often treated with antimicrobial therapy based on clinical suspicion of bacterial infection rather than on bacterial culture results. In fact, according to the study, after excluding antibiotics used for prophylaxis, 49% of infants receiving antibiotics received prolonged courses without microbiologic evidence of infection.

In many cases, the perception of antimicrobial use in babies born preterm seems to be "better safe than sorry," says Dr. Prusakov. That is, better to use the antibiotics and prevent or treat possible sepsis than miss a case.

"This is a particularly challenging philosophy to change, because most of the adverse outcomes to antibiotics are not immediate. Often, it is hard to convince people of the adverse consequences associated with the antibiotic courses they prescribe," Dr. Prusakov says.

"The importance of antibiotic stewardship programs cannot be over-emphasized," adds Dr. Prusakov, who helps to lead the Neonatal Antimicrobial Stewardship Committee at Nationwide Children's. "Ultimately, they may help decrease antimicrobial resistance in NICUs worldwide, as well as reducing the number of negative outcomes due to dysbiosis in premature infants."

Prusakov P, Goff DA, Wozniak PS, Cassim A, Scipion CEA, Urzua S, Ronchi A, et. al. A global point prevalence survey of antimicrobial use in neonatal intensive care units: The no-more-antibiotics and resistance (NO-MAS-R) study. *EClinicalMedicine*. 2021;32:100727.

— Abbie Roth

Can Neurocognitive Functioning Tests Help Predict Future Suicide Attempts?

Researchers identify sex-specific deficits in measures of working memory and affective processing associated with suicidal behavior in youth with depression.



To prevent youth suicide, researchers are working to identify factors associated with suicide attempts in adolescents at elevated risk for suicidal behavior. In a new study, researchers from Nationwide Children's examined neurocognitive functioning in suicidal and non-suicidal youth with a history of major depressive disorder and explored whether neurocognitive dysfunction predicted future suicide attempts.

The researchers administered a battery of psychiatric and neurocognitive tests to three groups of adolescents aged 12-15 years with a lifetime history of major depressive disorder:

- Those with a history of suicide attempt
- Those with a history of suicidal ideation but no history of a suicide attempt
- Those with no history of suicidal ideation or suicide attempt

The results showed sex-specific deficits in neurocognitive functioning that differentiate suicidal and non-suicidal youth.

“In females, neurocognitive domains associated with affective bias, which refers to how emotions can impact cognitive processes, were found to be significantly different based on past suicidal ideation and attempts,”

says Donna Ruch, PhD, a research scientist in the Center for Suicide Prevention and Research at the Abigail Wexner Research Institute at Nationwide Children's Hospital and the study's lead author.

“Similar results were found on tests for spatial working memory in males, where more errors occurred among those who had suicide ideation and attempts compared to never-suicidal subjects,” she says.

Prospective analyses also showed that deficits in these same domains predicted future suicide attempts. Females who made a future attempt made more errors in response to happy words on a test of affective processing compared to those with no future attempts.

Among males, less efficient strategies on the spatial working memory test predicted future suicide attempts. “This is a critical first step in identifying potential targets for future risk evaluation and treatment,” says Dr. Ruch.

“Findings from these exploratory analyses suggest that cognitive vulnerabilities in adolescents may predict future suicide attempts over and above the presence of major depressive disorder and attempt history.”

Knowledge of how neurocognitive impairments may distinguish youth at risk for suicide could help inform the development of clinically feasible neurocognitive evaluations and preventive intervention strategies to target specific risk factors for suicide in youth with depression.

“Future research should examine longer term follow-up data to better identify unique facets of neurocognitive functioning that most strongly predict youth suicidal behavior, including important sex differences,” says Dr. Ruch. “This can enable clinicians to more effectively intervene as early as possible and, ideally, respond with methods that target unique vulnerabilities of individual patients.”

Ruch D, Sheffall AH, Heck K, McBee-Strayer SM, Tissue J, Reynolds B, Ackerman J, Brent DA, Campo JV, Bridge JA. Neurocognitive vulnerability to youth suicidal behavior. *Journal of Psychiatric Research*. 2020;131:119-126.

— Mary Bates, PhD



The First Opioid-Prescribing Guidelines for Children Who Require Surgery

Providers should recognize the risks of opioids, maximize nonopioid regimens, and educate families appropriately.

The first opioid-prescribing guidelines to address the unique needs of children who require surgery have been published by an expert panel in *JAMA Surgery*. The new guidelines aim to help health care professionals caring for children and adolescents in the perioperative period optimize pain management and engage patients and families in opioid stewardship efforts.

“This was a team effort and part of an initiative to decrease the exposure of kids to opioids and also to decrease the number of opioids available for abuse in the community,” says co-author Karen Diefenbach, MD, director for Minimally Invasive Surgery at Nationwide Children’s Hospital. “This led us to ask—should we even be prescribing opioids for certain procedures?”

The multidisciplinary team of health care experts and leaders in opioid stewardship reviewed literature on opioid use and risks unique to pediatric populations published between 1988 and 2019. After screening 14,574 articles, they identified 217 unique articles to include in a qualitative synthesis. Based on the results, the team developed 20 evidence-based opioid prescribing guidelines for children who require surgery.

“We acknowledge that one-size-fits-all approaches do not work and took this on as an opportunity to make sure kids have their surgical pain optimally managed by using multimodal analgesia,” says Sharon Wrona, DNP, CPNP-PC, pediatric nurse practitioner in the Department of Anesthesiology & Pain Medicine and leader of the Opioid Task Force at Nationwide Children’s.

After the guidelines were drafted, they were externally reviewed, edited and, ultimately, endorsed by pediatric

surgical specialists, the American Pediatric Surgery Association Board of Governors, the American Academy of Pediatrics Section on Surgery Executive Committee, and the American College of Surgeons Board of Regents.

“The evidence shows that following some surgical procedures opioids are normally not required,” says Dr. Diefenbach. “But we have to customize regimens for individual patients because certain patients fall outside of the curve; for example, some are more sensitive to pain or have underlying inability to tolerate anti-inflammatory medications.”

The guideline statements focus on three primary areas. First, “health care professionals caring for children who require surgery must recognize the risks of opioid misuse associated with prescription opioids.” Second, “nonopioid analgesic use should be optimized in the perioperative period.” Third, “patient and family education regarding perioperative pain management and safe opioid use practices must occur both before and after surgery.”

“It is critical for the prescriber to have these important conversations about pain management and risks associated with opioids to help families set their expectations and watch for risky behavior,” says Dr. Wrona. “Prescribers need to be mindful and respect those risks by being diligent when prescribing opioids but not afraid to prescribe them when it is appropriate.”

Download Guidelines on Opioid Prescribing at PediatricsNationwide.org/Opioid-Prescribing

Kelley-Quon LI, Kirkpatrick MG, Ricca RL, et al. Guidelines for opioid prescribing in children and adolescents after surgery: an expert panel opinion. *JAMA Surgery*. 2021;156(1):76-90. doi:10.1001/jamasurg.2020.5045

— Lauren Dembeck, PhD



How Can We Make Child Health Equitable?

Researchers in the Center for Child Health Equity and Outcomes Research at Nationwide Children's Hospital are tackling this question by identifying health disparities and uncovering exactly how social drivers of health impact outcomes.

Written by Abbie Roth, Jeb Phillips and Natalie Wilson

“**H**ealth equity means that everyone has a fair and just opportunity to be as healthy as possible.”

That's how the Robert Wood Johnson Foundation, the largest health-focused philanthropic organization in the United States, defines the concept of health equity.

The widely recognized definition goes on to say that achieving health equity “requires removing obstacles to health such as poverty, discrimination, and their consequences, including powerlessness and lack of access to good jobs with fair pay, quality education and housing, safe environments and health care. For the purposes of measurement, health equity means reducing and ultimately eliminating disparities in health and its determinants that adversely affect excluded or marginalized groups.”

Income, education, employment and systemic bias are all related to health and health outcomes. These social

drivers of health are the subject of a growing body of research that is dedicated to understanding underlying causes of health disparities and inequities experienced by racial/ethnic, sexual orientation and gender identity minorities.

Achieving health equity has long been a priority at Nationwide Children's Hospital. Its founding mission in 1892 was that all children should receive care regardless of a family's ability to pay, a statement of “health equity” before that term had been defined. In the decades since, strategic plans have been built around the idea that a “zip code should not determine a child's health,” in the words of Steve Allen, MD, the hospital's CEO emeritus.

Research throughout the Nationwide Children's organization has guided those plans by revealing that social drivers of health affect health equity and access to care. Now, that work is forming the basis of the new Center for Child Health Equity and Outcomes



“You can’t talk about child health equity without acknowledging the impact of racism on the health of communities, families and children. Structural racism, and the unconscious biases that accompany it, has created and enabled many of the biggest health disparities American children face.”

– Deena Chisolm, PhD, vice president of Health Services Research at Nationwide Children’s Hospital

Research at the Abigail Wexner Research Institute at Nationwide Children’s.

“Health disparities are not usually rooted in biology. They are created and supported by social constructs and systems that limit access to health care and upward mobility,” says Deena Chisolm, PhD, vice president of Health Services Research at Nationwide Children’s and director of the new center. “And barriers to health equity exist in all areas of clinical care, health services and communities.”

“Our mission in the Center for Child Health Equity and Outcomes Research is to address inequities and outcomes through research across all of these areas. We are here to support and be integrated with existing research and clinical programs across the Nationwide Children’s enterprise.”

Health Equity and Anti-Racism

“You can’t talk about child health equity without acknowledging the impact of racism on the health of

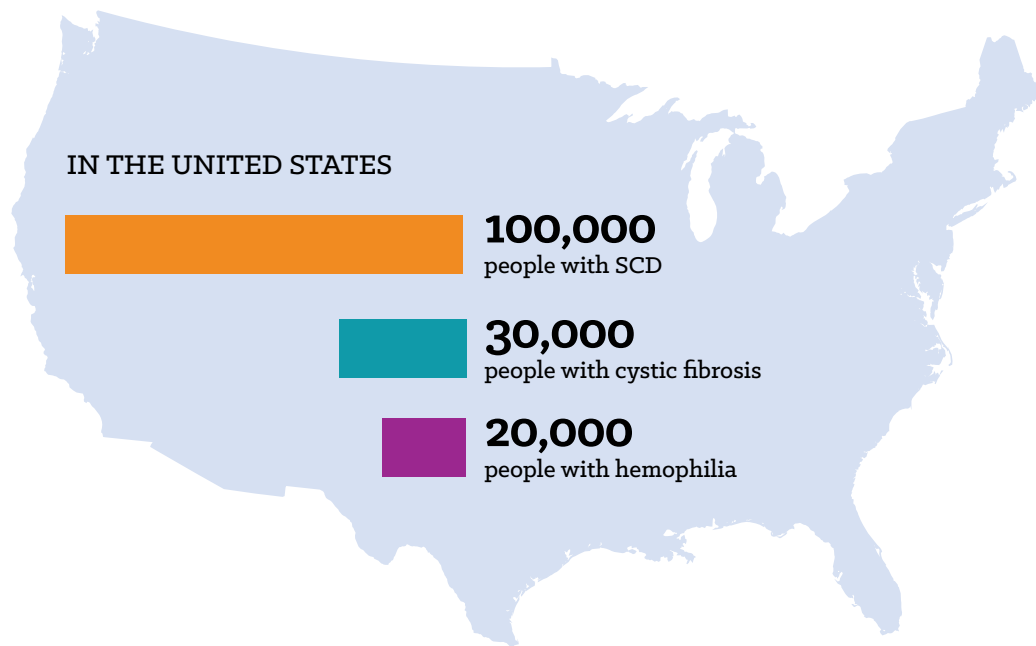
communities, families and children,” says Dr. Chisolm. “Structural racism, and the unconscious biases that accompany it, has created and enabled many of the biggest health disparities American children face.”

These biases can affect the quality of communication between providers and patients. A recent paper published by Dr. Chisolm and her team found that African American teens with chronic illnesses and their parents are less likely to report that their doctors spent enough time with them. According to Dr. Chisolm, whether this is the results of overtaxed providers in minority communities or unconscious biases, the end result is African American patients getting less of the support, education and counseling needed for good health management.

Understanding the Health Needs of Minority Populations

Medical conditions that are concentrated in minority populations, who already face many other disparities, have historically received less attention than other similar conditions. One such condition is sickle cell disease





(SCD), which is more commonly diagnosed in African American children, and specifically SCD pain management.

Approximately 1 in 365 African Americans and 1 in 16,300 Hispanic Americans are born with SCD. And while SCD is three times more common than other genetic disorders in the United States, there are fewer treatment options and less public education about the disease. Studies have shown that SCD research receives less federal funding and foundation expenditures compared to these other disorders.

Studies have also shown that black children are less likely to receive adequate pain control compared to white children.

“Severe pain is common in SCD, and few treatments other than opioids provide adequate SCD pain relief.

While Ohio’s opioid guidelines were implemented to curb the opioid epidemic, their impact on children with SCD who require access to opioids to manage their pain had not been studied,” says Susan Creary, MD, hematologist and principal investigator in the center.

Dr. Creary and her colleagues had concerns about whether these guidelines could worsen pain management among patients who already faced the most challenges to adequate pain control. Results of their 2020 study, published in *Pain Medicine*, showed that Ohio’s 2013 and 2016 opioid prescribing guidelines to limit excessive opioid prescribing, filling and misuse were associated with significant but non-sustained changes to opioid prescription filling among children with SCD.

“Our findings showed that these guidelines resulted in only temporary changes in opioid filling among these children and may suggest that access to opioids among



“Severe pain is common in SCD, and few treatments other than opioids provide adequate SCD pain relief. While Ohio’s opioid guidelines were implemented to curb the opioid epidemic, their impact on children with SCD who require access to opioids to manage their pain had not been studied.”

– Susan E. Creary, MD, hematologist and principal investigator in the Center for Child Health Equity and Outcomes Research at the Abigail Wexner Research Institute at Nationwide Children’s Hospital



“In comparing small towns to urban centers, nearly 90% of the 5.7 percentage-point gap was explained by patient, parent and provider social drivers. The largest part of the rural-urban preventive care gap can be explained by differences in provider type, poverty, unemployment, and education levels. We have more work to do in addressing these factors to improve pediatric preventive care in all communities.”

– Kelly Kelleher, MD, MPH, vice president of Community Health at Nationwide Children's

children with SCD at baseline is not excessive,” says Dr. Creary.

The Rural—Urban Divide

Access to care is a challenge that can be compounded by a range of factors, including transportation, number of providers available and, in the age of telehealth, internet access. And while children everywhere can experience barriers to accessing care, children living in rural areas often experience unique challenges.

“Some rural counties may not have any pediatricians — not to mention pediatric subspecialists,” says Kelly Kelleher, MD, MPH, vice president of Community Health at Nationwide Children's and a principal investigator in the new center. “When we look at health equity for rural communities, we have to consider this.”

In a study published in *Academic Pediatrics* in 2020, Dr. Kelleher and his team investigated the contributions of social drivers of health to rural-urban preventive care differences among Medicaid enrollees.

Among the more than 450,000 Medicaid enrollees in the study, just over 61% of urban children received a well-child visit. In large rural cities and small rural towns, 58% and 55.5% received well-child visits, respectively.

“In comparing small towns to urban centers, nearly 90% of the 5.7 percentage-point gap was explained by patient, parent and provider social drivers. The largest part of the rural-urban preventive care gap can be explained by differences in provider type, poverty, unemployment, and education levels,” says Dr. Kelleher. “We have more work to do in addressing these factors to improve pediatric preventive care in all communities.”

Institutions and organizations most involved in health equity issues are often located in metropolitan areas, and their initiatives often focus in those areas — either because of proximity or the expectation that more children can be impacted.

Nationwide Children's began a school-based asthma therapy program in Columbus City Schools, for example, improving access to preventive medications and ultimately reducing pediatric emergency department visits throughout Franklin county, where the school system is located. While the program has now expanded into many other districts, progress in rural counties has lagged.

In addition, health equity-focused organizations located in cities haven't earned the trust of health care providers and consumers in rural counties.

“While we might have some ideas about what could work in rural counties, it is important that we not rush into those areas dictating changes, telling the providers there how to run things,” says Dr. Kelleher. “Particularly in Appalachian areas, communities may not broadly trust an outsider from an urban area who wants to come in and tell them how to do things.”

Furthermore, in many rural, particularly Appalachian counties, in Ohio, there simply isn't the funding or workforce available to implement many of the guidelines or recommendations that come from large urban-based institutions.

“We need to build partnerships — the providers in these rural areas have a deep connection to the people they serve and a deep understanding of social drivers of health unique to the community that impact the people's health there. They also know what resources



“Even when you adjust for demographic factors like race, ethnicity and disability, and housing-related issues like inability to pay rent or neighborhood safety, poor housing quality has an independent association with poorer health and higher health care use.”

– *Samantha Boch, PhD, RN, assistant professor at the University of Cincinnati College of Nursing and an affiliate faculty member of the James M. Anderson Center for Health Systems Excellence at Cincinnati Children’s Hospital Medical Center*

are available and how to make those resources stretch,” says Dr. Kelleher. “Only by working together will we be able to move the needle on health outcomes in rural communities.”

Housing and Health Equity

A huge body of medical literature, dating from at least the 1980s, has examined the intersection of homelessness or housing instability and health. Health issues can lead to homelessness, and homelessness can lead to health issues. Homelessness and housing instability can also impact the way that people can seek care for their health issues. All of this is compounded for children, who have little say in where or how they live.

In fact, housing is sometimes considered the central social driver of health. It is difficult to be healthy without a stable home. Racism, poverty, job opportunities, neighborhood safety and a host of other factors influence housing, and housing has an influence on those factors as well. It’s why Nationwide Children’s has made housing a core focus of research and interventions.

In January, a study led by the Center for Child Health Equity and Outcomes Research showed for the first time that overall poor housing quality, not just homelessness and housing instability, is independently associated with poorer children’s health. Each housing quality issue, such as large holes in the floor or pest infestation, was linked to worse health status.

“Even when you adjust for demographic factors like race, ethnicity and disability, and housing-related issues like inability to pay rent or neighborhood safety, poor housing quality has an independent association with poorer health and higher health care use,” says Samantha Boch, PhD, RN, the lead author of the study, who

completed it as a postdoctoral fellow at Nationwide Children’s. She is now an assistant professor at the University of Cincinnati College of Nursing and an affiliate faculty member of the James M. Anderson Center for Health Systems Excellence at Cincinnati Children’s Hospital Medical Center.

This kind of research has led Nationwide Children’s to make real-world changes in community housing. Its Healthy Neighborhoods Healthy Families initiative, founded in 2008, has now built or improved more than 400 homes and 115 rental units and drawn investments of more than \$40 million to the historically disadvantaged South Side of Columbus. The initiative also coordinates workforce development, educational mentoring, tax preparation clinics and other programs.

That is not enough, however. Dr. Chisolm, Dr. Kelleher and others are conducting research around Healthy Neighborhoods Healthy Families to learn how the interventions are working. Some results will take decades to fully materialize, but there is some evidence of overall positive effect on high school graduation, health care utilization and neighborhood safety.

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Above: Numerous homes in the South Side neighborhood have been repaired or improved as a result of HNHF homeowner grants and rehab projects. Below: A home in the neighborhood is shown before and after renovations.



Learn more about these studies and more from the Center for Child Health Equity and Outcomes Research: PediatricsNationwide.org/Health-Equity-Research.



A SURPRISING APPROACH TO CLASSIC BLADDER EXSTROPHY

A procedure developed at Nationwide Children's Hospital comes with possible risks but can have a huge impact on quality of life.

written by Jeb Phillips



It's become clearer over the last two years that a “good outcome” for children born with classic bladder exstrophy is in the eye of the beholder.

One of the best outcomes, nearly everyone would agree, is that a child with this complex congenital defect — often requiring multiple procedures over the course of years — would ultimately be able to urinate like a “normal” child. In fact, that is the question parents most often ask after a diagnosis, says V. Rama Jayanthi, MD, chief of Urology at Nationwide Children's Hospital:

“Will my child be normal?”

For decades, surgeons believed that many children could have that outcome. There were certainly individual examples of it. But the condition is relatively rare, and a patient's potential procedures so spread out over time, so it was tough to track long-term outcomes.

Then, in late 2019 and early 2020, came the two largest studies ever published on bladder exstrophy outcomes

— one from Nationwide Children's and its peers in the Pediatric Urology Midwest Alliance, and another from Johns Hopkins Medical Institutions. They brought the bad news that experienced pediatric urologists had begun to suspect: true continence with normal urination was unusual, and only then with many major surgeries.

The outcome that most patients could expect was “staying dry” through clean intermittent catheterization every few hours for the rest of their lives, the studies found. From a medical perspective, that may well be considered a success, says Dr. Jayanthi.

“You have to consider quality of life as an outcome too,” he says. “The quality of life for a child who must catheterize every three hours, the quality of life for that child's family, can be difficult. Many children are unhappy needing to catheterize. Is there a way we can address that?”

Dr. Jayanthi at Nationwide Children's, and perhaps a handful of other pediatric urologists in the United States, believe there is one. The procedure is unusual

enough that it doesn't have a formal name, and Dr. Jayanthi himself admits many of his peers wouldn't consider doing it.

In the right circumstances, though, and for certain children, it has been life changing.

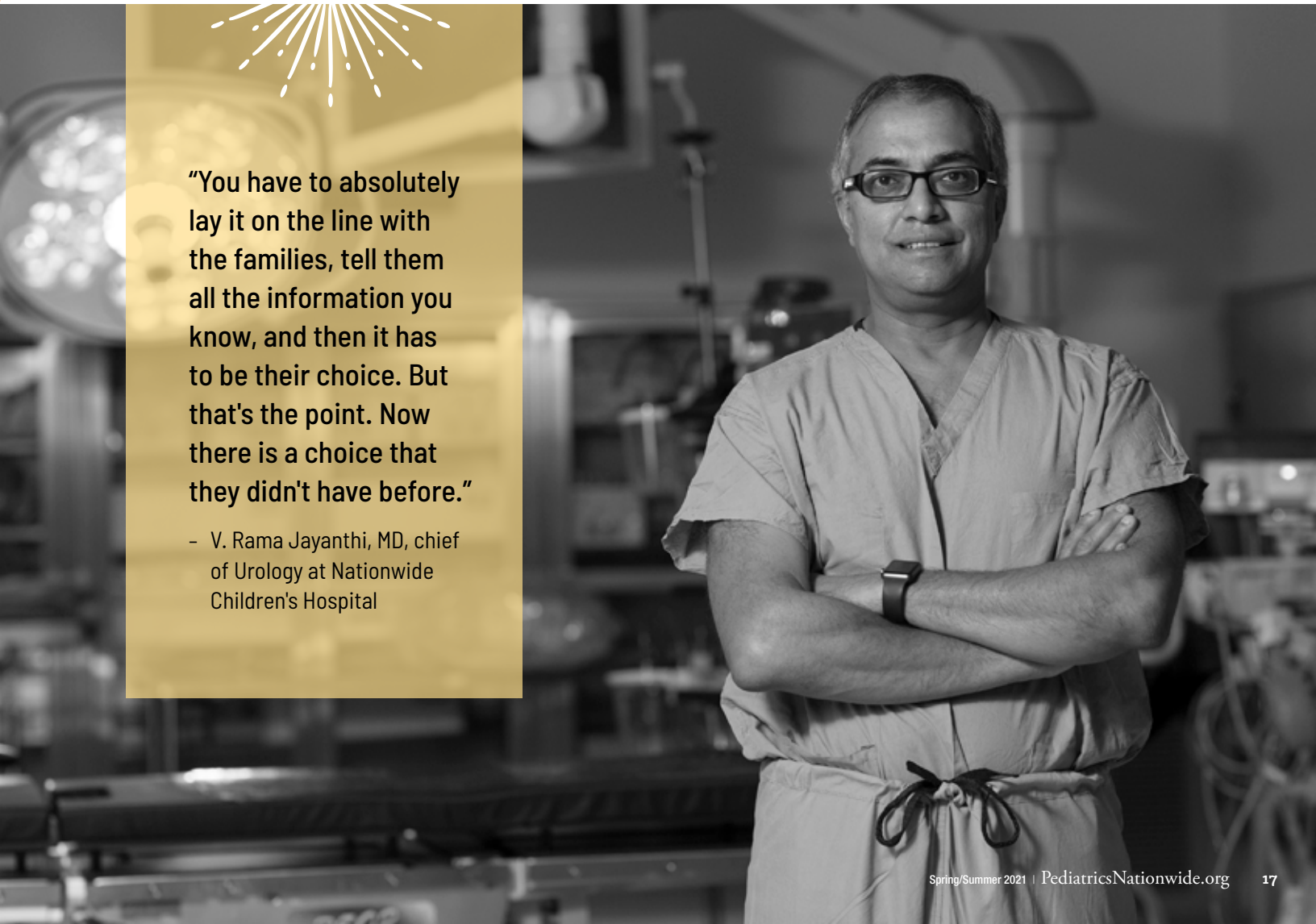
TRADITIONAL APPROACHES TO EXSTROPHY

Bladder exstrophy is most obviously characterized by a malformed bladder protruding through the abdomen and exposed outside of the body. The urinary sphincter doesn't work or doesn't exist, so urine continually leaks, and often the urethra doesn't exist either. Other body

systems, especially the reproductive system, can be affected.

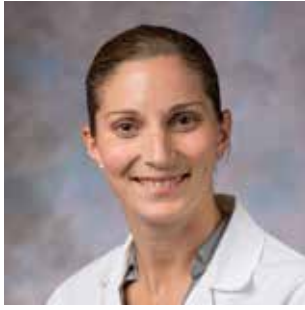
Many children born with the condition undergo an initial procedure at a few months of age to enclose the bladder inside the body. Reconstruction of the urethra and/or the penis may occur as well (the condition is about twice as prevalent in males as females).

Then, typically when a child would begin preschool or kindergarten, come complicated procedures intended to make a child continent. The bladder neck is tightened in an attempt at developing some urine control. However,



"You have to absolutely lay it on the line with the families, tell them all the information you know, and then it has to be their choice. But that's the point. Now there is a choice that they didn't have before."

- V. Rama Jayanthi, MD, chief of Urology at Nationwide Children's Hospital



“I knew Dr. Jayanthi had done a handful of these when I joined Nationwide Children’s as a fellow, and I honestly found it shocking. Rectal diversion would be considered only a salvage procedure by most people because of the risks of cancer. This fear is why we are taught not to do it. That being said, for a family that fully understands the risks, though, this can result in a great quality of life.”

– Molly Fuchs, MD, urologist at Nationwide Children's Hospital

as the large studies showed, the majority of bladder neck procedures in exstrophy cases don't actually have that result. Incontinence continues and regular urination isn't possible.

At that point, a child's bladder neck may need to be closed or retightened, the bladder may need to be enlarged by adding intestinal tissue, and urine permanently diverted for the child to stay dry. The most common current approach creates a channel from the bladder through the abdomen using the appendix (called a Mitrofanoff procedure). The child is able to catheterize through the channel to remove urine. This method works and works well.

That's a successful outcome with a potentially challenging quality of life for children who otherwise have no health issues.

The Division of Urology at Nationwide Children's has spent the last decade more closely tying “successful outcome” with “quality of life.” Dr. Jayanthi began thinking about a new bladder exstrophy approach after he saw a patient who, in contrast to similar patients, had a relatively easy time voiding urine. The child had been adopted from Asia and treated there with a procedure largely abandoned in the United States called ureterosigmoidostomy. With that approach, ureters are detached from the bladder and attached to the sigmoid colon; urine bypasses the bladder entirely and exits the body through the rectum.

The child needs to go to the bathroom somewhat more often than other children, but no catheter is needed.

“She was just so much happier, and her family was so much happier, than other patients I have,” said Dr. Jayanthi. “She was a competitive gymnast growing up, and her bladder exstrophy diagnosis had little impact on her day-to-day life. I started thinking, can we do this here without the risks that usually come with it?”

The risks are why ureterosigmoidostomy had been abandoned. The connection of the ureters with the high-pressure system of the sigmoid colon can lead to feces reflux into the ureters, causing infection. More catastrophically, the incidence of colon cancer was shown to be many times greater than in the general population, presumably driven by the intermixing of feces and urine in the colon.

Dr. Jayanthi had a new take on this old idea that even his bladder exstrophy partner at Nationwide Children's calls “shocking.”

A NEW WAY

With this new approach, urine still leaves the body through the rectum as it would in ureterosigmoidostomy, but the ureters stay connected to the bladder. The bladder is augmented, serves as a low-pressure reservoir and is connected to the rectum (instead of the colon) via a new channel. Urine flows from the reconstructed bladder to the rectum and leaves the body that way with no catheterization. The rectal sphincter maintains continence. (For a detailed illustration of these procedures, see 20.)

There is little chance for feces reflux into the ureters because they remain connected to the bladder, not



“Each child with bladder exstrophy is different, and every family has an individual perspective on it. Rectal diversion is not going to be the best approach for many families. What our study helped show, though, is that what most urologists are doing now may not be the best approach for some families either. This is another option.”

– Patricio Gargollo, MD, pediatric urologist at Mayo Clinic

attached to the colon or the rectum. Most of the urine is held in the bladder instead of the colon or rectum, so mixing with feces is reduced. Conceptually, infections should be less likely, and the patients who have had this procedure have experienced very few, says Dr. Jayanthi. The risk of cancer may be reduced as well.

But there’s no way to know that yet, says Molly Fuchs, MD, a urologist at Nationwide Children’s who works with Dr. Jayanthi on exstrophy cases. That lack of evidence would give anyone pause, she says, and causes most urologists to avoid any sort of rectal diversion approach.

“I knew Dr. Jayanthi had done a handful of these when I joined Nationwide Children’s as a fellow, and I honestly found it shocking,” she says. “Rectal diversion would be considered only a salvage procedure by most people because of the risks of cancer. This fear is why we are taught not to do it. That being said, for a family who fully understands the risks, this procedure can result in a great quality of life.”

Another pediatric urologist in the United States who has performed a version of a rectal diversion surgery is Patricio Gargollo, MD, of the Mayo Clinic. Dr. Gargollo was the senior author of the large exstrophy study published in late 2019 by the Pediatric Urology Midwest Alliance (Dr. Fuchs was a co-author). The group includes Nationwide Children’s, Mayo, Lurie Children’s Hospital, Cincinnati Children’s Medical Center, and Riley Hospital for Children, and was formed by the five large institutions in part to share expertise on extremely rare conditions such as bladder exstrophy.

“Each child with bladder exstrophy is different, and every family has an individual perspective on it,” says Dr. Gargollo. “Rectal diversion is not going to be the best approach for many families. What our study helped show, though, is that what most urologists are doing now may not be the best approach for some families either. This is another option.”

Dr. Jayanthi, Dr. Gargollo and Dr. Fuchs all stress this. Most families may still be best served by the procedures that result in regular catheterization. Nationwide Children’s and Mayo have used it and will continue to use it in the future. A family who is presented with the rectal diversion option must have a clear understanding of the possible benefits and future risks.

Honest conversations about classic bladder exstrophy and its outcomes are more possible now than they have ever been, thanks to the studies of the last two years. For Dr. Jayanthi, those studies show a new approach is warranted.

“You have to absolutely lay it on the line with the families, tell them all the information you know, and then it has to be their choice,” he says. “But that’s the point. Now there is a choice that they didn’t have before.”

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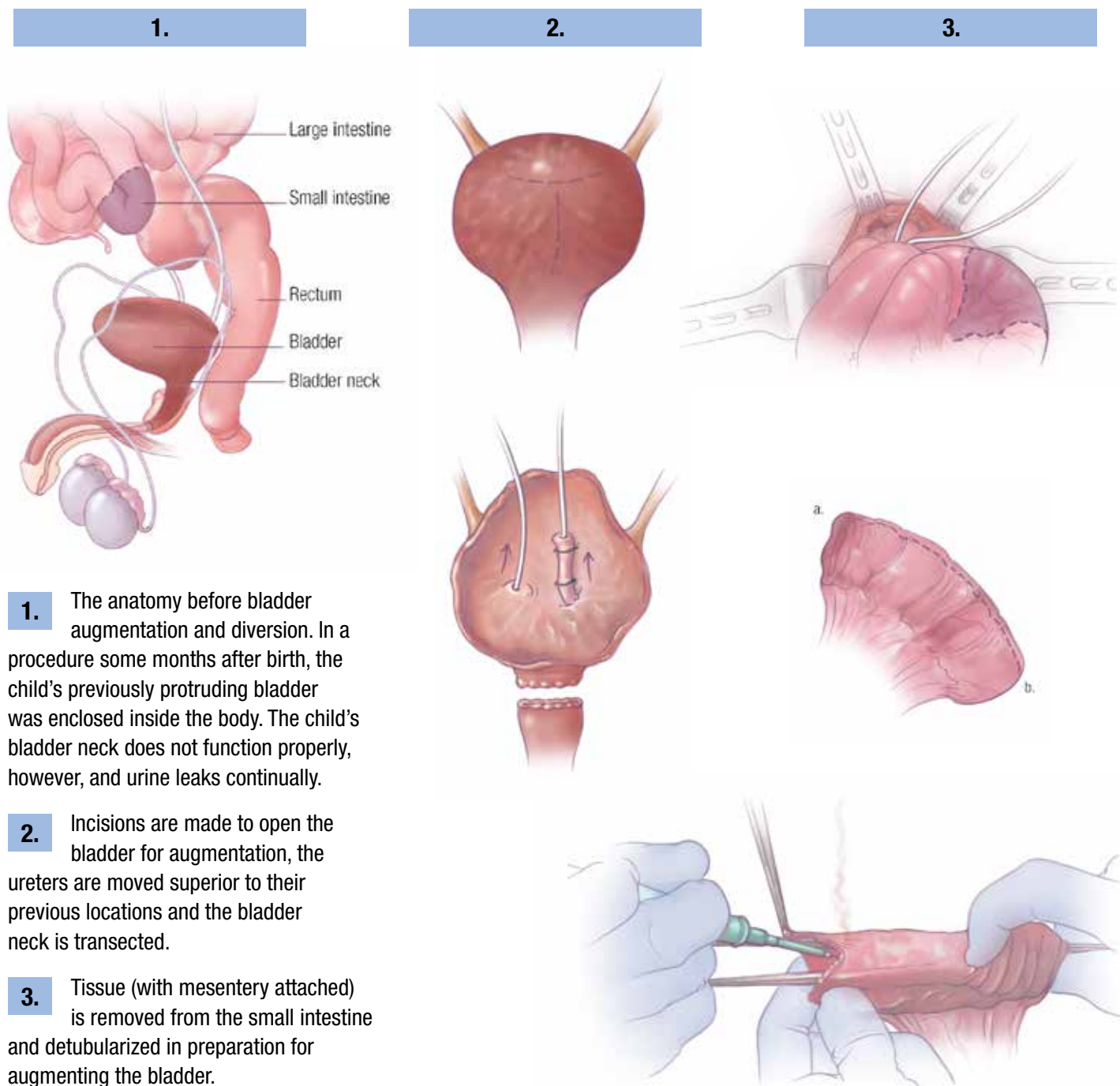
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A New Kind of Rectal Diversion in Classic Bladder Exstrophy

When children with classic bladder exstrophy approach school age, they may undergo bladder augmentation and urine diversion procedures that allow them to remain “dry.” Most children ultimately will have a channel from the bladder through the abdomen and void urine with clean intermittent catheterization.

An approach developed at Nationwide Children’s Hospital diverts urine to the rectum instead, allowing children to void urine without catheterization. While not appropriate for all children with classic bladder exstrophy, it may improve quality of life for some.



1. The anatomy before bladder augmentation and diversion. In a procedure some months after birth, the child’s previously protruding bladder was enclosed inside the body. The child’s bladder neck does not function properly, however, and urine leaks continually.

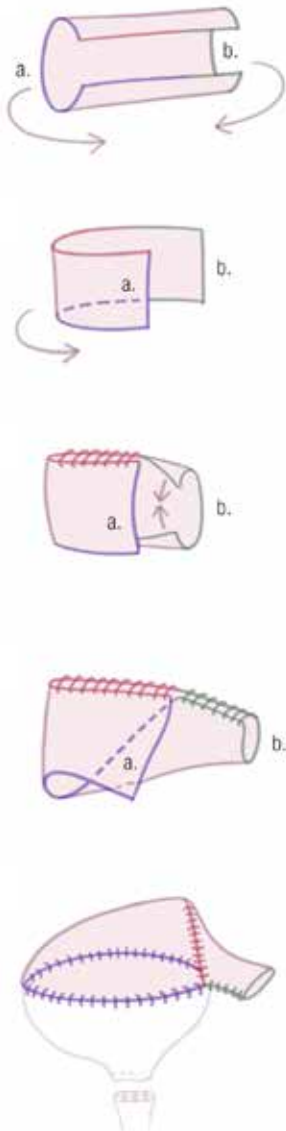
2. Incisions are made to open the bladder for augmentation, the ureters are moved superior to their previous locations and the bladder neck is transected.

3. Tissue (with mesentery attached) is removed from the small intestine and detubularized in preparation for augmenting the bladder.

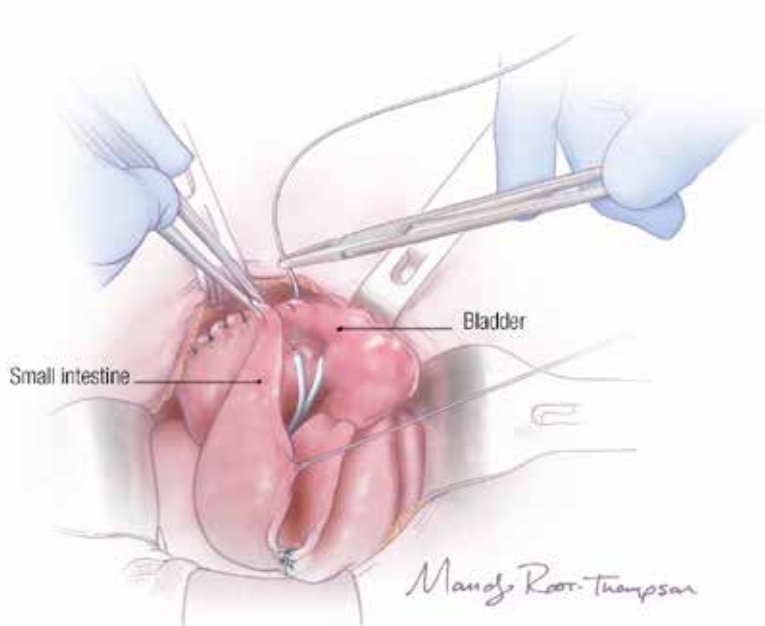
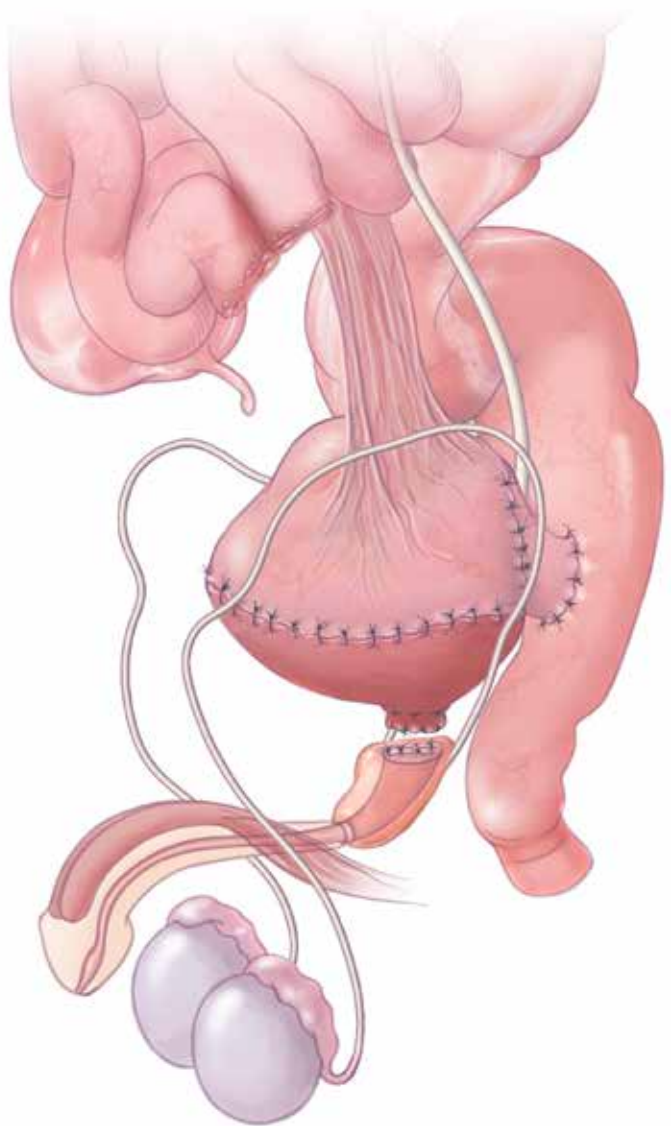
4. The detubularized small intestine tissue is reconfigured to disrupt the normal peristalsis of the bowel. One end of the reconfigured tissue is shaped into a channel that can be attached to the rectum. The resulting patch is sutured to the bladder.

5. Post-surgical anatomy. The augmented bladder is now attached to the rectum, and urine can be voided that way without catheterization.

4.



5.



TARGETING DIPG: THE MOST PUZZLING OF PEDIATRIC BRAIN TUMORS

Survival has dramatically improved for numerous pediatric cancers over the last several decades, with a notable and very deadly exception: diffuse intrinsic pontine glioma (DIPG). Now, a community of researchers and clinician-scientists have set the stage for a renewed — and better-armed — assault against this beast of a brain tumor.

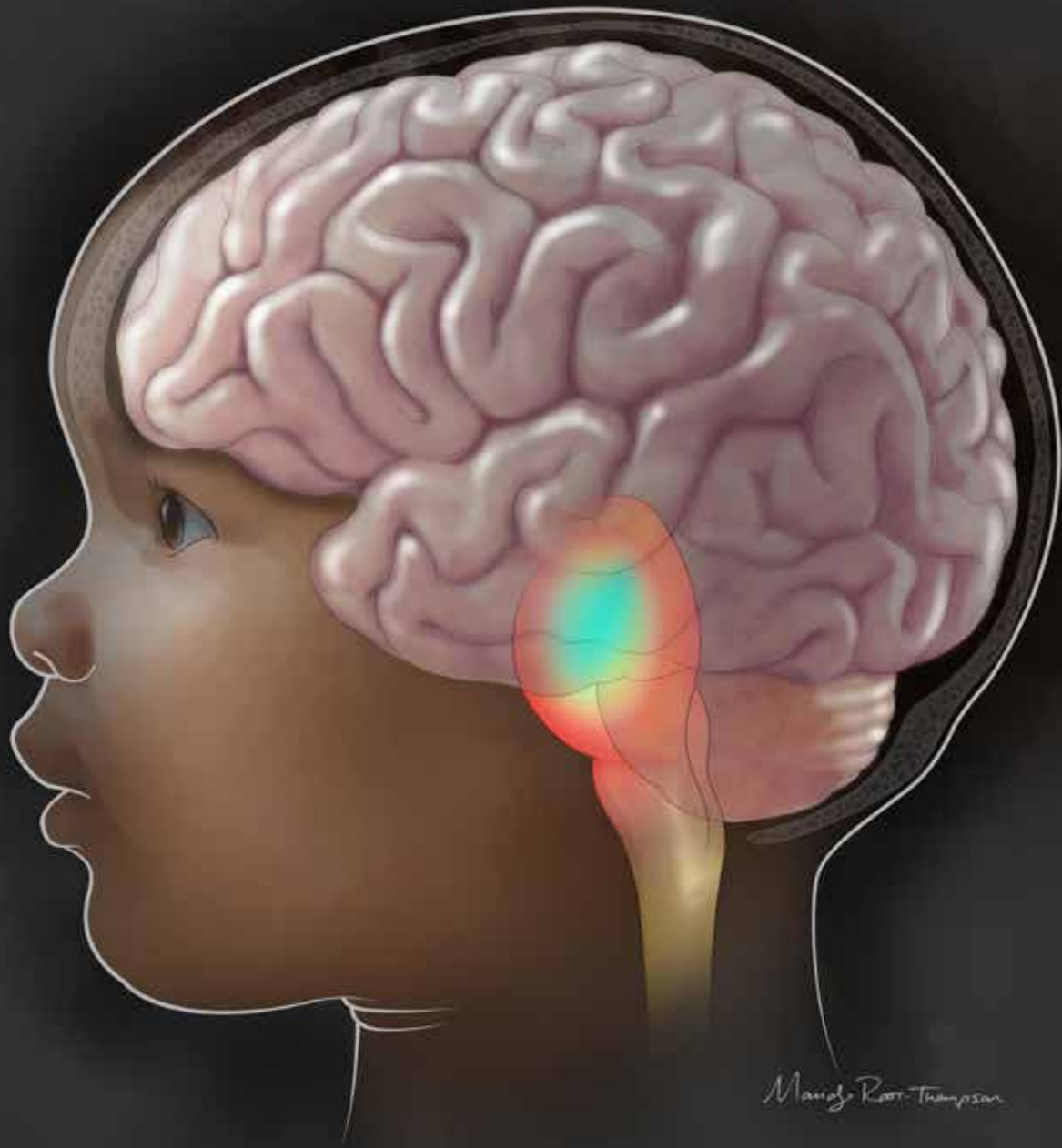
written by Katie Brind'Amour, PhD

In the past half-century of oncology care and research, pediatric cancer patients have benefited from skyrocketing survival rates for many diagnoses, with an overall 5-year survival of 83%. Not so for DIPG, for which nearly all efforts have failed: only 2% of children survive 5 years, and more than half are dead in less than a year.

While other cancers benefitted from targeted therapies and advances in tumor resection techniques, DIPG tumors have remained virtually untouchable despite inclusion in more than 250 clinical trials for chemotherapies, targeted therapy, combination therapies and immunotherapies. Although some patients respond briefly to radiation (which may extend life about 3 months), the cancer virtually always returns quickly, and to deadly effect.

The tumor is rare, with only 200-300 cases diagnosed each year in children in the United States. Its location in the brain's pons — the control center, directing the body's most basic and essential functions — makes DIPG hard to access for biopsy or drug delivery. The diffuse nature of the tumor also makes it essentially unresectable; tumor cells cannot be removed without taking vital healthy tissue with them.

These characteristics have made DIPG both difficult to treat and difficult to learn about. As the advent of molecular profiling and cancer genomics catapulted numerous cancer types into the realm of targeted therapies and increased cure rates, DIPG tissue samples to study were in short supply.





“THAT’S WHERE, AS A BASIC SCIENTIST, I BECAME VERY INTERESTED IN DIPG. IF IT IS INCURABLE, THAT MEANS WE DON’T KNOW THE BIOLOGY. OTHERWISE, WE WOULD FIND THE WEAKNESS AND TARGET THAT WEAKNESS. SO THE QUESTION WE ALL NEED TO ANSWER IS SIMPLE: WHAT IS THE BIOLOGY OF DIPG?”

– Rachid Drissi, PhD, principal investigator in the Center for Childhood Cancer and Blood Diseases in the Abigail Wexner Research Institute at Nationwide Children’s Hospital

“It’s a rare disease, but it’s killing people — it’s like a death sentence,” says Rachid Drissi, PhD, who recently joined the Center for Childhood Cancer and Blood Diseases in the Abigail Wexner Research Institute at Nationwide Children’s Hospital as a principal investigator. He has dedicated his career to studying the biology of high-risk pediatric brain tumors. “That’s where, as a basic scientist, I became very interested in DIPG. If it is incurable, that means we don’t know the biology. Otherwise, we would find the weakness and target that weakness. So the question we all need to answer is simple: What is the biology of DIPG?”

DIPG scientists and clinicians have faced an uphill battle. But dedicated experts from around the world — together with the families and patient advocacy organizations providing financial and practical support to make this work possible — are methodically tackling each hurdle in turn. And as they set the stage for more rapid advancements against this deadly disease, members of the DIPG research community are becoming increasingly optimistic about what the next 5-10 years will hold.

GETTING PAST LOCATION

After years facing down DIPG’s disappointing track record in clinical trials, researchers have pinpointed one likely physical reason as the blood-brain barrier: a cellular filtration system that prevents systemic therapies from crossing into the brain.

Many experts now believe that the majority of chemotherapy and other treatments delivered historically via standard methods to children with DIPG didn’t reach the tumors at all, or did so in such small quantities as to be rendered ineffective. To get around this natural barrier, clinician-scientists have been busy exploring and fine-tuning novel delivery methods, such as focused

ultrasound technology (which may temporarily disrupt the blood-brain barrier to allow the drugs to pass into the brain), nanoparticles and direct drug delivery of chemotherapy into the tumor.

“If we deliver drugs directly into target tissue, we will achieve higher concentrations than conceivable via the systemic route, with less toxicity,” says Mark Souweidane, MD, director of Pediatric Neurosurgery, New York-Presbyterian/Weill Cornell Medical Center and Memorial Sloan Kettering Cancer Center.

Dr. Souweidane has been working nearly two decades to operationalize the mechanical and technical aspects of chemotherapy infusion directly into brain tumors through a small catheter or cannula. His work with DIPG patients has demonstrated that direct injection can enable more than 1000-times the drug concentration in the target tissue than anywhere in systemic circulation, with no appreciable systemic toxicity.

“That has been a huge leap forward,” says Dr. Souweidane, who published his Phase I findings in *The Lancet: Oncology* in 2018. “Now the challenge is how to optimize this approach to make a positive clinical impact on this disease.”

In addition, basic scientists now also have the key resource at their disposal that, for decades, was denied them: tissue samples.

For many years, biopsies of DIPG were not performed. The location of the tumor in the pons left many clinicians and families fearing that any misstep during the procedure could result in significant morbidity — or even death. As a result, researchers had only limited amounts of postmortem tissue to study, which may

have mutated considerably after diagnosis due to treatments or tumor evolution.

“The biggest thing hindering research progress was the lack of tumor tissue,” says Chris Jones, PhD, head of the Glioma Team and full professor of Childhood Brain Tumor Biology at The Institute of Cancer Research in London. “Families on both sides of the Atlantic pushed for safe biopsy procedures to provide labs like mine with the tissue we needed to study DIPG, so the next generation of kids hopefully won’t have to go through what they did. They came together and catalyzed the last 15 years of DIPG research.”

The result was transformative. In 2012, researchers including those now leading the Steve and Cindy Rasmussen Institute for Genomic Medicine (IGM) at Nationwide Children’s, profiled the genome of seven DIPG tumors (and then performed targeted screening in an additional 43 tumors) and uncovered an abnormality common to nearly four in every five cases: a mutation called *K27M* in the histone H3 family of genes. Previously thought of as an untouchable portion of the genome in terms of mutations, the group of histone H3 variants were unique to human biology at the time.

That’s when the clock started ticking toward a biology-based cure for DIPG.

A NEW ERA FOR DIPG BIOLOGY

With the seminal genomic study and almost a decade of research to follow, scientists now have preliminary genome-based classifications for DIPG tumors. The work has shown, however, that numerous mutations — sometimes within a single tumor — may all be materially involved in the disease and its progression.

“We now know there is important heterogeneity across patients, in that no two patients have the same list of mutations as one another. And there is heterogeneity within an individual’s DIPG tumor as well — mutations occur at different stages and in different cells, creating a complicated mosaic of tumor subclones with different mutations interacting with each other,” says Professor Jones, who led a multi-institutional effort to identify key mutations in 322 DIPG tumors (and more than 600 other high-grade gliomas), published in *Cancer Cell* in 2017. The effort identified numerous additional genomic subgroups for DIPG and examined prognosis related to the mutations.

“It’s a complicated profile,” Professor Jones says, “and genomics helps unravel the details and may guide treatments we might give to patients with this disease.”

Histone tail involvement points to a role for the cellular microenvironment and epigenetics in the development of DIPG. The histone tail interacts with the rest of a cell’s DNA strand, signaling to turn certain genes on or off. Unfortunately, *K27M* mutations remain elusive targets from a therapeutic standpoint; new drugs must precisely impact the histone tail so that it sends proper signals for gene expression.

Utilizing other information revealed by the genomics studies, Professor Jones and his research team are developing what may be the first drug designed to specifically target a childhood brain tumor mutation, expected to enter clinical trials in the coming year or two. His compound targets somatic mutations in *ACVRI*, which are present in about 25% of DIPG cases.

Additional efforts aim to connect clinical practice with existing genomic information to allow refinement of the current subgroups and prognostic data.

“We wanted to see if there was a correlation between tumor features seen in serial clinical imaging and those actual tumors’ genomics and expression of genes,” says Dr. Drissi.

He and his team have explored this concept of “radiogenomics” in DIPG and successfully identified imaging characteristics for certain prognoses and DIPG subgroups, such as those with *H3F3A* mutations (who have a poor response to radiation therapy) or those with numerous mutations and inflammatory tumor profiles (who have a favorable initial response radiographically to radiation). They published the work this year in *Acta Neuropathologica Communications*.

Radiogenomics may be imminently helpful in the clinic, as imaging is the first thing done when a neurological abnormality is suspected. For example, *H3F3A* cases could potentially benefit from upfront craniospinal irradiation, Dr. Drissi suggests, while those with initial responses to radiation could potentially benefit from post-radiation immunotherapy.

“Time is of the essence for these patients,” says Dr. Drissi. “The ultimate goal is that from initial imaging, we can tell what each patient’s subtype is, the best treatment options and what their prognosis will be.”



“IN RECENT YEARS, BASIC SCIENCE RESEARCH IN DIPG HAS PROVIDED NEW AND EXCITING INSIGHTS IN THE CELL-INTRINSIC VULNERABILITIES OF DIPG CANCER CELLS, THE INTERACTIONS WITH HEALTHY BRAIN CELLS THAT DRIVE THE GROWTH OF DIPG AND IMMUNO-THERAPEUTIC OPPORTUNITIES FOR DIPG. TRANSLATING THOSE DISCOVERIES TOWARDS EFFECTIVE THERAPIES FOR CHILDREN WITH DIPG IN THE NEXT 5-10 YEARS WILL REQUIRE COOPERATION AND COLLABORATION AMONG ACADEMIC CHILDREN’S HOSPITALS, LIKE THOSE THAT PARTICIPATE IN PEDIATRIC BRAIN TUMOR CLINICAL TRIALS CONSORTIA.”

— Michelle Monje Deisseroth, MD, PhD, associate professor of Neurology and Neurological Sciences at Stanford University

Dr. Drissi’s continued work in genomics-informed DIPG research will now involve the IGM team at Nationwide Children’s, which offers genomic profiling for research purposes and for patients with recurrent, treatment-resistant or rare tumors. Theoretically, radiogenomic data could also be paired with knowledge obtained from another emerging research tool: “liquid biopsies,” or samples of cerebrospinal fluid and blood taken periodically post-diagnosis.

“We need to make sure that any child with DIPG entering clinical trials contributes tissue and other samples in order to understand the changes in the tumor and its environment across time and treatment,” says Professor Jones, who is also the preclinical lead for the CONNECT Consortium, an international research collaborative focused on DIPG and other high-risk pediatric brain cancers. “We need to understand the basic biology of the tumor itself in order to develop rational, smart combination therapies, test them in preclinical models and collectively figure out what’s working, so we can get it to the next phase more rapidly.”

Genomics profiling work and science-based clinical studies have also prompted tumor microenvironment studies of DIPG. Together they may further explain why the cancer has not fallen prey to natural immune system defenses or immunotherapies tried to date.

DIPG is considered an immunologically “cold” tumor in that it incites very little, if any, immune response or inflammation, likely because it results from relatively few mutations (compared to adult cancers) and has no obvious antigen that tells the immune system to target it.

“We are in the process of understanding the tumors’ strategies for hiding from the immune system,” Dr. Drissi says. “Once we get to know how the tumor avoids it, our job will be to push DIPG cells to express genes to make them look like invaders, to tell the body, ‘You need to attack these cells!’”

These unique and varied approaches all attempt to exploit the biology of the tumor as information accrues from tissue samples, novel models and genomics studies. Just having access to this robust information that enables thorough biological examination — for the first time since the cancer’s discovery — means research is able to progress on many fronts.

ACCELERATING TRANSLATIONAL RESEARCH

“In recent years, basic science research in DIPG has provided new and exciting insights in the cell-intrinsic vulnerabilities of DIPG cancer cells, the interactions with healthy brain cells that drive the growth of DIPG and immuno-therapeutic opportunities for DIPG,” says Michelle Monje Deisseroth, MD, PhD, associate professor of Neurology and Neurological Sciences at Stanford University. “Translating those discoveries towards effective therapies for children with DIPG in the next 5-10 years will require cooperation and collaboration among academic children’s hospitals, like those that participate in pediatric brain tumor clinical trials consortia.”

To this end, Maryam Fouladi, MD, pediatric neuro-oncologist and the new co-executive director of the Pediatric Neuro-Oncology Program at Nationwide Children’s, founded the CONNECT Consortium in

2012. The international collaborative of pediatric cancer research and clinical care centers exists to improve outcomes for children with high-risk brain tumors such as DIPG and other high-grade gliomas, and will now be based out of Nationwide Children's.

“DIPG is a wily tumor,” says Dr. Fouladi, who is currently leading a trial to test efficacy and safety of combining a BMI-1 inhibitor with radiation therapy in children with DIPG and other high-grade gliomas (CONNECT1702); the study is based on findings from basic science collaborations with Dr. Drissi and others, described in a 2020 publication in *Molecular Cancer Research*. “It develops resistance and survives through multiple different pathways, so we will need a multi-pronged approach to trying to cure it.”

The 18 member centers of the CONNECT Consortium examine (in their own labs and models) promising therapies emerging from preclinical and Phase I studies, hoping to identify the most fruitful potential drug combinations for DIPG. Provided positive early results are replicable, CONNECT members rapidly design scientifically rational pilot studies to evaluate these combination therapies in the clinic — often with seed money made available by the companies that developed the drugs — to gather preliminary safety and efficacy data. Then they share the group's findings with larger consortia, such as the Children's Oncology Group, so that tolerable and auspicious combination therapies can be rapidly moved into more mainstream Phase II/III testing.

“We want to build on what we know works right now — radiation — not just throw every method at these children and adversely affect their quality of life,” says Dr. Fouladi. “We want to judiciously, carefully conduct clinical trials looking at both toxicity and efficacy, combining radiation with chemotherapy, immunotherapy or targeted therapy. Progress will be incremental, but in the end, all of these are likely to become part of an effective armamentarium against DIPG in some way.”

Greater understanding of biology and scientifically sound drug combinations revealed by consortium-based studies have also aided further study of clinically viable tools for drug delivery.

Dr. Souweidane has a multi-center Phase II clinical trial in development to examine the capacity of the highly technical platform of direct chemotherapy injection to reach a far greater community. Anecdotally, direct

chemotherapy injection has already yielded some encouraging results, with a handful of patients from Dr. Souweidane's Phase I trial surviving beyond 3 years (median survival was 15.3 months) and another two patients considered cured.

“We've taken care of the technical, mechanical and surgical hurdles, so the next step is to demonstrate clinical benefit: optimizing direct chemotherapy injection for enhanced distribution of the drug, maximizing tumor coverage, defining tumor response criteria, adding rounds of treatment and building on the solid conceptual foundation of the platform,” says Dr. Souweidane. “If we can control the tumor at its major point of origin, then supplement with multimodal therapy — systemic treatment, external beam radiation or another modality to help avoid distant recurrence — I have no misgivings about what we can accomplish with this.”

With thoughts of multimodal care in mind, Dr. Fouladi will collaborate with The Ohio State University Wexner Medical Center as the two institutions open central Ohio's first proton therapy center for targeted radiotherapy in 2021. Together with colleagues in radiation oncology at the university, Dr. Fouladi hopes to explore numerous additional ways to optimize radiation for children by minimizing dosage and toxicity.

Coupled with the efforts from the DIPG Registry — also founded and chaired by Dr. Fouladi to advance DIPG research via the collection and sharing of tissue samples — and other, larger pediatric cancer consortia (such as the Pediatric Brain Tumor Consortium, the Pacific Pediatric Neuro-Oncology Consortium and the NEXT Consortium, all of which now claim Nationwide Children's as a member or host institution), things are looking up.

The DIPG Registry, for example, includes more than 1200 patients at about 115 sites in 15 countries, pooling clinical imaging, pathology findings and tissue samples to enable large-scale studies of DIPG biology. The registry has enabled 140 disease models and more than 30 collaborative studies, with numerous publications to share valuable data with the broader scientific community. The registry's genomics efforts will now be based out of Nationwide Children's IGM.

“Being part of multiple large, organized consortia is really a major privilege, as it opens the door to our patients to be part of clinical trials and receive novel



“THIS IS NOT A DISEASE ANYONE CAN CURE ON THEIR OWN—IT WILL TAKE MORE THAN JUST NEUROSURGEONS, JUST CLINICIANS, JUST GENETICISTS OR JUST PHARMACOKINETICISTS—IT’S TRULY GOING TO TAKE A VILLAGE. THE BEAUTY OF THE DIPG COMMUNITY IS THAT PATIENTS AND PARENTS ARE UNBELIEVABLY SUPPORTIVE AND THE RESEARCHERS AND CLINICIANS ARE EXTREMELY COLLABORATIVE. BY BEING SO, WE’VE MADE HUGE STRIDES TOGETHER. NOW WE HAVE TO TAKE ALL OF THIS UNDERSTANDING OF BIOLOGY AND FIGURE OUT HOW TO TURN IT INTO A CURE.”

– Maryam Fouladi, MD, pediatric neuro-oncologist and the new co-executive director of the Pediatric Neuro-Oncology Program at Nationwide Children’s Hospital

treatments that wouldn’t be available otherwise,” says Ralph Salloum, MD, another recent addition to the neuro-oncologist team at Nationwide Children’s; he is a principal investigator for the Pediatric Brain Tumor Consortium and study chair of two studies through the consortium. “DIPG tumors are rare. These consortia allow our trials to open to patients at other institutions, so that they get access to the trial and we get enough patients to answer research questions and advance the field — it’s a mutually beneficial relationship.”

IMPROVING SURVIVAL, AS FAST AS POSSIBLE

For decades, DIPG has been the biggest challenge in the world of pediatric cancer. But with biology and genomics data, tissue samples, consortia, funding opportunities and new delivery techniques falling into place, experts around the world believe they are well positioned to make major inroads in DIPG care and survival.

“This is not a disease anyone can cure on their own — it will take more than just neurosurgeons, just clinicians, just geneticists or just pharmacokineticists — it’s truly going to take a village,” says Dr. Fouladi. “The beauty of the DIPG community is that patients and parents

are unbelievably supportive and the researchers and clinicians are extremely collaborative. By being so, we’ve made huge strides together. Now we have to take all of this understanding of biology and figure out how to turn it into a cure.”

These combined advances are likely to result in incremental progress, through which a true “cure” is really more of a steady crawl toward improved survival.

“There is a desperation we all feel, but I can’t say we’re going to cure it in the next 5 years — a whole lot still needs to be done,” says Jeffrey Leonard, MD, co-executive director of the Pediatric Neuro-Oncology Program and chief of Neurosurgery at Nationwide Children’s. His research focuses on the genetics of pediatric brain tumors and potential immunomodulatory and exosome therapies. “There needs to be a significant advancement in our understanding of DIPG tumor pathogenesis, and we are grateful to be one of the centers leading that.”

As advancements roll in, neuro-oncologists may eventually be able to shift some of their efforts to other positives that come with climbing survival statistics: what happens



“THERE IS A DESPERATION WE ALL FEEL, BUT I CAN’T SAY WE’RE GOING TO CURE IT IN THE NEXT 5 YEARS — A WHOLE LOT STILL NEEDS TO BE DONE. THERE NEEDS TO BE A SIGNIFICANT ADVANCEMENT IN OUR UNDERSTANDING OF DIPG TUMOR PATHOGENESIS, AND WE ARE GRATEFUL TO BE ONE OF THE CENTERS LEADING THAT.”

– Jeffrey Leonard, MD, co-executive director of the Pediatric Neuro-Oncology Program and chief of Neurosurgery at Nationwide Children’s Hospital

after DIPG treatment success, when patients finally have a future ahead of them.

When that time arrives, Dr. Fouladi and Dr. Salloum will have additional fuel for their research, which has long included the reduction of post-therapy late effects of treatment, often via a better understanding of tumor biology, improved treatment techniques or the reduction in dosage required to shrink tumors. Dr. Salloum joined Nationwide Children’s in part to spearhead the development of a new multidisciplinary brain tumor survivorship program.

The prospect of survivors has been elusive to date, but it is an exciting one for those who have devoted their careers to DIPG research.

“If we can find a cure for this, it would be huge, because if you asked what cancer has the worst prognosis in pediatrics, most people would tell you it is DIPG,” says Dr. Fouladi. “One day I hope to say it isn’t. That’s why we need to focus on it. We have a lot of great people working together now — without any egos and for the right reasons — to get this done.”

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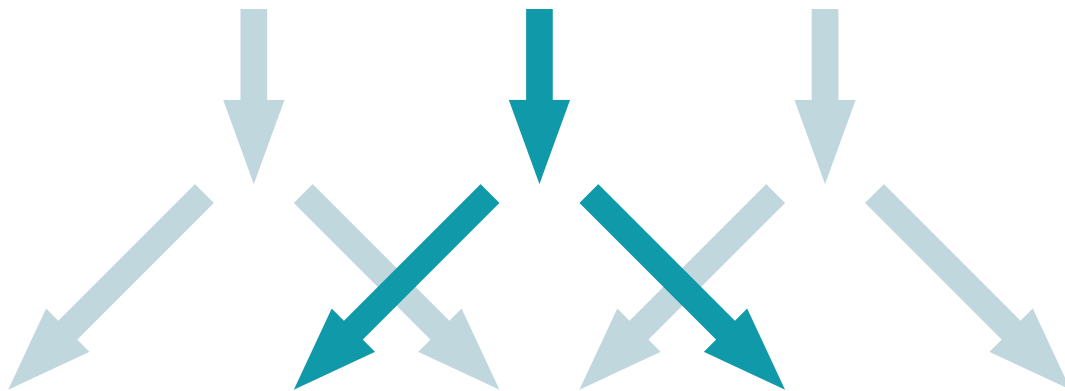
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Understanding Immune Responses to Build a Better Vaccine

Researchers have used studies of respiratory syncytial virus and infant immune responses to develop a promising vaccine candidate.



Written by Abbie Roth

Respiratory syncytial virus (RSV) is an incredibly common yet potentially deadly pathogen. Almost everyone becomes infected with RSV during their first three years of life, but for certain populations — infants and elderly or immunocompromised people — RSV infection can lead to hospitalization or even death. According to the Centers for Disease Control and Prevention (CDC), RSV causes an average of 2.1 million outpatient visits and 58,000

hospitalizations among children younger than 5 years old each year in the United States alone.

Unfortunately, the search for a vaccine for this dangerous virus has been long and complicated. Researchers have been working on a vaccine since the virus was identified more than 60 years ago. Many vaccine candidates have been proposed over the decades, and all have ultimately failed to provide a satisfactory protective response — but that may be changing.

“One of the most problematic barriers to developing an RSV vaccine in the past was the lack of collaboration. We need more people working together with different types of expertise to make progress in this field — that approach is what has helped us to be successful.”

– *Stefan Niewiesk, DVM, PhD, professor in the Department of Veterinary Biosciences at The Ohio State University*



Teamwork Makes the Dream Work

In 2015, a team of six researchers received a \$6.75 million program project grant from the National Institutes of Health to study immune responses to RSV with the ultimate goal of developing a vaccine candidate.

The team spans multiple areas of expertise and three research institutions: Nationwide Children’s Hospital, The Ohio State University and the University of South Florida. Its principal investigators include Octavio Ramilo, MD, Asuncion Mejias, MD, PhD, Mark Peeples, PhD, Jianrong Li, DVM, PhD, Stefan Niewiesk, DVM, PhD, and Michael Teng, PhD.

“Program project grants are not easy to obtain, but they are an effective mechanism to bring investigators together,” says Dr. Teng, who is a virologist at the University of South Florida. “With this group, we can play off of each other, building on each other’s strengths and insights.”

That spirit of collaboration has resulted in a prolific research publication record. The team has published

more than 46 peer reviewed articles based on grant-funded research. And even more importantly, they’ve achieved their initial goal of developing a vaccine candidate for RSV.

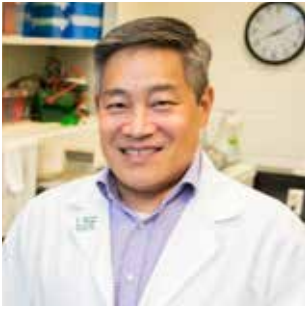
“One of the most problematic barriers to developing an RSV vaccine in the past was the lack of collaboration,” says Dr. Niewiesk, a professor in the Department of Veterinary Biosciences at Ohio State. “We need more people working together with different types of expertise to make progress in this field — that approach is what has helped us to be successful.”

“Forty six papers from our team — 39 with at least two of the six principal investigators in the group — is a remarkable feat,” says Dr. Ramilo, chief of Infectious Diseases and principal investigator in the Center for Vaccines and Immunity at Nationwide Children’s. “Many of these papers have been in high-impact journals, and some describe research that has led to patents. We have been able to greatly add to the knowledge about RSV and immune responses in infants.”



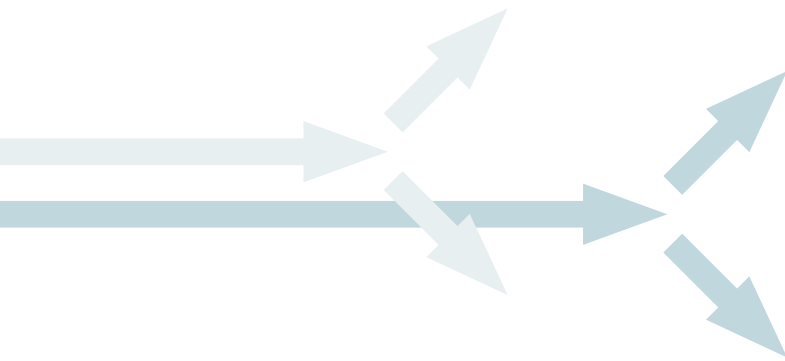
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“To have a successful vaccine, you need to reduce viral replication — that is, attenuate the virus. In the past, vaccine candidates were often so attenuated that they could not induce an effective immune response, and if they could, they were not attenuated enough.”

– Michael Teng, PhD, Allergy and Immunology, Department of Internal Medicine, University of South Florida



Laying the Foundation

The researchers say that another key to their success has been to focus on the immune profiles of infants affected by RSV — those who have mild disease and those who get severe disease.

In short, if you know what the immune profile of a baby who successfully recovers from RSV disease looks like, you can design a vaccine candidate that produces that same response in babies who haven't been infected, preparing them to better protect themselves from a future encounter with the virus.

“To have a successful vaccine, you need to reduce viral replication — that is, attenuate the virus. In the past, vaccine candidates were often so attenuated that they could not induce an effective immune response, and if they could, they were not attenuated enough,” says Dr. Teng.

“If we can attenuate the virus in a way that also enhances the host immune response, we will be successful,” says Dr. Li, professor of virology at Ohio State.

“The work of Drs. Mejias and Ramilo helps us to identify signals that the virus-infected cells in children produce that lead to a protective immune response. Those signals become our goals for vaccine candidates,” says Dr. Teng.

To find the right signals, Drs. Mejias and Ramilo have led numerous studies teasing apart the complicated

web of immune responses in infants and children with RSV infection.

Even before the program project grant brought the larger team together, Drs. Mejias and Ramilo were analyzing the RNA profiles — biosignatures — of RSV-infected children to understand which genes were activated in children with mild disease compared to those who develop severe disease. In a 2013 study published in *PLoS Medicine* they showed the benefits of using RNA profiles as a diagnostic tool for differentiating RSV and influenza or rhinovirus infections and for objectively assessing RSV disease severity.

This research formed the bedrock of much that has followed.

“There is so much to learn about how different variables affect immune responses in children and infants with RSV,” says Dr. Ramilo. “We use many techniques, genomics, transcriptomics and metabolomics to look at how age, viral load, immune response and disease severity interact.”

Sometimes, the team's findings have surprised them.

A 2019 study published by the team in *Journal of Infectious Diseases* showed that children with milder disease actually were producing more virus than children with severe disease.

“This result was counterintuitive, because it was assumed that greater amount of virus in nasal secretions during the acute infection would be associated with more severe disease,” says Dr. Mejias. “But this is not the case with RSV. It appears that higher RSV loads trigger a more robust mucosal immune response that in turn is associated with better outcomes.”

Additional research by the team, including their 2020 publication in *Science Translational Medicine*, confirmed these surprising results. This led to an insight in clinical outcomes.

“Among babies who were hospitalized, those that received systemic steroids, which are not routinely indicated for the management of RSV infection, cleared the virus at a slower pace and had worse outcomes,” says Dr. Ramilo. “This observation is specifically relevant for children with severe RSV infection hospitalized in the PICU, for whom treatment with steroids should be avoided.”

But how do immune profiles help researchers develop vaccines?

“By defining what a protective immune profile looks like, we can design the vaccine candidates that should stimulate that response,” says Dr. Mejias. “For example, we know based on *in vivo* and *in vitro* studies that higher levels of IL-6 indicate a more severe illness. But higher levels of IP-10 are protective. Understanding a ‘good’ immune response is critical to our success in developing an effective vaccine.”

While the team’s understanding of the immune response to RSV has greatly improved and has influenced the development of a vaccine candidate, they say there’s still more to learn. Further understanding, defining and

potentially manipulating immune responses to RSV could lead to a better vaccine.

Building the Vaccine

With a better understanding of successful immune profiles, the team of researchers has been able to develop vaccine candidates that achieve that immune response with weakened viruses that don’t cause illness.

The team’s novel approach, described in a recent publication in the *Journal of Virology*, uses a recombinant RSV carrying mutations in two viral proteins, one in the RSV G protein that attaches the virus to the ciliated cells lining the airways, and one in the RSV polymerase protein that replicates the virus genome.

“We learned several years ago that the G protein is cut when RSV is produced in cultured cells, making the virus less able to infect the cells lining the nose, that’s where this vaccine will be given. We located the site of the cut and mutated it to prevent this cleavage. As a result, we increased the amount of vaccine we can produce by 5 times. That will make the vaccine more economical to produce, another of our goals,” says Dr. Peeples.

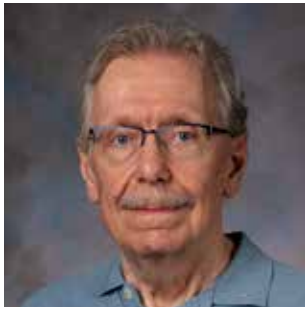
Dr. Li’s focus is the other side of this vaccine candidate: the large polymerase (L) protein. The main function of the L protein is to make viral RNA, genome RNA and messenger RNA that is translated into viral proteins. By modifying the L protein, researchers can slow down the production of RNA and therefore the speed of virus replication, attenuating the virus so it cannot cause disease. And, as a bonus, these same mutations induce a protective immune profile, more like that found in patients with mild RSV disease.

The result is a virus that grows well in cultured cells,



“By defining what a protective immune profile looks like, we can design the vaccine candidates that should stimulate that response. For example, we know based on *in vivo* and *in vitro* studies that higher levels of IL-6 indicate a more severe illness. But higher levels of IP-10 are protective. Understanding a ‘good’ immune response is critical to our success in developing an effective vaccine.”

– Asuncion Mejias, MD, PhD, principal investigator in the Center for Vaccines and Immunity at Nationwide Children’s Hospital



“While we are very excited about the candidate vaccine that we’ve already developed by applying what we’re learning about the immune response of children, we’re looking forward to enhancing the response to the virus in hopes of making our vaccine candidate even better. We’ll compare all these candidates in cultured cells from the airways and in cotton rats to identify the best possible vaccine by all the criteria we have developed, before moving into clinical trials.”

—Mark E. Peeples, PhD, principal investigator in the Center for Vaccines and Immunity at Nationwide Children’s Hospital

initiates infection efficiently *in vivo*, but is also highly attenuated *in vivo*, while inducing a protective immune response.

“Our work on the vaccine components is synergistic,” says Dr. Li, who has been collaborating with Dr. Peeples on different projects for more than 15 years. “By addressing both attenuation and immunogenicity, we knew we could develop an effective vaccine for RSV.”

Testing the Candidate

The vaccine candidate was evaluated in the cotton rat model for *in vivo* immunogenicity and protection. Dr. Niewiesk is an expert in using this model for respiratory viruses.

“We use the cotton rat for RSV, rather than mice, because the cotton rat is much more susceptible to RSV infection and more predictive of human neutralizing antibody production in response to RSV,” he explains. Neutralizing antibodies are those that can act against the virus in the respiratory tract — preventing illness within a person as well as infection between people.

Intranasal delivery of a small dose of the RSV vaccine candidate provided complete protection of both the upper and lower respiratory tracts.

What’s Next?

Experiments are already underway to improve the recently published candidate even further — the team isn’t satisfied with “good” when “better” is within sight.

Part of the reason to push for the best possible vaccine is the vulnerable nature of the intended recipients. Infants and elderly patients who are at highest risk for severe RSV disease are also the highest risk for vaccine complications.

Dr. Peeples’ work on the F (fusion) protein is the other half of the immunogenicity coin. The researcher says the F protein on the surface of RSV is the target for nearly all neutralizing antibodies. The F protein grabs the target membrane and initiates fusion with its own membrane, delivering the virus genome to the target cell.

“We know that antibodies to the F protein are the best at neutralizing RSV. And we know that the original form of



“Our work on the vaccine components is synergistic. By addressing both attenuation and immunogenicity, we knew we could develop an effective vaccine for RSV.”

—Jianrong Li, DVM, PhD, professor in the Department of Veterinary Biosciences at The Ohio State University

the F protein — pre-fusion F — is by far the best form for inducing neutralizing antibodies. Our next goal is to add a stabilized version of the pre-fusion F protein to the vaccine to increase its potency,” says Dr. Peeples.

“We also must ensure that our live attenuated vaccine remains attenuated,” says Dr. Li. “If it were to revert to the wild-type RSV, it could harm patients. To avoid this possibility, we are combining multiple mutations, and using deletion or insertion mutations where possible because they are much less likely to revert.”

Additionally, the team is interested in long-term protection against RSV. Several types and strains of RSV circulate in the community, and individuals can get repeatedly infected. One way to achieve a longer-term immunity is to enhance the innate immune response to the virus. However, RSV is notorious for bypassing interferon responses.

“We have developed a strategy to enhance the type 1 interferon response to improve long-term immunity,” says Dr. Li. “And we look forward to testing it to see if, as we predict, it will improve the vaccine.”

“While we are very excited about the candidate vaccine that we’ve already developed by applying what we’re learning about the immune response of children, we’re looking forward to enhancing the response to the virus in hopes of making our vaccine candidate even better,” says Dr. Peeples. “We’ll compare all these candidates in cultured cells from the airways and in cotton rats to identify the best possible vaccine by all the criteria we have developed, before moving into clinical trials.”

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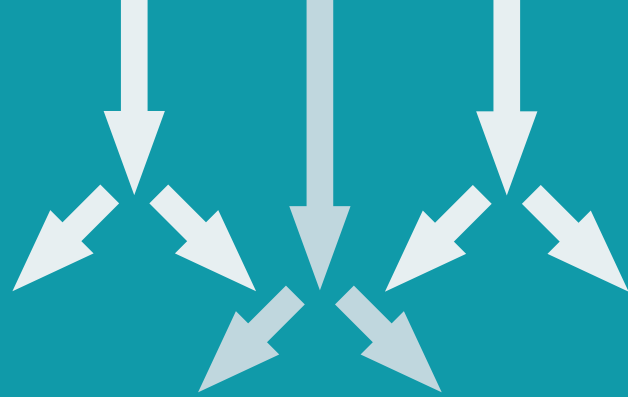
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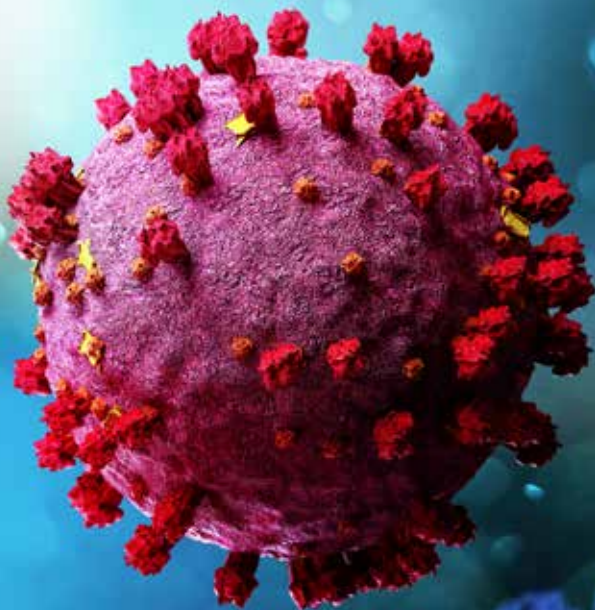


An RSV-COVID Connection

A team of researchers from Ohio State and Nationwide Children’s have built a novel vaccine candidate against SARS-CoV-2. The vaccine candidate, published in *Proceedings of the National Academy of Science* (PNAS), used some of the techniques learned and inspiration from their RSV research.

The team added a pre-fusion version of the SARS-CoV-2 spike protein to the measles vector to create the candidate. Learn more about the vaccine candidate born from collaboration between the teams of Drs. Li, Niewiesk and Peeples.

PediatricsNationwide.org/Measles-COVID-Vaccine



LESSONS LEARNED THROUGH A GLOBAL PANDEMIC

Written by Lauren Bakaletz, PhD, director of the Center for Microbial Pathogenesis, Tillie E. Coleman Endowed Chair in Pediatric Research and vice president for Basic Sciences Research at Nationwide Children's Hospital, as well as the recipient of the 2021 Steve Allen Distinguished Scholar Award

As a microbiologist and vaccinologist, I spend nearly every day thinking about viruses and bacteria and the diseases they cause, as well as how to best prevent them from doing so.

While in graduate school, we were taught about the great 'flu' pandemic of 1918 that infected one-third of the world's population and killed 20-50 million people, as well as the lessons learned from that tragic event.

Given all the advances in public health since that time, I never thought I would experience a global pandemic of those proportions in my own lifetime. And yet, we're all experiencing a similarly catastrophic event with 110 million cases of COVID-19 worldwide as of mid-February 2021. One that will require additional vigilance to overcome.

I was asked recently if there was likely any good to come out of this situation and what lessons I believe we will learn this time. I believe there are many.

First, we learned that we don't need decades to make a vaccine.

There was nothing typical about the race to develop vaccines to prevent SARS-CoV-2 disease, but it's important to remember that no important steps in the painstaking process to create a safe and effective vaccine were compromised, despite the rapid pace. Normally, this process can take 10-20 years. For example, in 2004, my team demonstrated that one

of the bacteria, nontypeable *Haemophilus influenzae* (NTHI), expressed an appendage called a 'type IV pilus.' We reported this for the first time early in 2005. Since then, there were 10 more years of extensive studies in laboratory before the vaccine candidate we developed to prevent otitis media or exacerbations of COPD was first injected into a human being. These clinical trials are still underway, 17 years later.

But in the face of a pandemic of this proportion, for a virus this transmissible and due to an intolerably high death rate, a greater sense of urgency prevailed. The needed resources were provided. Further, prior experience with outbreaks of both SARS in 2002 and MERS in 2012, which are also members of the coronavirus family, helped jumpstart efforts to develop vaccines against SARS-CoV-2, as much was learned in those efforts.

Now, we have a far greater understanding of messenger RNA and how mRNA vaccines work. My hope is that this experience will allow us to now consider mRNA vaccines for other viral pathogens (e.g. measles, mumps, rubella, vaccinia, varicella-zoster, yellow fever, rotavirus and influenza) thereby increasing efficacy and/or facilitating delivery to immunocompromised or pregnant individuals. Additionally, my hope is that we have learned how to better streamline the process for other long-sought or needed vaccines and even more public-private partnerships will be aligned to achieve similar goals.



“SARS-CoV-2 has taught a Master Class to the entire world about how incredibly powerful these invisible-to-the-naked-eye entities [viruses] can be.”

— Lauren Bakaletz, PhD

Second, SARS-CoV-2 has taught a Master Class to the entire world about how incredibly powerful these invisible-to-the-naked-eye entities can be. With only a fraction of the genetic material that a human has, microbes have the power to bring us to our knees. This has also brought renewed attention to the need for scientists, physicians and public health workers to help us through the current pandemic. And to help prevent a future pandemic of this magnitude.

I believe there is enhanced appreciation for the real need for scientists, bench researchers and those who both conduct and participate in clinical trials. The Association of American Medical Colleges report an 18% increase in applications to enter medical school in 2021. Many attribute this fact to the “Fauci effect” due to the high visibility of, and confidence in, Anthony

Fauci, MD, the director of the National Institute of Allergy and Infectious Diseases, during the pandemic.

The New York Times reports that COVID-19 has changed how the world does science, “creating a global collaboration unlike any in history.” And Pew Research reports that Americans’ confidence in scientists has grown, along with perceptions that physicians hold high ethical standards. In my experience, any increase in interest in, knowledge and understanding of the work of basic scientists, clinician scientists and physicians is welcome. My hope is that this will translate into greater support for funding of the work that we do.

Finally, this pandemic has taught me to never again take for granted all the simple things in life that I have missed so dearly this past year.

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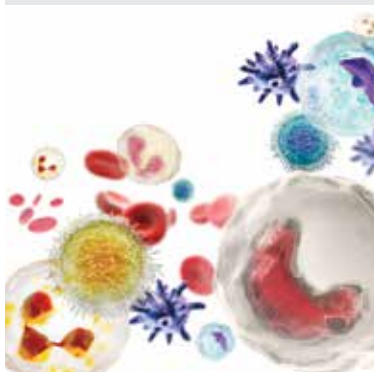


Targeting FSHD With Designed Antisense RNAs

Written by Abbie Roth

Facioscapulohumeral muscular dystrophy (FSHD) arises from genetic and epigenetic changes that result in expression of the *DUX4* gene in muscle. Researchers have described small nuclear RNA antisense expression cassettes as a way to silence the *DUX4* gene underlying facioscapulohumeral muscular dystrophy.

[PediatricsNationwide.org/FSHD-antisense-RNAs](https://www.PediatricsNationwide.org/FSHD-antisense-RNAs)



Modifying NK Cells With CRISPR/Cas9

Written by Mary Bates, PhD

In a new proof-of-concept study, researchers used CRISPR/Cas9 technology to genetically modify natural killer immune cells, which they then showed are able to address a recognized hurdle in immunotherapy of multiple myeloma.

[PediatricsNationwide.org/NKCells-CRISPRCas9](https://www.PediatricsNationwide.org/NKCells-CRISPRCas9)



Investigating Youth Suicides Among Children Involved With the Welfare System

Written by Natalie Wilson

To better understand and prevent suicide in this at-risk group, researchers at conducted the first study to compare characteristics and health service utilization patterns of youth suicide decedents (those who died by suicide) and non-decedents who were involved with the child welfare system.

[PediatricsNationwide.org/Youth-Suicide-Welfare](https://www.PediatricsNationwide.org/Youth-Suicide-Welfare)

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