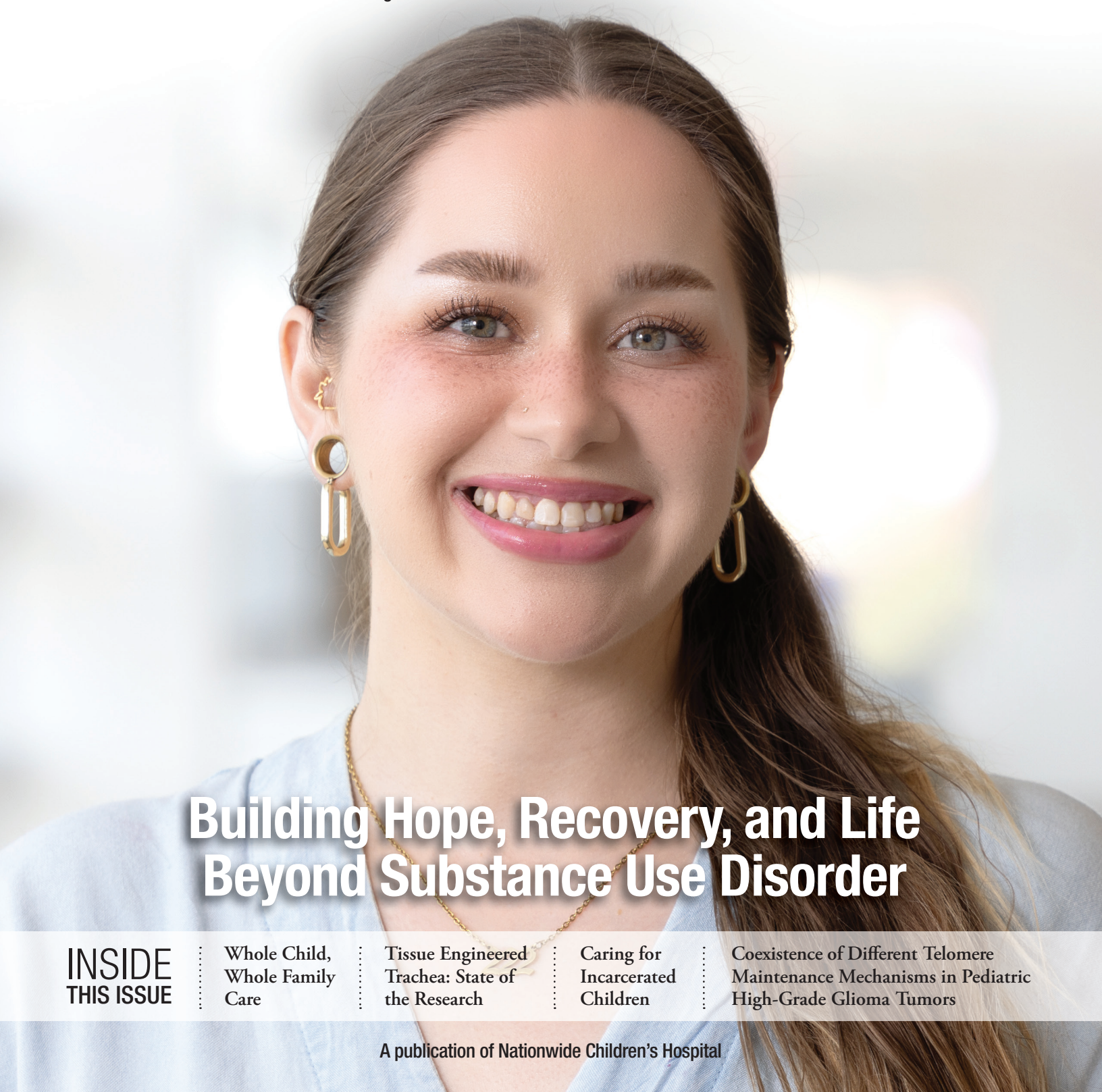
Pediatrics NATIONWIDE

Advancing the Conversation on Child Health | Fall/Winter 2023



Building Hope, Recovery, and Life Beyond Substance Use Disorder

INSIDE THIS ISSUE

A publication of Nationwide Children's Hospital

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Substance use disorder is treatable. Accidental ingestion and overdose are preventable.

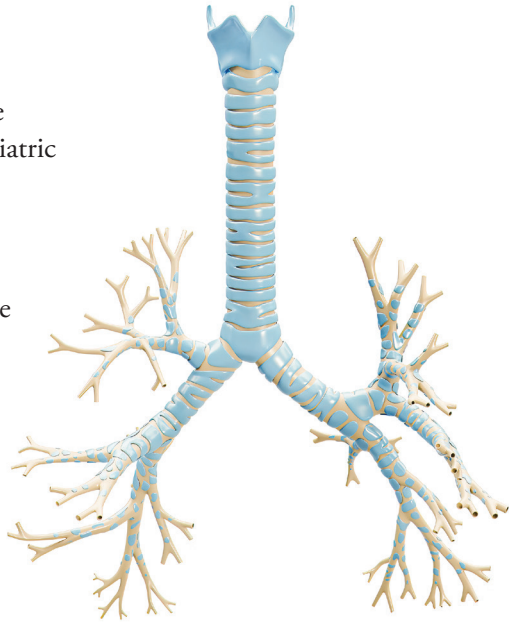
This issue features important information about the critical role pediatricians have in protecting kids. They're at the center of helping families, children and adolescents navigate a world where substances pose significant threats.

The cover story "Building Hope, Recovery and Life Beyond Substance Use Disorder" introduces you to Sarah, who is in recovery thanks to her hard work and the support and compassion of her providers at Nationwide Children's Hospital. She and Dr. Erin McKnight, pictured together above, are proof that providers can offer hope to troubled youth and that treatments work.

We also hear from experts in toxicology and emergency medicine about how the increasing availability of marijuana products puts young children at risk. Safe storage education and having open conversations with families are part of the role pediatricians play in protecting children and empowering parents.

DEPARTMENTS

FEATURES



"An ideal tracheal replacement will permit the replacement of diseased or absent tissue with a living construct capable of renewal and regeneration. To develop these grafts, we need mechanistic studies and basic science work."

– Tendy Chiang, MD, FACS, principal investigator in the Center for Regenerative Medicine at Nationwide Children's Hospital

"It's much more a conversation about how we can holistically help these kids than it used to be. I can say, in a way I couldn't before, that their health is better off when they leave than when they arrive. I hope I will be able to say in the future that their health kept improving when they left the center and that their lives improved, too."

– Alexandra Price, CPNP, PMHS, Nationwide Children's lead medical provider at the Franklin County Juvenile Intervention Center

Increasing Same-Day Amoxicillin Graded Dose Challenges

A quality improvement initiative overcomes several barriers to de-labeling penicillin allergies.

In a study published in *The Journal of Allergy and Clinical Immunology: In Practice*, a research team led by Margaret Redmond, MD, a pediatric allergist at Nationwide Children's Hospital, reported on a quality improvement (QI) initiative that sustainably increased rates of same-day amoxicillin graded dose challenges (GDC) from 2% to 33%.

"Studies estimate that 5 to 10% of pediatric patients have a documented penicillin allergy," says Dr. Redmond. However, over 90% of these children can tolerate a subsequent penicillin dose.

She notes that benign, delayed rashes that commonly occur after aminopenicillin administration complicate understanding pediatric penicillin allergies.

The medical consequences of documented penicillin allergies, such as antibiotic resistance, underscore the need to clarify this allergy. But lack of family and patient interest and the time and effort required for GDCs, among other barriers, impede allergy de-labeling.

The researchers collected and analyzed same-day amoxicillin GDCs data for new Nationwide Children's allergy clinic patients referred because of a documented penicillin allergy. The baseline 2% GDC rate was established between January and August 2018.

Same-day GDCs, the researchers note, limit the need for follow-up visits and reduce health care costs.

"Before we could perform same-day challenges, many of my patients wished that they did not need to come back on a separate day, secondary to missing work and school or the travel required to get to clinic," says Dr. Redmond.

The patients were first assessed for risk of an IgE-mediated drug allergy. Patients at low risk for this allergy or other severe adverse drug reactions could receive a GDC without prior skin testing.

For the GDC, patients were given 10% of the treatment dose of oral amoxicillin and monitored for 30 minutes. Patients were then given the remaining 90% and monitored for 60 minutes.

Several QI interventions were implemented in 2018 and 2019. The first was to pre-order the amoxicillin from the pharmacy before the patient's arrival. However, this approach ended up being unsuccessful because a patient's updated weight needed to be recorded in the electronic medical record before the pharmacy could fill the order.

The second intervention was to make amoxicillin available in the allergy clinic, which successfully increased the same-day GDC rate to between 19% and 36%.

The final intervention was to schedule GDC appointments earlier in the day, given that some eligible patients had appointments that were too late in the day to allow for challenge completion. This intervention increased the rate to between 23% and 42%.

These successes established a new baseline GDC rate of 33%.

Several changes in clinic processes were also executed, such as educating patients and families on the benefits of same-day GDCs.

"These results are generalizable to allergy clinics at other pediatric institutions, but potential barriers to implementation include availability of staff to administer the medication and having the space to monitor patients after administration," notes Dr. Redmond.

Redmond M, Scherzer R, Hardy C, Macias C, Samora J, Stukus D. In-office amoxicillin to increase graded dose challenges at initial evaluation for penicillin allergy. *The Journal of Allergy and Clinical Immunology: In Practice. 2023;11(7):2190-2195.*

— JoAnna Pendergrass, DVM

User Experiences With Subcutaneous Depot Medroxy

Survey reveals high satisfaction among adolescents and young adults using subcutaneous DMPA

Depot medroxyprogesterone acetate (DMPA) is a progestin-only injectable contraceptive that is used as a birth control method and in the treatment of heavy or painful menstrual periods, endometriosis, and for menstrual suppression. DMPA can be injected intramuscularly or subcutaneously, with no difference in effectiveness or side effects.

In the spring of 2020, the COVID-19 pandemic disrupted access to contraceptives and limited in-person health care visits. This led to a clinical protocol at Nationwide Children's to improve access to subcutaneous DMPA, which can be administered at home. Because few studies have focused on adolescents and young adults using subcutaneous DMPA, researchers at Nationwide Children's leveraged this opportunity to survey their patients' experiences. The results were recently published in the *Journal of Pediatric and Adolescent Gynecology*.

The researchers identified 108 eligible patients in the electronic health record who had received a prescription for subcutaneous DMPA between November 2019 and October 2021.

"To recruit them, we first sent MyChart messages," says Hunter Wernick, DO, an adolescent medicine physician at Nationwide Children's and the study's lead author. "If they didn't have an active MyChart, we sent a letter. And then if they never responded to that letter, which was most of them, we called."

The team ended up with completed surveys from 29 patients who received at least one subcutaneous DMPA injection.

Most patients (about 93%) reported high satisfaction with subcutaneous DMPA. Of the 79.3% with previous intramuscular DMPA injection experience, nearly 70% preferred the subcutaneous injection, most often citing convenience, personal control, and injection comfort. Survey responses also indicated subcutaneous DMPA was a feasible option, and problems obtaining the prescription were uncommon. Most respondents reported administering the injection within the time window and planned to continue the method.

Dr. Wernick says the study is not without limitations, as it was conducted retrospectively and has a small sample size.

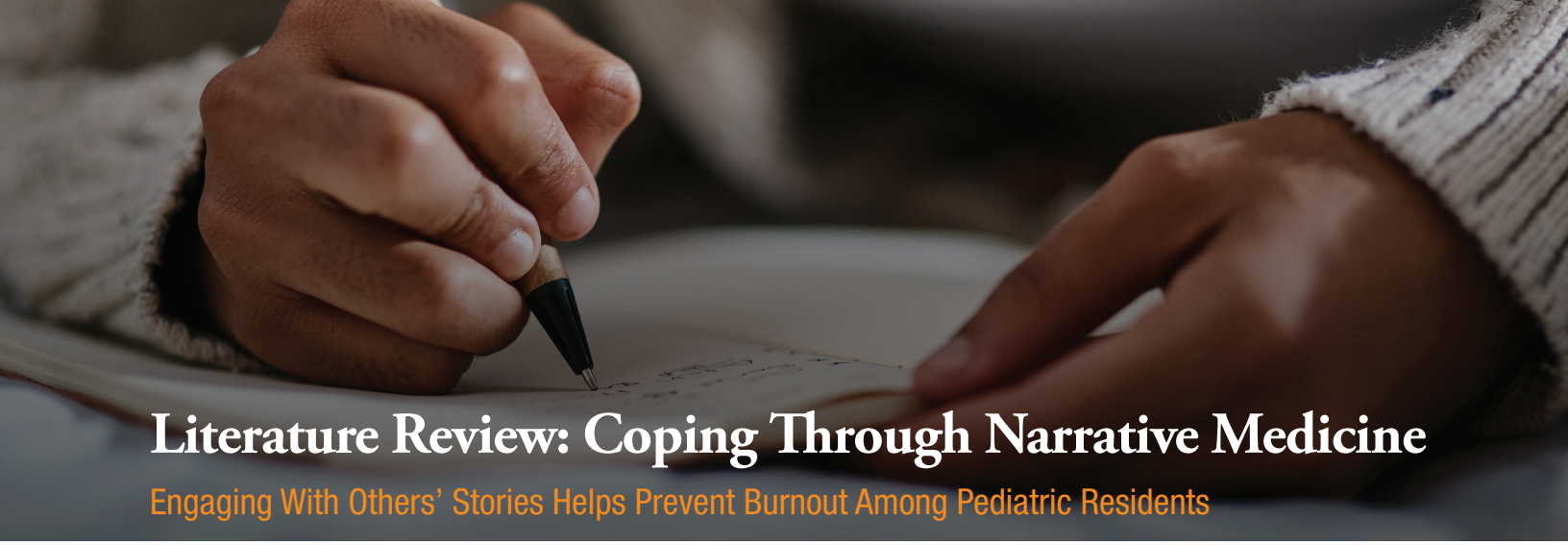
"The study tells us that the people who responded to our survey liked the subcutaneous option," she says. "There is no way of knowing if respondents may have had different experiences compared with those who did respond."

The researchers suggest future research that prospectively investigates subcutaneous DMPA use among adolescents over time and at multiple sites. In the meantime, they say clinicians caring for adolescents should consider including subcutaneous DMPA as an option, especially for adolescents and young adults who value convenience and user control.

"I think it is a good option, especially if there are any difficulties in the patient getting to the clinic," says Dr. Wernick. "Overall, subcutaneous DMPA should be included as an option with the caveat that everybody's a little different and insurance coverage could be different for everybody."

Wernick HJ, Wentzel E, Jackson K, Schmuhl K, Valenti O, Bonny AE, Berlan E. A pilot study of adolescent and young adult experience with subcutaneous depot medroxyprogesterone acetate. *Journal of Pediatric and Adolescent Gynecology*. 2023 Jun 22:S1083-3188(23)00343-1.

— Mary Bates, PhD



Literature Review: Coping Through Narrative Medicine

Engaging With Others' Stories Helps Prevent Burnout Among Pediatric Residents

A recent publication in *Annals of Medicine* shows pediatric residents practicing narrative medicine reported sustained improvements in their perceived levels of stress, self-compassion, empathy, mindfulness, burnout and resilience. This marks the first study to demonstrate the value of a narrative medicine intervention in promoting lasting well-being among residents.

"Approximately half of pediatric residents in the United States report experiencing burnout during their training," says Nimisha Bajaj, MD, PhD, who completed her pediatric residency at Nationwide Children's Hospital in 2022 and is now a is now a pediatric palliative care physician at Children's National Hospital.

Long work hours, financial stressors, exposure to patient death and other factors impact trainees. Without the right tools, she says, burnout, moral distress and compassion fatigue are significant concerns for medical professionals.

Research shows increased empathy, self-compassion, mindfulness, resilience and confidence in providing compassionate care are associated with lower burnout rates. However, many strategies that pediatric residency resilience and wellness programs have implemented do not directly target these qualities.

In contrast, narrative medicine, which involves encouraging medical professionals to engage with, interpret and respond to stories that highlight relationships among physicians, patients, colleagues and society, has been shown to promote wellness, increase empathy and decrease burnout.

At Nationwide Children's, Dr. Bajaj led a team to develop and evaluate a longitudinal narrative medicine intervention within the framework of relationship-centered care. The intervention, which took place over a five-month period in late 2020 and early 2021 and comprised six, one-hour video-conferencing sessions, aimed to improve residents' empathy and mindfulness to enable enhanced self-compassion and resilience and reduce stress and burnout, with sustained effects beyond the intervention period.

Before each session, participants were assigned a short literary piece to read related to stressors the group identified. To decrease barriers to participation, reading selections gradually increased in length with each session, each was summarized during its respective session, all six sessions were offered twice and each participant received a journal and a copy of Paul Kalanithi's memoir, *When Breath Becomes Air*, which served as the reading for the final session. During the calls, participants reviewed and discussed the assigned readings, responded to writing prompts and shared their reflections with their peers. Only residents were permitted at the sessions, and it was emphasized that the calls were intended to create a confidential, judgment-free "safe space."

In survey responses, participants reported meaningful and persistent emotional and mental health benefits and noted that the intervention fostered a sense of community, facilitated personal growth, and improved empathy, self-compassion, and resilience. No statistically significant changes in quantitative metrics were observed compared to the control group, but study size was a limiting factor.

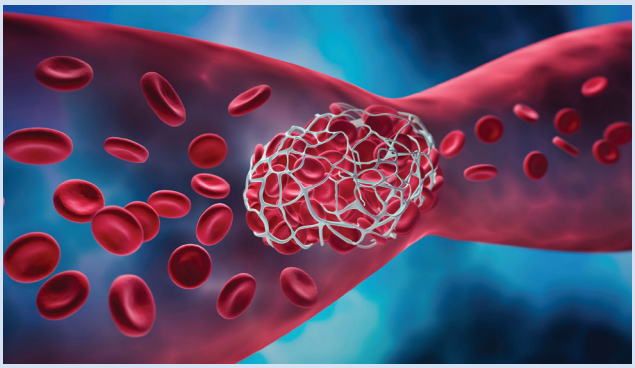
"Our study showed narrative medicine intervention can cultivate qualities associated with sustained reduced burnout among pediatric residents without requiring them to commit significant time or resources," says Dr. Bajaj. "It also provides compelling evidence that narrative medicine interventions align with the principles of relationship-centered care, fostering genuine connections between physicians and patients."

Bajaj N, Phelan J, McConnell EE, Reed SM. A narrative medicine intervention in pediatric residents led to sustained improvements in resident well-being. Annals of Medicine. 2023;55(1):849-859.

— *Natalie Wilson*

Combined Pediatric-Adult Anticoagulation Program Exceeds Goals

The program achieved excellent quality of anticoagulation therapy in children and adults.



The goal of most anticoagulation programs is to improve the care of adult patients on warfarin therapy, specifically by treating and preventing thromboembolic events while minimizing bleeding risk. In a new study, researchers from Nationwide Children's report excellent outcomes for a combined pediatric and adult anticoagulation program, and credit multidisciplinary teamwork and integrated practices.

The combined pediatric-adult anticoagulation program at Nationwide Children's was established in 2014. The program provides care to both adults and children on long-term warfarin therapy, in addition to a smaller group of patients on short-term warfarin therapy or other anticoagulants. While most other programs serve adult patients living near the host hospital, the program at Nationwide Children's serves adult and pediatric patients across the state of Ohio. The team is made up of physicians, nurse practitioners, and registered nurses who serve as clinician nurse coordinators, as well as collaborators in hematology, laboratory medicine, pharmacy, cardiology, and other subspecialties.

For the new study, researchers reviewed patient medical records from 2014 to 2019 to compare the quality of anticoagulation therapy before and after implementation of the program (as measured by percent of time spent in the therapeutic range (%TTR) and compliance). They also assessed bleeding and thrombotic complications.

Overall, the findings demonstrate that a multidisciplinary team using an integrated approach can help diverse patients achieve high-quality anticoagulant therapy, says lead author Vilmarie Rodriguez, MD, a pediatric hematologist and director of the thrombosis and anticoagulation program.

Post-program implementation, patients achieved a median %TTR of 78.9%, easily exceeding the minimum 60% target previously proposed as an acceptable measure of anticoagulation therapy quality for adults. Compliance, measured as at least one international normalized ration (INR) blood test per month per patient, also increased following program implementation by 34.3% (50% vs. 84.3%, pre- vs. post-, respectively).

Dr. Rodriguez and colleagues found that these high %TTR and compliance rates were sustained during the study period, resulting in relatively low bleeding and thrombotic events. In addition, there was no association between bleeding and thrombotic events and %TTR, likely due to the high median %TTR achieved by this approach.

"We did not find a difference in the quality of anticoagulant care between the adult and pediatric patients," says Dr. Rodriguez. "This shows that our anticoagulation program team is able to provide equal, excellent care for adults and children across a wide geographic area using this approach."

Dr. Rodriguez and colleagues say much of this success is a result of the integrated, multidisciplinary nature of the program.

"Every member of the team is invested in providing the best care for our patients, whether they are on short-term or long-term anticoagulation," says Dr. Rodriguez. "I think the impressive volume and complexity of patient care we provide, and the very good outcomes we achieve, ultimately result from teamwork and collaboration."

Rodriguez V, Stanek J, Cua CL, Sankar A, Giver J, Monda K, Canini J, Dunn AL, Kerlin BA. A regional anticoagulation program improves safety and outcomes for both children and adults. *Journal of Thrombosis and Thrombolysis*. 2023 Apr 24. [Epub ahead of print]

— Mary Bates, PhD

Coexistence of Different Telomere Maintenance Mechanisms in Pediatric High-Grade Glioma Tumors

by Lauren Dembeck, PhD

Due to within-tumor heterogeneity, telomere-based therapeutic interventions will likely need to target both known telomere maintenance mechanisms to prevent resistance and recurrence.

Normal differentiated somatic cells can divide only a limited number of times due to loss of the physical ends of their chromosomes, the telomeres, with each replication. When the telomeres reach their limit, the cell undergoes an irreversible cell cycle arrest or senescence. This phenomenon is known as the Hayflick limit.

"Scientists view this cellular senescence as a tumor suppression mechanism," explains Rachid Drissi, PhD, a principal investigator in the Center for Childhood Cancer Research in the Abigail Wexner Research Institute at Nationwide Children's Hospital. "By limiting the number of times each cell type can divide, the cells may avoid mutations that can lead to the development of cancer."

To achieve replicative immortality, tumor cells must activate telomere maintenance mechanisms. Because these mechanisms are present in most human cancer cells but are undetectable in the majority of healthy somatic cells, they represent rational therapeutic targets for cancer treatment.

The primary telomere maintenance mechanism used by most (85 to 95%) human cancers is reactivation of telomerase, an enzyme normally deactivated in most cells at birth. However, some cancer cells repurpose homologous recombination pathways to maintain their telomeres, a mechanism referred to as alternative lengthening of telomeres (ALT). The ALT mechanism appears to be particularly prevalent in tumors of mesenchymal and neuroepithelial origin, including brain tumors. In pediatric high-grade gliomas, it is found in 44 to 53% of cases.

"Targeting the ALT mechanism in pediatric gliomas is especially promising because this mechanism only occurs in cancer cells, meaning we may be able to kill cancer cells while avoiding side effects, and this is a very important aspect when treating pediatric cancers because some side effects are irreversible," says Dr. Drissi, whose research is focused on understanding high-risk pediatric brain tumor biology and the mechanisms of resistance in these malignancies.

Dr. Drissi and colleagues are exploring the prognostic significance of ALT activation in pediatric high-grade gliomas, including diffuse intrinsic pontine glioma (DIPG). These highly aggressive tumors are associated

with dismal prognoses, with 5-year overall survival rates of less than 10%, despite multimodal therapeutic options.

In a recent publication in the journal *Cancers*, Umaru et al. from the Drissi lab, reported heterogeneity of telomere maintenance mechanisms in pediatric high-grade gliomas and associations of previously identified genetic alterations with ALT activity.

"We discovered that different cells within the same tumor can use both mechanisms. Thus, when we develop therapies for these brain tumors based on telomerase or telomere length, we need to be careful. We will have to target not only the telomerase/telomeres but also the ALT pathway," explains Dr. Drissi, who is also an associate professor of Pediatrics at The Ohio State University College of Medicine.

The team made this discovery using nine samples of DIPG cells from patients' tumors matched with normal brain tissue. They detected ALT activity alone in 33% of samples, telomerase activity alone in 22% of samples, both ALT and telomerase activity in 11% of samples, and no evidence of either telomere maintenance mechanism in 22% of samples.

They also found that all tumors using ALT harbored mutations in the H3-3A gene (encoding a histone variant), but none harbored mutations in two other genes (ATRX or DAXX) previously associated with ALT activity in other tumor types.

Contrasting with previous reports of hypersensitivity of ALT-positive cancer cells to inhibitors of ATR, a protein involved in a key DNA damage response pathway, the team evaluated the sensitivity of a panel of pediatric glioblastoma cell lines to these inhibitors. They found that sensitivity to ATR and CHK1 inhibitors is not specific to ALT-positive cells compared to telomerase-positive cells. These findings suggest the ATR-CHK1 pathway is not a specific determinant of ALT phenotype in pediatric glioblastoma.

The findings from the new study highlight the need for novel therapeutic strategies targeting ALT in pediatric high-grade glioma tumors. Dr. Drissi and his colleagues are now finalizing preclinical studies evaluating a novel therapeutic agent targeting telomeres in telomerase positive pediatric high-grade gliomas. Unlike direct telomerase inhibition, this novel approach is telomere length independent. The prediction using this strategy is that treatment of children with high-risk brain tumors will require a shorter time period to achieve a rapid effect on tumor growth and progression than direct telomerase inhibition-based therapy.

"Time is very limited for many of these children with high-grade gliomas," says Dr. Drissi. "At Nationwide Children's, we have some of the best experts in pediatric brain tumors in the world, and we have published preclinical data demonstrating that this novel agent starts acting on telomeres within days, not weeks or months like telomerase-targeting agents. So, it's an exciting moment in this field where new treatments are urgently needed."

Umaru B, Sengupta S, Senthil Kumar S, Drissi R. Alternative Lengthening of Telomeres in Pediatric High-Grade Glioma and Therapeutic Implications. *Cancers* (Basel). 2023 Jun 6;15(12):3070. doi: 10.3390/cancers15123070. PMID: 37370681; PMCID: PMC10296514.

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CARING FOR INCARCERATED CHILDREN

by Jeb Phillips

Young people in juvenile detention centers need health care. In fact, decades of studies show they most often need it more urgently than their peers who are not involved in the justice system – nearly 70% of "confined youth" have an unmet health care need. (2010 study)

So it makes some sense that "urgent care" has been the dominant delivery model in juvenile detention centers across the United States. Those centers are designed for short stays while a case is adjudicated or other arrangements are found — some adolescents spend no more than a few days there.

But some stay longer. Weeks, months or years. There is an opportunity in that time to address chronic medical issues, to deliver a level of basic health education and to transform the future health trajectory for a child, which may ultimately reduce the activities that led them to juvenile detention in the first place. Even children who spend brief periods in detention can benefit from more comprehensive care.

Over the last decade, Nationwide Children's Hospital and the Franklin County, Ohio, juvenile justice system have developed a partnership to create what is effectively a primary care clinic inside the county's juvenile detention facility, the Juvenile Intervention Center. It's not only a shift in how detained young people are cared for in Franklin County; it appears to be a relatively rare arrangement in the United States, says Judge Beth Gill, who was lead Franklin County Juvenile Court Judge from 2012 to 2021 and was instrumental in the change.

"In juvenile justice, sometimes people are afraid of these kids," she says. "You have to see their humanity. You have to realize these are just someone's hurting children. You understand that they need a lot of care that goes beyond just the immediate physical needs."

Judge Gill, her colleagues on the bench and providers at Nationwide Children's are starting to build a model of how to do that.

AN EXTREMELY AT-RISK POPULATION

By nearly every available metric, American youth who are arrested have had significantly more difficult lives than their peers. A 2013 study found that the average young person in detention has experienced five different kinds of childhood trauma — loss or bereavement,

> *"In some cases, children come to the facility dealing with medical conditions they have had their entire lives without diagnosis or proper management."*
>
> – **Alexandra Price, CPNP, PMHS, Nationwide Children's lead medical provider at the Franklin County Juvenile Intervention Center**

domestic violence, impaired caregivers and emotional abuse are the most common.

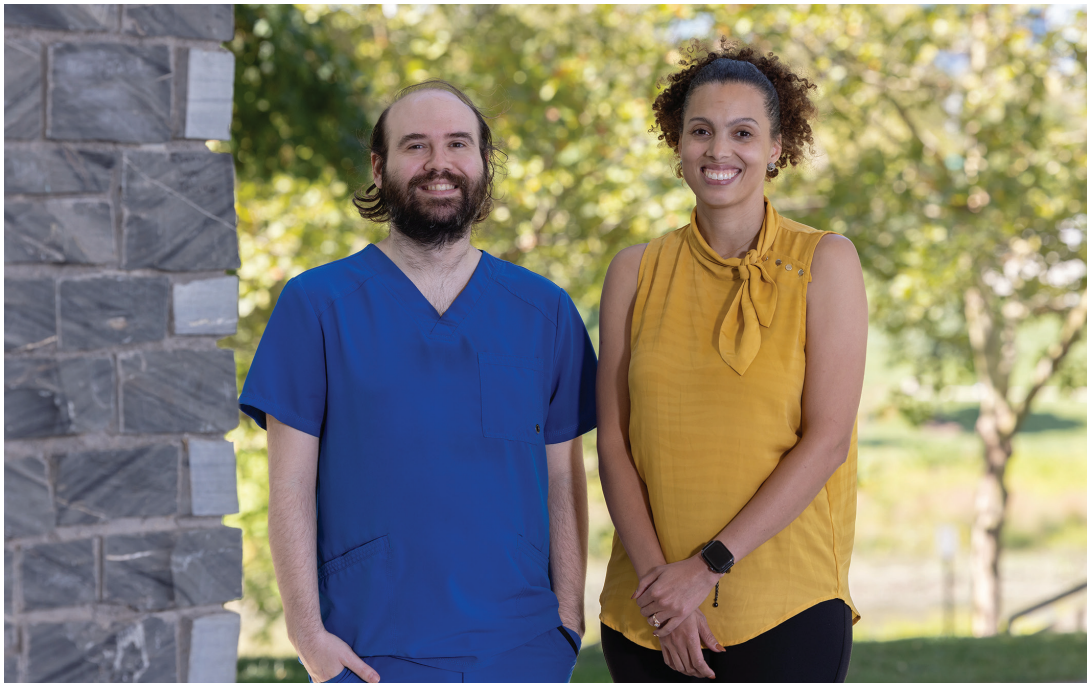
They have 10x the rate of sexually transmitted infections (STIs) as their peers. More than 25% have a mental health disorder that warrants immediate treatment. More than half need dental care, some urgently. Black adolescents are 5× more likely to be detained, and Latino youth are 3× more likely to be detained, than White adolescents.

These are national statistics, but they reflect what is happening in Franklin County as well, says Alexandra Price, CPNP, PMHS, Nationwide Children's lead medical provider at the county's Juvenile Intervention Center. The average daily census of the center ranges from 85 to 100, and nearly all come to the Nationwide Children's clinic inside the center at some point.

"In some cases, children come to the facility dealing with medical conditions they have had their entire lives without diagnosis or proper management," says Price.

Until recent years, the purpose of the health care in the Juvenile Intervention Center was to provide services that absolutely could not wait.

There were and are systemic reasons. The great majority of these young people and their families are covered by Medicaid, but a federal rule suspends Medicaid coverage at the time of arrest. The financial burden shifts from insurance to the individual jurisdiction, such as the county. Care, billing and reimbursement become trickier. Those issues are often worked out in contracts that are business transactions and not focused on optimal health outcomes.



Drew Brookover, RN, and Alexandra Price, CPNP, PMHS, lead the clinical care teams at the Franklin County Juvenile Intervention Center.

Beyond that, the electronic health record shared by Nationwide Children's and other health care systems was not used at the Franklin County Juvenile Intervention Center. Nationwide Children's medical staff did not have access inside the center to a child's medical history, medication information, chronic conditions and other data that are standard in modern health care.

In addition, young people who leave the center after adjudication — either back to their homes and communities or to other juvenile justice facilities — could not be followed easily. That was partially because of the disjointed records and partially because there was no mechanism for a "warm handoff" between the center's staff and community health providers.

This was the situation in 2010, when Judge Gill began discussing the problems with Steven C. Matson, MD, who was Nationwide Children's chief of Adolescent Medicine. Dr. Matson, now retired, had experience with juvenile detention health care in previous positions. Judge Gill had become interested in many issues of juvenile justice reform, particularly through the Annie E. Casey Juvenile Detention Alternatives Initiative, which Franklin County had joined.

Both recognized the issues with health care inside the Juvenile Intervention Center. In Judge Gill's view, the families of these children are overwhelmed before they even get there, and health care takes a backseat to what some families perceive as more pressing issues. The opportunity to get care inside the juvenile shouldn't be wasted.

"We have surveys showing that the average family connected to the juvenile justice system has seven other government systems they must traverse, such as the food stamps and unemployment systems," she says. "What if that family's child also needs lots of different kinds of health care? It can be very difficult for any family to navigate. That's why our partnership with Nationwide Children's is so crucial."

IMPROVEMENTS, AND LOOKING AHEAD

Nationwide Children's is one of the country's largest pediatric health systems, with an integrated model that allows children to get all the care they need regardless of their family's ability to pay. Dr. Matson and Judge Gill began talking about how to make that work for detained young people, some of whom might need prenatal care, mental health care, dental care and orthopedic care at the same time.

Instead of just a business transaction, the county's contract with Nationwide Children's started to incorporate the clinical judgement of health care providers. It became easier for Nationwide Children's providers inside the detention center to refer children to specialty clinics at the hospital. Over the last few years in particular, there have been some big changes.

Nationwide Children's, like many institutions, began a more focused, hospital-wide effort to address racial disparities in the aftermath of the death of George Floyd in 2020. The hospital's "Stand Against Racism, Stand For Health Equity," initiative has many projects, including some focused on incarcerated children and children of incarcerated parents.

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

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This became a priority across the hospital. In July 2021, after long negotiations to ensure privacy rules were maintained by all parties, Nationwide Children's electronic medical record, EPIC, became accessible in the Juvenile Detention Center. A month later, Nationwide Children's extended its "care coordination" program to the children inside the Juvenile Intervention Center, helping link children with follow-up care once they go back to their communities. About 60% now get that follow-up care, with the percentage rising all the time.

In 2023, for the first time, there is a full-time Nationwide Children's behavioral health provider inside the center, paid for by the county. The combination of these efforts has made a difference, says Price.

"Because we are operating more like a primary care clinic, we are able to see the resolution of long-term conditions while a child is in the center," she says. "We have medication to treat STIs in the clinic. We stabilize children who have Type 2 diabetes who have not had consistent medication, who have not had a consistent diet. Some who are prediabetic leave with normal labs. And our ability to work with our psychiatry colleagues means we can help children get prescriptions they need, and care coordination can ensure that they get refills."

It's not perfect, as every person involved in the Nationwide Children's/Franklin County partnership will say. Judge Gill would love for care coordination services to extend to other members of a detained child's family and even more access to behavioral health.

The Nationwide Children's team would like to provide more services, too. The Juvenile Intervention Center is in need of updated health education materials. Price and Brookover would like to better track health outcomes, to see if care in the center is lowering the rate of recidivism for youth.

But anecdotally, the new Franklin County and Nationwide Children's model is having an impact.

"It's much more a conversation about how we can holistically help these kids than it used to be," says Price. "I can say, in a way I couldn't before, that their health is better off when they leave than when they arrive. I hope I will be able to say in the future that their health kept improving when they left the center and that their lives improved, too."

Dierkhising CB, Ko SJ, Woods-Jaeger B, Briggs EC, Lee R, Pynoos RS. Trauma histories among justice-involved youth: findings from the National Child Traumatic Stress Network. *European Journal of Psychotraumatology*. 2013 Jul 16;4.

Owen MC, Wallace SB, AAP COMMITTEE ON ADOLESCENCE. Advocacy and Collaborative Health Care for Justice-Involved Youth. *Pediatrics*. 2020;146(1).

Whole Child, Whole Family Care

Meeting the needs of children and caregivers with evidence-based programming and intentional support for access.

by Abbie Miller and Jeb Phillips

Parenting a young child can be tough in the best circumstances. But when you overlay poverty, inequity, and concerns about employment and education on top of it, parenting a young child can feel overwhelming.

Whitney Raglin Bignall, PhD, has dedicated her career to meeting children and families where they are. She's a pediatric psychologist at the Nationwide Children's Hospital's Linden Primary Care Center. And this spring she added the role of associate clinical director of The On Our Sleeves Movement For Children's Mental Health.

To date, she's helped develop and implement two programs that support parents by challenging systems and barriers to care.

Proof of Concept: Behavioral Parent Training in Primary Care

In behavioral parent training (BPT), parents attend sessions with a therapist to learn strategies to help their child modify behaviors. In between sessions, parents practice what they learn, while continuing to receive support from the therapist.

According to the Centers for Disease Control (CDC), parent training is recommended for families with children under 12 years with ADHD. Evidence shows that this approach yields lasting benefits such as improved family relationships and increased success at school.

While she was on practicum at the Center for ADHD at Cincinnati Children's Hospital Medical Center, Dr. Raglin Bignall noticed that many of the urban, Black families who would benefit from a BPT course offered at the center were not attending. She began thinking about a project that would work to improve access to the programming.

"The population of people who were coming to the center for support wasn't mirroring the population of the community," Dr. Raglin Bignall explains. "When you see that, there are opportunities to improve health equity and look at the systems that may be creating barriers to access."

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>
> – *Whitney Raglin Bignall, PhD, pediatric psychologist at Nationwide Children's Hospital's Linden Primary Care Center*

When she moved on to a fellowship offering behavioral health care in the primary care setting, the opportunity to implement her ideas in a project opened up. Her team's project was recently published in *Families, Systems & Health*.

"BPT is the first-line treatment for children in preschool with disruptive behavior," says Dr. Raglin Bignall. "We have the science, but systems kept the door closed for people who needed to get in. Our project showed that we can adapt programs and systems to make accessible an evidence-based program for an urban, predominantly Black population."

Dr. Raglin Bignall's team use materials from the Center for ADHD, but they diversified the imagery used, improved the readability for health literacy, and made examples more concrete and less abstract.

Other adjustments that Dr. Raglin Bignall says helped the program be successful included:

- Adjusting the format to be modular so that attendance could be more flexible
- Changing the referral process to build relationships with families through integrated behavioral health care in the primary care setting
- Involving the school much sooner to identify and address immediate needs

Building Community With the Proud Linden Parent Program

Now at Nationwide Children's, Dr. Raglin Bignall has worked with the hospital, primary care network and community partners to begin a neighborhood-specific parenting initiative called the Proud Linden Parent Program. It takes evidence-based, positive parenting strategies and contextualizes them with the concerns and challenges that families in the diverse Columbus neighborhood of Linden may face.

"Some families are struggling with housing, or they really need resources that traditional positive parenting programs don't focus on," Dr. Raglin Bignall says. "Many of the principles are the same as you find in positive parenting programs. We talk about family

routines, or discipline, or praising children. But we also talk about the real-world situations that these families face in Linden, and how to address them."

The curriculum is based on the Chicago Parent Program, which was validated in an urban, racially diverse, low-income population. Many of the parents in the Linden program are identified through the Linden Primary Care Center, where 75% of patients are Black and 12% are Latino.

Dr. Raglin Bignall guides the program, "but I am not up there telling people how to parent," she says. The 11-session program (with a separate graduation) is heavily discussion-based and respectful of the caregivers' opinions and values. It often begins with questions like "What goals do you have for yourself?" or "Where do you see your child in five years?" The parents also have access to the Linden Primary Care Center's community health worker, an expert in connecting people to the resources they need.

Parents of children ages 1-8 are eligible. Dr. Raglin Bignall and her team recognize that it's not easy to ask busy, stressed parents to commit to three months of classes, so they try to remove every barrier possible. They serve dinner. They have childcare — so far, led by Akua Amponsah, MD, medical lead at the Linden Primary Care Center and associate chief for population health in the Division of Primary Care Pediatrics (known affectionately in the community as "Dr. A").

"The kids love playing together. They love seeing Dr. A. The parents get to have a pediatrician as their childcare provider," says Dr. Raglin Bignall. "Parents and families really end up wanting to do this and are sad once it's over."

But one of the great benefits of the Proud Linden Parent Program is that it helps build a community of parents,

Akua Amponsah, MD, medical lead at the Linden Primary Care Center and associate chief for population health in the Division of Primary Care Pediatrics with Proud Linden Parent Program participants

she says. These parents now know other parents that they can support, or who can support them. In fact, a program graduate is now the community health worker for the Linden Primary Care Center.

Given the program's popularity and success, Dr. Raglin Bignall is looking at ways to expand.

"Getting medical and psychology trainees as well as other clinicians involved in the program will not only give them valuable experience in working with the community, but it will give us the opportunity to expand across the neighborhood," Dr. Raglin Bignall says. "Ultimately, I envision a community of Proud Linden Parents, trained in positive parenting strategies and empowered to make a difference for children and families in their neighborhood."

"We're really just getting started — I have high hopes and big dreams for this program and the benefits it can bring to families."

Raglin Bignall WJ, Herbst RB, McClure JM, Pero MB, Loren REA, Burkhardt MC. Adapting a preschool disruptive behavior group for the underserved in pediatric primary care practice. *Families, Systems & Health.* 2023;41(1):101-111.

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Building hope, recovery, and life

BEYOND SUBSTANCE USE DISORDER

by Abbie Miller

Five years ago, Pediatrics Nationwide dedicated its fall issue to a comprehensive look at the effects of the opioid crisis on children and families. At that time, Sarah Parker was working hard to stay sober, recovering from the very crisis holding the nation's attention.

Parker grew up in Chillicothe, Ohio, halfway between Portsmouth, Ohio, the city prominently covered in "Dreamland," the popular book about the opioid crisis, and Columbus, Ohio, home to Nationwide Children's Hospital. Experimentation with pills starting at age 12 turned into heroin addiction and an arrest by age 19. But her story does not end there.

Parker is a success story — a beacon for youth and the doctors who care for them. Her story shows what is possible when an adolescent or young adult with substance use disorder gets the support and medical care they need.

THE FIRST STEPS TO SOBRIETY

"Gradually, then suddenly."

This is a quote from Ernest Hemingway's book "The Sun Also Rises" about how a man went bankrupt. For Sarah Parker, it's the way she describes her journey to sobriety.

"As early as age 15 I didn't feel good or proud about my drug usage," Parker says. "I felt a lot of shame. I noticed that even though my friends were also using drugs, they weren't going home and continuing to use like I was."

In the following years, she moved on to IV heroin use.

"After my first time using a needle, after the drugs wore off, I was embarrassed and disgusted. But I couldn't cope with not being high," she explains. "It wasn't just the physical addiction. I didn't like myself."

Eventually, Parker says, she had an epiphany moment that made her get serious about sobriety. Going through detox alone in a jail cell made her realize that her life needed to change. But even that experience wasn't the answer for the long term.

"I tried to get sober on my own, to quit cold turkey, but I couldn't do it. I wanted it, but I couldn't do it on my own," Parker explains.

It wasn't until her friend's mom told her about a program at Nationwide Children's for teens and young adults with substance use disorder that she got the help she needed.

"When I got to Nationwide Children's, I felt so relieved," Parker says. "They were sweet, compassionate, kind and safe. After my first appointment, I was clean for the longest I had been in years."

Recently, Parker celebrated her 30th birthday. She's coming up on 11 years sober, and proud of the life she's made for herself.

"I have good relationships and a good job," she says. "I'm proud of how far I've come. I still have bad days, I still get triggered, but I've learned that it's okay that I'm not fine all the time. We all struggle with different things. I don't have to be perfect."

By working with the physicians at Nationwide Children's, she says she's learned to be vulnerable, accept compassion and be kinder to herself.

THE CHANGING LANDSCAPE OF DRUGS IN THE UNITED STATES

In the years since Parker began her journey of healing, the environment of drugs in the United States has changed.

"We never see heroin in Ohio anymore," says Erin McKnight, MD, MPH, adolescent medicine and addiction medicine physician, and the medical director of Nationwide Children's Substance Use Treatment and Recovery Program. "It's all fentanyl."

Fentanyl

Fentanyl, a synthetic opioid, is cheaper, 100 times stronger than morphine, and deadly.

"When people are using opioids now, they can pretty much count on getting fentanyl — not oxycodone or heroin — if they are buying it in the illicit market," says Dr. McKnight. "And this simple fact increases their risk of overdose."

In fact, fentanyl is so common, it's often laced into illicit substances where users don't expect to find them. This has been a significant contributor to the increasing rates of overdose in the United States.

According to Dr. McKnight, over one in four pressed pills purchased online are not from a true prescription. And they are probably laced with fentanyl. Pressed pills look like normal pills, such as Xanax (alprazolam), Percocet (oxycodone/paracetamol), or oxycodone, but they are counterfeit pills made for selling in the trafficking pipeline and are much cheaper.

"When we are counseling patients and families about the risks of drug use, we have to include the fact that benzodiazepines, stimulants (including Adderall (dextroamphetamine-amphetamine)) and even marijuana may be laced with fentanyl," she says.

Xylazine

Xylazine (also known as Tranq) is a veterinary medication not intended for human use. But it's cheap and accessible,

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— Erin McKnight, MD, MPH, adolescent medicine and addiction medicine physician and the medical director of Nationwide Children's Substance Use Treatment and Recovery Program

so it has become increasingly common in the illicit drug supply, particularly on the East Coast. It's reportedly in 95% of the drug supply in Philadelphia. But it's been making inroads in Ohio and other Midwestern states.

"Xylazine is being added to fentanyl to 'give it legs,' or make it last longer," says Dr. McKnight. "This complicates overdoses."

Fentanyl overdose affects respiration. As an opioid, fentanyl responds to naloxone, though it may take more than one dose.

Xylazine, however, affects heart rate and blood pressure, and it does not respond to naloxone.

If someone overdoses on what is presumed to be fentanyl, even multiple doses of Narcan (naloxone) might not be enough if the substance was laced with Xylazine. Xylazine leaves the body quickly and is difficult to pick up on a drug test, making its use challenging to confirm and track.

Other substances of concern may seem less scary, but their risks and effects are no less devastating. Alcohol, nicotine and marijuana are high-risk substances for adolescents.

Alcohol

Among youth, binge drinking remains a significant risk to health and well-being. In addition to the risk of physical addiction to alcohol, risks for pregnancy, violence and other harms are increased with binge drinking behaviors.

Nicotine

Nicotine is still one of the most addictive and dangerous substances that youth may use. With the accessibility of vape pens, nicotine use is much easier to hide from parents and providers. It is also much easier to become addicted to nicotine using vapes, says Dr. McKnight.

"With smoking, there's a slow start to nicotine addiction," she explains. "You cough, the smoke is caustic, and you get sick. But with vaping, you don't have that causticness. It's easier to become addicted much more quickly."

Medication-Based Treatment Options for Commonly Misused Substances

MEDICATION	SUBSTANCE	DELIVERY	HOW IT HELPS
Buprenorphine	Opioids	Daily pill	Blocks opioid receptors to lessen withdrawal and prevent users from experiencing a "high."
Methadone	Opioids	Daily pill or oral solution	Blocks opioid receptors to lessen withdrawal and prevent users from experiencing a "high."
Naltrexone	Opioids, alcohol	Daily pill or monthly injection	Blocks the reward feelings that come from drinking. Shown to be effective on its own or paired with cognitive behavioral therapy.
Nicotine replacement	Nicotine	Combination therapy with long-acting patches and short-acting gum/ lozenge/spray	Allows slow reduction of the amount of nicotine used. Prevents withdrawal from a sudden decrease in usage.

"The good news is that now we have a lot more tools available for mainstream primary care providers to treat patients who screen positive for substance use disorder. Not that long ago, we didn't really know what to do to help a kid with a positive screen. We have more options now, and looking forward, there will be even more."

— Andrea Bonny, MD, section chief of Adolescent Medicine and principal investigator in the Center for Clinical and Translational Research at Nationwide Children's

Long-term effects of nicotine use include a host of cardiovascular problems, but short-term withdrawal is also an important consideration when educating families and teens. Withdrawal can be hard to identify when it comes to nicotine dependency because the moodiness, uncomfortableness and other symptoms mirror other mental health issues common in teens.

Marijuana

Marijuana products today are vastly more potent than in the past. In the 1970s, the amount of THC in marijuana was about 1-4%, says Natalie Powell, LPCC-S, LICDC-CS, clinical manager in the Big Lots Behavioral Health Services at Nationwide Children's. In the 1990s, THC in marijuana concentrates (oils, waxes, gummies) was about 12%. And now, marijuana concentrates could contain anywhere from 30 to 90% THC.

With the increase in dispensaries, the gummy, candy and other food-like formulations, and increased legalization, marijuana is accessible. Because users aren't necessarily smoking it, they can also hide their use more easily.

"Marijuana is really confusing for teens," says Dr. McKnight. "They are getting mixed messages everywhere. They hear that it's safe and natural, it's medicine, it's illegal or legal depending on where you live, and they have it marketed to them all the time."

THE GOOD NEWS: SUBSTANCE USE DISORDERS ARE TREATABLE

"The good news is that now we have a lot more tools available for mainstream primary care providers to treat patients who screen positive for substance use disorder," says Andrea Bonny, MD, section chief of Adolescent Medicine and principal investigator in the Center for Clinical and Translational Research at Nationwide Children's. "Not that long ago, we didn't really know what to do to help a kid with a positive screen. We have more options now, and looking forward, there will be even more."

Medication Treatment

At Nationwide Children's, the Substance Use Treatment and Recovery Program is housed within Adolescent Medicine.

"We have many more treatments to offer than in the past," says Dr. McKnight. "Substance use disorder is a chronic disease, but it is treatable. We have so much evidence now that shows that it's true."

Medication treatment for substance use disorder received a lot of attention when the opioid crisis took center stage. Using buprenorphine or methadone to treat withdrawal symptoms gives patients with opioid use disorder a chance to engage in their lives while detoxing. The medications can also help them by reducing cravings and blocking the effect of opioids.

"Using medication to help with my cravings and withdrawal was a big part of my success," says Parker. "They helped so much. I was able to feel in control of my recovery."

MENTAL HEALTH AND SUBSTANCE USE

According to experts who treat patients with substance use disorders daily, mental health concerns are almost always part of the equation.

"This patient population is one of my absolute favorites," says Powell, who has worked with adolescents with substance use disorders and mental health concerns for her entire postgraduate career. "They are looking for a way to feel better. And with the right support and resources, we can help them. And help them avoid the risks associated with illicit substances."

To help explain why adolescents may turn to illicit substances for mental health concerns, she tells a story about hearing someone describe marijuana as sunglasses for their brain.

Just like adults sometimes use alcohol as a social lubricant, easing the awkwardness of uncomfortable social situations, teens are turning to substances, marijuana especially, to help manage the stresses and pressures they face, says Powell.

But teens and adolescents are not small adults. Alcohol, nicotine, and marijuana have significantly higher risks and more complex consequences for youth.

"Asking someone why they are using illicit substances is a critical part to counseling and recovery. Nearly every young person I talk with who has a problem with substances also has mental health concerns," Powell says. "To be most effective, you have to address both."

SCREENING FOR SUBSTANCE USE

"If an adolescent comes out and tells you about their substance use without prompting, it is probably really bad," Dr. McKnight says. "We need to be asking questions, building trusting relationships and proactively engaging with these patients."

So, the Division of Adolescent Medicine at Nationwide Children's implemented standardized screening that was given routinely with depression screening.

"We recommend screening for substance use routinely like we do for anxiety and depression," says Dr. Bonny. "Nicotine use may start as early as 9 or 10 years old. We see other substances take off as early as 12."

Screening in this case is as simple as a 5-minute questionnaire that can be filled out by the teen digitally.

"One of the questions we get asked is 'how do we know what 'normal' experimentation is, and what is possible substance use disorder?'" says Dr. Bonny. "While no experimentation is considered safe, we have a five-question survey that helps us identify which youth are most at risk."

This survey, the CRAFFT questionnaire, doesn't diagnose substance use disorders, but flags patients who may need a formal referral or additional counseling. If a patient answers "yes" to two or more of the questions in the CRAFFT, they are considered high risk. CRAFFT has been validated for youth aged 12 to 21 and is recommended by the American Academy of Pediatrics.

Following screening, the physician has a clear idea of what counseling and potential referrals are needed. While it is not part of the CRAFFT, Drs. Bonny and McKnight stress the importance of also asking about family history of substance use disorder.

"When it comes to treating adolescents with a family history of substance use disorder, we need to normalize it like every other illness," says Dr. Bonny. "There is great power in destigmatization of substance use

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CRAFFT*

The CRAFFT questionnaire doesn't diagnose substance use disorders, but helps to identify patients who may need a formal referral or additional counseling. If a patient answers "yes" to two or more questions, they are considered high risk.

Car – have you ever driven under the influence of substances or ridden with someone who was?

Relax – do you ever use substances to help you relax, feel better about yourself or fit in?

Alone – do you use substances when you are alone (vs. with friends or at parties)?

Forget – have you ever forgotten what things you did while you were under the influence?

Friends/Family – do your friends or family ever suggest you should cut down on drinking or drug use?

Trouble – Have you ever gotten into trouble while you were using drugs or alcohol?

**Paraphrased from the CRAFFT questionnaire, available at CRAFFT.org.*

disorder and treating it as a chronic and relapsing brain disease. We are at the forefront of changing people's minds."

Parker agrees. "Looking back, I can see that I had a predisposition for addiction. If I had known more about addiction and genetic risk, I might have been more cautious," she says. "But no one talked about it. By the time the adults in my life said, 'you're partying too much,' it was too late. I was already deep in addiction."

THE THERAPEUTIC ALLIANCE

Screening for substance use in primary care is the beginning of the conversation. And with parents, many times the conversation includes whether or not to conduct drug testing.

"If a provider is going to do urine drug testing, it's important to discuss beforehand how that information will be used, and how it will help in recovery, as often a good social history focusing on substance use will give enough information," says Dr. McKnight. "It is important to have the adolescent assent to urine drug testing. We don't want to use a positive drug test as a 'gotcha' moment."

For treatment to work best, the relationship between provider and patient should be one of trust and shared goals. When parents are part of this therapeutic alliance, best outcomes can be achieved.

"We encourage patients to be honest and open with their caregivers and families," says Dr. Bonny. "That's very difficult for some, but most families are supportive and want their child to thrive. It's important that everyone know that recovery is a journey, and often times relationships are a huge part of that."

The therapeutic alliance of patient, provider and caregiver is a powerful one. If the caregivers aren't part of that, patients can still be successful. But so much more can be gained when everyone is working together.

3 Essentials of Substance Use Prevention in Primary Care

1. Start screening all patients at age 9.
2. Start anticipatory education early and focus on nicotine and marijuana.
3. Keep pamphlets or educational materials in the office where families see them.

SHOULD YOU OFFER FENTANYL TEST STRIPS IN YOUR OFFICE?

Harm reduction approaches support the use of fentanyl test strips for individuals who are taking illicit substances but want to avoid fentanyl.

Nichole Michaels, PhD, a principal investigator in the Center for Injury Research and Policy at Nationwide Children's, is conducting two studies about the efficacy of offering and educating about fentanyl testing among adults. Project Dawn is focused on distributing naloxone to any user who wants it. The other project involves offering fentanyl test strips for users with criminal justice involvement for substances such as stimulants, cocaine, methamphetamines – things that might be laced with fentanyl.

"In Ohio, more than 85% of fatalities from overdoses involve fentanyl," she says. "We are working with the courts across the state to help distribute naloxone and fentanyl testing strips as a way to reduce harm among adults with substance use disorder. Most overdoses are polysubstance, and it is possible that users are getting drugs laced with fentanyl when they did not intend it."

When to offer fentanyl test strips to a patient is a judgment call, says Dr. McKnight.

"We know that fentanyl is everywhere and our patients with opioid use disorder who are actively seeking out fentanyl don't feel they need test strips. However, if you have a teen who is experimenting with drugs at parties, you can counsel them about the dangers, talk about a plan, and maybe offer test strips. If they want to use marijuana but are concerned that it could be laced with fentanyl, it's about preventing overdose deaths," she says.

Regardless of whether or not providers distribute fentanyl test strips, Dr. McKnight and her colleagues recommend that all providers prescribe Naloxone/Narcan to patients using substances as they are at risk of being exposed to fentanyl and having an overdose. Naloxone is a big component of harm reduction, and it has been approved by the FDA to be over the counter. As of fall 2023, a limited supply of naloxone has hit drug store shelves at a cost of about $45 for two doses. This cost may be prohibitive for some consumers. So, Dr. McKnight adds, a prescription still may be needed for some.

In some states, including Ohio, Naloxone is available for free from public health departments and some pharmacies without a prescription.

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Preventing Accidental Ingestion of Marijuana

If you are a child, and you find a bag of fruit snacks — you don't eat just one piece.

The THC/marijuana products on the market today have an average of 10-20 mg in one serving. That's one square of a chocolate bar, one gummy (which looks like a fruit snack) or one chip.

"THC gummies are the most common accidental overdose we see," says Hannah Hays, MD, chief of Toxicology at Nationwide Children's and medical director of the Ohio Poison Control Center. "Adults or teens who are using these think that the small children in the home can't find them. They can, and they do."

For a child who eats even one piece, the results are dangerous. When they are eating more, it can be devastating.

Children are not just small adults.

There's a myth that you can't overdose from marijuana/THC. And while the effects of having "too much" are generally not life-threatening for adults, for kids and teens, ingesting large amounts (like a whole bag of gummies or a candy bar) can lead to seizures, heart problems, brain damage and death.

"Small children with accidental exposure to THC may end up needing a ventilator to help them breathe," says Dr. Hays. "They can become comatose."

Leah Middelberg, MD, emergency medicine physician at Nationwide Children's, says that in the Emergency Department, parents don't always know their child ate a THC product.

"It's a scary situation for everyone. We train our teams to ask about marijuana when we are trying to find the cause of the symptoms," she says. "But sometimes they don't think the child could have possibly found the product,so we have to go through a lot of testing, which can be invasive."

Effects also take a while to kick in with these products, posing another challenge.

"By the time they start feeling bad, feeling the effects of the THC, they've probably eaten most of the product," adds Dr. Middelberg, who is also a principal investigator in the Center for Injury Research and Policy at Nationwide Children's.

Safe storage is essential.

Out of sight.

Out of reach.

Locked.

These are the recommendations for safe storage of prescription medications, including opioids. It's also the recommendation for marijuana/THC products.

"Educating families about the risks of marijuana products for young children and talking about safe storage in a nonjudgmental way is the first step to protecting kids," Dr. Middelberg says. "We prefer that these products not be in homes with small children, but if they are, they need to be stored appropriately."

"These products are marketed to look like food," adds Dr. Hays. "We can't expect young children to know the difference."

"These products are marketed to look like food. We can't expect young children to know the difference."

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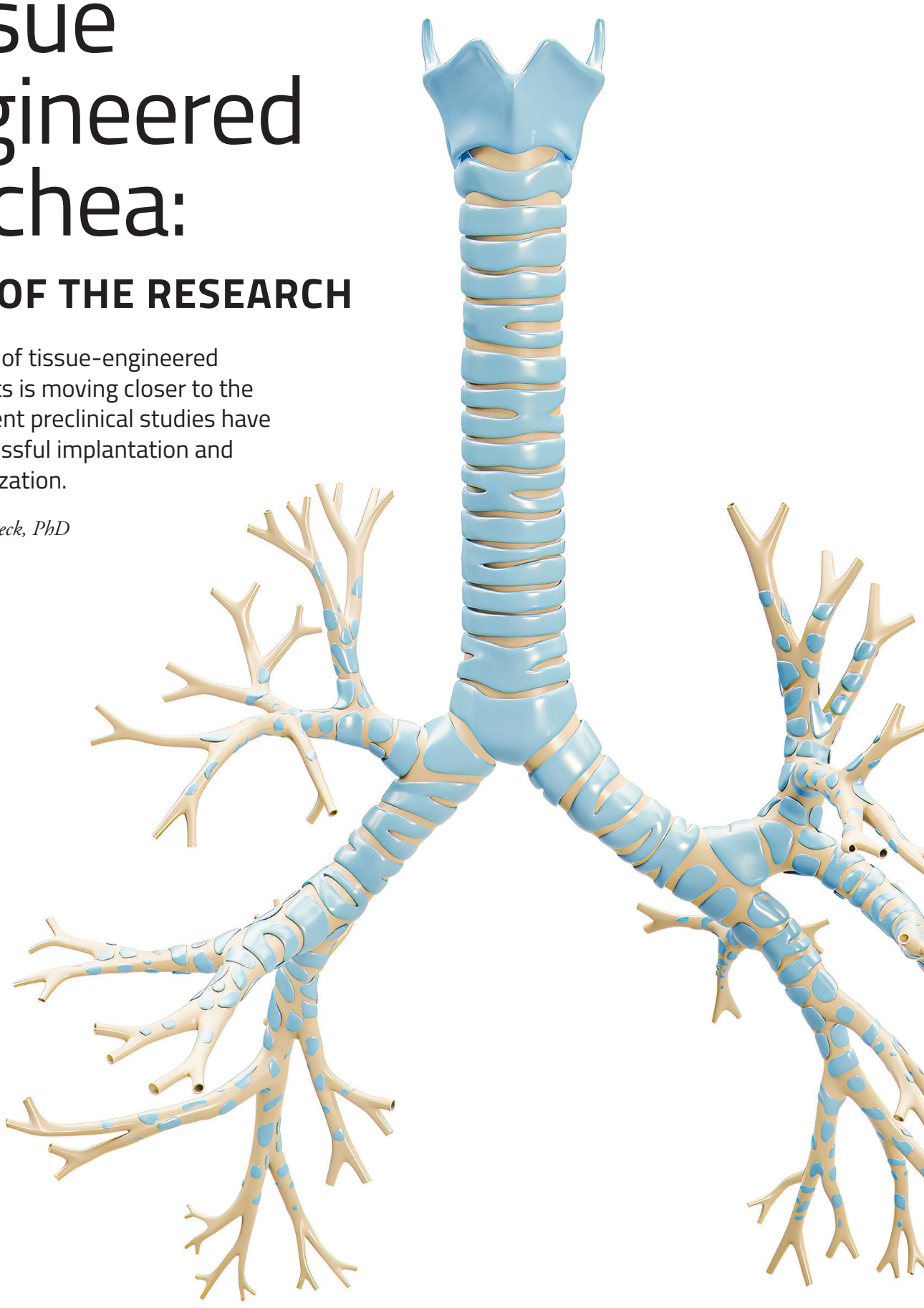
Tissue Engineered Trachea:

STATE OF THE RESEARCH

The promise of tissue-engineered trachea grafts is moving closer to the clinic, as recent preclinical studies have shown successful implantation and neovascularization.

by Lauren Dembeck, PhD



Breathing is an essential biological function that provides our bodies with the oxygen necessary for survival. However, most of us rarely think about the biological structures that make it possible.

The trachea, commonly called the windpipe, is an indispensable part of the respiratory system. It acts as a conduit for air, filters foreign particles, humidifies the inhaled air, provides structural support to keep the airway open and contributes to vocalization. Its proper functioning is crucial for maintaining efficient respiration and overall health.

Tracheal defects may occur as congenital anomalies or develop as acquired conditions following malignancy, trauma or infection. Small tracheal defects can be repaired using various open and endoscopic airway surgical techniques. However, long-segment tracheal defects, those involving one-third or more of the trachea, are associated with high morbidity and mortality, and a standard of care has not yet been established.

Unfortunately, no autologous tissues can be used for tracheal replacement. Furthermore, techniques using foreign materials for tracheal replacement and allograft tracheal transplantation have had limited success due to complications, including chronic infection, narrowing, rejection and malacia, an abnormal softening of tissue. However, emerging techniques in regenerative medicine and tissue engineering hold promise for repairing long-segment tracheal defects.

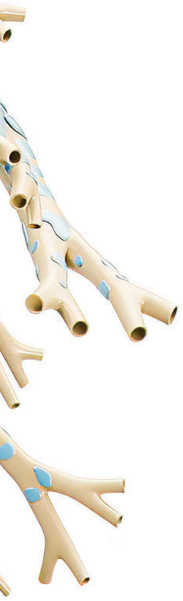
The life-threatening nature of long-segment tracheal defects has led to the compassionate use of tissue engineered tracheal grafts in the clinic, with the first report published in 2005. Since that time, the clinical application of tissue-engineered tracheal grafts has yielded some successes, but the optimal techniques for the generation of tissue-engineered tracheal grafts, in terms of safety and efficacy, have yet to be determined.

Researchers at Nationwide Children's Hospital are at the forefront of regenerative medicine, leading pre-clinical studies that are moving a new generation of tissue-engineered trachea grafts closer to clinical use.

"Regenerative medicine is a relatively new, interdisciplinary science that aims to create tissues that are made from the patient's own cells," says Christopher Breuer, MD, director of the Center for Regenerative Medicine at the Abigail Wexner Research Institute at Nationwide Children's, whose lab is designing a tissue-engineered vascular graft that will grow with pediatric patients. "In any field of reconstructive surgery, especially tracheal surgery, one of the main issues is when there is not enough of the patient's own tissue for reconstruction. Tissue engineering does have real promise and significant potential for advancement here."

Fundamentals of Tissue-Engineered Trachea

Within the body, our cells make and secrete their own scaffolds, the extracellular matrix, and receive signals that stimulate normal growth and repair, explains



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Tendy Chiang, MD, FACS, principal investigator in the Center for Regenerative Medicine at Nationwide Children's. Tissue engineering relies on those three primary components — a scaffold, cells and growth, and mechanical signaling factors that stimulate new tissue formation. The new functional tissue can then be used to restore, maintain or improve damaged tissues or organs.

"An ideal tracheal replacement will permit the replacement of diseased or absent tissue with a living construct capable of renewal and regeneration. To develop these grafts, we need mechanistic studies and basic science work," says Dr. Chiang.

Dr. Chiang and his team focus their research on understanding how airway tissue repairs and regenerates itself. And they are using that information to design tissue-engineered tracheal grafts. They and their collaborators are taking a back-to-the-bench approach to define the mechanisms of cartilage formation, epithelialization and vascular regeneration. This method entails systematically analyzing how the tissue forms at a molecular and cellular level.

"These experiments allow us to rationally design strategies for making tracheal tissues," says Dr. Breuer. "There is hope that we would then have the ability to help many more patients and positively change their lives."

The researchers have made steady progress. They recently developed techniques to create a tracheal graft that appears to overcome many of the complications associated with other graft types.

Partially Decellularized Tracheal Grafts

Decellularized tracheal scaffolds offer a potential solution for the repair of long-segment tracheal defects. However, complete decellularization of trachea is complicated by tracheal collapse. Recently, Dr. Chiang's lab developed a method of creating tracheal grafts through partial decellularization. Partial decellularization is a way of removing the immunogenic cell types, which can cause the graft to be rejected, while preserving the chondrocytes and key proteins of the extracellular matrix, such as collagen, glycosaminoglycans, laminin and fibronectin. Retaining these cells and proteins allows the partially decellularized tracheal graft to maintain the mechanical properties of the trachea and also creates a natural scaffold for the regeneration of the epithelium.

3 Essential Components for Tissue Engineering

- A scaffold.
- Cells and growth.
- Mechanical signaling factors.

"Decellularization is a method to strip all cells from donor tissue. Partial decellularization is very similar to conventional decellularization techniques, but it aims to preserve the cartilage and the cells within the cartilage while removing all of the cells around the cartilage," explains Dr. Chiang.

In a 2021 *Journal of Tissue Engineering* publication, the Nationwide Children's team along with collaborators at The Ohio State University created and characterized a partially decellularized tracheal scaffold in a mouse model of tracheal transplantation. They found that following partial decellularization, the graft maintained its integrity, including chondrocytes and predominant extracellular matrix proteins. After transplantation, they assessed the performance of the graft *in vivo*. The grafts formed a functional neo-epithelium and demonstrated restoration of native tracheal rigidity by the end of the study.

"We demonstrated that, unlike our previous experience with synthetic scaffolds, these grafts are able to support the growth of an epithelium that has all the cell types that are characteristic of the native trachea," explained Dr. Chiang. "We believe this partially decellularized scaffold offers a solution for long-segment tracheal defects, and it is an approach that is being adopted by more research groups. We are currently in the midst of additional preclinical testing of this graft."

With further study of the partially decellularized tracheal grafts, the team confirmed that they are able to overcome another key challenge in the field: rejection by the graft recipient's immune system. Earlier this year, they published a study in the journal *Bioengineering & Translational Medicine* demonstrating that partial decellularization eliminated allograft immunogenicity,

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– Tendy Chiang, MD, FACS, principal investigator in the Center for Regenerative Medicine at Nationwide Children's

with no histologic signs of rejection observed in mouse models following implantation of the graft. This represents a critical step toward clinical translation.

The researchers have extended their findings in a new article published in the journal *NPJ Regenerative Medicine*. They used a combination of cellular and genetic approaches to compare the neotissue that developed on the partially decellularized tracheal grafts in transplanted individuals with tissue in the native airway of individuals that did not undergo surgery and surgical controls. The study showed that the neotissue of the partially decellularized tracheal grafts was composed of the same cell populations found in the native trachea. Additionally, the regenerated epithelium and microvasculature, which included tubular blood vessels filled with red blood cells, persisted for at least 6 months.

The team also found that the graft attracted tissue-specific stem cells that maintain the tracheobronchial airway epithelium, called basal cells, and these stem cells exhibited normal proliferation and differentiation. The basal cells were able to differentiate into multiciliated and club cells that restored the mucociliated airway epithelium, implying mucosecretory clearance. As of the end of the study, none of the study animals exhibited signs of respiratory distress.

"There is a vast array of molecular tools that can be used in mouse models. These allow us to turn genes on and off to examine the roles of different proteins and to label cells to see where they are migrating in the tracheal grafts. It is a powerful system that allows us to study how all the components fit together," adds Dr. Breuer.

Decellularization: removing all cells from the donor scaffold

Partial decellularization: preserves cartilage and cells within the cartilage

> *"There is a vast array of molecular tools that can be used in mouse models. These allow us to turn genes on and off to examine the roles of different proteins and to label cells to see where they are migrating in the tracheal grafts. It is a powerful system that allow us to study how all the components fit together."*
>
> – Christopher Breuer, MD, director of the Center for Regenerative Medicine

Together, these findings demonstrate that partially decellularized tracheal grafts are not rejected and support neotissue formation within the recipient. The regenerated tracheal tissue recapitulates the structure and function of the host trachea, including spatially appropriate recellularization. The studies provide strong support for further evaluation of partially decellularized tracheal grafts in the next stages of preclinical study.

"We have found that, in our mouse model, this graft is able to support regeneration of host-derived tissue, all the different components of a trachea, including regrowth of blood supply and regrowth of an epithelium that appears to be identical to the native trachea. That gives us hope of being able to create a graft that is able to respond to injury and grows with the patient," explains Dr. Chiang.

Future Directions

Now that Dr. Chiang and his team have demonstrated that growth and restoration of the tracheal epithelium and microvasculature occurs in the mouse model, the next step is to assess the performance of a partially decellularized tracheal graft in a large animal model.

The researchers also are interested in exploring the potential application of partially decellularized tracheal grafts in populations that have airway disease and in those who have had previous airway surgery. To do so, Dr. Chiang is collaborating with Susan Reynolds, PhD, a principal investigator in the Center for Perinatal Research at Nationwide Children's, whose research is focused on stem cells that maintain the airway epithelium. Dr. Reynolds contributed to the previously mentioned studies of stem cell viability, migration and differentiation in the mouse models.

"We would like to understand how the presence of airway disease or previous airway surgery affects the stem cells of the host and their ability to regenerate tissue," says Dr. Reynolds. "Some of our basic science work indicates that lung disease actually causes biological aging of the airway stem cell population, meaning the biological age of the cells is older than the chronological age. For instance, a 3-year-old patient could have a stem cell population that is similar to that of a 10-year-old patient, and vice versa. This can have implications for the ability of those stem cells to proliferate and differentiate."

Dr. Reynolds and her team are using molecular techniques to estimate the biological age of patients' cells, for example, assessing the absolute number of stem cells within the epithelium and determining the telomere length, which typically decreases as cells age. So far, her team has identified an inverse correlation between the biological age and the function of the stem cell population (the ability to proliferate and to produce differentiated cell types). They hope that information will help identify patients who would be more or less likely to do well if they were to receive a partially decellularized tracheal graft.

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– Susan Reynolds, PhD, principal investigator in the Center for Perinatal Research at Nationwide Children's

Collaboration: The Key to Future Success

The future of tissue-engineered tracheal grafts hinges on the collaborative and translational commitment of the researchers involved. In the Center for Regenerative Medicine at Nationwide Children's, teams are advancing the field of regenerative medicine and collaborating with a global network of biologists, clinicians, engineers and specialists in other related fields.

"The progress we have made thus far has been dependent on the multidisciplinary team of people working on the project and the great support from Nationwide Children's," shares Dr. Reynolds. "These are two levels of support that we have at Nationwide Children's that do not exist at all institutions, making the hospital a unique place to do this work."

"It is just a wonderful research ecosystem that we have here at Nationwide Children's. The kinds of studies being done are enabled by the facilities that the institution is supplying, such as a surgical suite and imaging facilities for animal research that are on par with what would be used for studies in humans," adds Dr. Chiang. "There are a lot of opportunities for truly multidisciplinary collaboration. We have clinicians working alongside scientists, as well as veterinary staff and engineers. Our success is really driven by the presence of these resources and the spirit of collaboration."

Chiang T, Pepper V, Best C, Onwuka E, Breuer CK. Clinical Translation of Tissue Engineered Trachea Grafts. *Annals of Otology, Rhinology & Laryngology*. 2016 Nov;125(11):873-885.

Liu L, Dharmadhikari S, Shontz KM, Tan ZH, Spector BM, Stephens B, Bergman M, Manning A, Zhao K, Reynolds SD, Breuer CK, Chiang T. Regeneration of Partially Decellularized Tracheal Scaffolds in a Mouse Model of Orthotopic Tracheal Replacement. *Journal of Tissue Engineering*. 2021 Jun 6;12:20417314211017417.

Tan ZH, Liu L, Dharmadhikari S, Shontz KM, Kreber L, Sperber S, Yu J, Byun WY, Nyirjesy SC, Manning A, Reynolds SD, Chiang T. Partial Decellularization Eliminates Immunogenicity in Tracheal Allografts. *Bioengineering & Translational Medicine*. 2023;8(5):e10525.

Tan ZH, Dharmadhikari S, Liu L, Yu J, Shontz KM, Stack JT, Breuer CK, Reynolds SD, Chiang T. Regeneration of Tracheal Neotissue in Partially Decellularized Scaffolds. *NPJ Regenerative Medicine*. 2023 Jul 12;8(1):35.

Learn more about Dr. Reynolds' research about biologically aging stem cells in the airway: PediatricsNationwide.org/StemCellAge

Growing Clinical Research at Nationwide Children's With Cynthia Gerhardt, PhD

Dr. Gerhardt was appointed Chief Clinical Research Officer at Nationwide Children's Hospital in April 2023. With integrating clinical care and research at the heart of the hospital's strategic plan, she has big plans for ensuring our clinical research infrastructure continues to grow and evolve to support the best bench-to-bedside-and-back science for best outcomes.

Learn more about Dr. Gerhardt's vision for clinical research at Nationwide Children's and what lies ahead.

Q: WHAT LED YOU TO PURSUE YOUR NEW ROLE?

A: I've been invested in supporting clinical research here for many years. About a decade ago, I became an investigator in and director of the Center for Biobehavioral Health. Since then, we've tripled in size and developed several training programs and core resources, such as the Behavioral Trials Office. Around the same time, Bill Smoyer, MD, invited me to become part of the Center for Clinical and Translational Science, which provides education, resources and pilot funds across The Ohio State University and Nationwide Children's.

I also truly enjoy mentorship and figuring out how to help others be successful. The opportunity to become chief clinical research officer seemed like a natural next step in my leadership journey.

Q: WHAT ARE YOU MOST LOOKING FORWARD TO ABOUT LEADING CLINICAL RESEARCH AT NATIONWIDE CHILDREN'S?

A: On an individual level, conducting research involves many challenges, and it can be hard to start a project, particularly when balancing clinical care and teaching. I'm a problem solver and hope that my skills in building teams, resources and training programs will be an advantage in this role.

I'm also looking forward to making an impact on a larger scale and am excited about the emphasis on clinical research in the new strategic plan. Nationwide Children's is leading on several frontiers in science, including gene and cell-based therapies, health equity and population health, and behavioral health. As our scientists continue to generate many exciting discoveries, our research infrastructure must grow with them. We must anticipate needs by expanding data science capabilities, considering the ethical implications of new technologies, keeping abreast of regulatory and compliance issues, and training and retaining a skilled scientific workforce. I want to bring forward-thinking strategies that will address new challenges to innovation.

Additionally, many pediatric conditions are relatively rare, making it difficult to study the affected population at any single institution. Clinical trials for these populations require collaboration across multiple institutions and/or decentralized approaches to effectively disseminate our work to community providers.

To truly impact public health, we must also expedite the timeline from bench to bedside to community by leveraging key partnerships and commercialization opportunities. With new strategic initiatives, we have a wonderful opportunity to fully integrate our clinical care and research to ensure our innovations quickly result in the best outcomes for our families.

Q: WHY SHOULD A CHILDREN'S HOSPITAL PRIORITIZE CLINICAL AND TRANSLATIONAL RESEARCH?

A: An effective learning health system constantly evolves to optimize quality, safety and care. Clinical research informs better clinical care and vice versa.

Our families are often our best teachers, and many know that their child can receive the best possible treatment

because another family agreed to participate in a research study. They want to help the families who will come next. Additionally, in some areas, such as pediatric oncology, participating in a clinical trial is essentially the standard of care. Research consortiums such as the Children's Oncology Group have allowed us to pool our resources, share knowledge and find cures faster. This approach to integrated clinical care and research is why we've had such incredible gains in survival rates for childhood cancer over the last 40 years.

If we strive to lead the *Journey to Best Outcomes* for children and families, we also need to lead the discoveries and innovations that will advance care.

Q: WHAT'S NEXT?

A: We're continuing to work with Business Planning and Development to refine and prioritize the strategic goals for clinical research. I am thrilled to partner with so many incredible individuals and teams across the hospital and research institute and at Ohio State to integrate clinical research resources across campuses and expand where needed.

Each clinical division now has a designated associate division chief for research who will serve as a liaison between me and their teams. Streamlined research onboarding, training and web-based resources are in development, along with renovation plans to provide new, integrated clinical research space. This space will include Clinical Research Services, the investigational pharmacy, testing rooms for social and behavioral research, and other lab space. As we build the Office of Clinical Research, we will continue to incorporate input from faculty and staff to ensure we meet the needs of the institution and our families.

Dr. Gerhardt and Myeshia Harmon, MHA, CCRP, senior director of Clinical Research Operations at Nationwide Children's, were recently guests on **PediaCast**, an educational podcast for parents and families. They discussed how pediatric clinical trials are designed, approved, funded and implemented, how safety is woven into the process, how results are shared with the public and translated into practice, and more.

Stream the episode here!

PediatricsNationwide.org/GrowClinicalResearch

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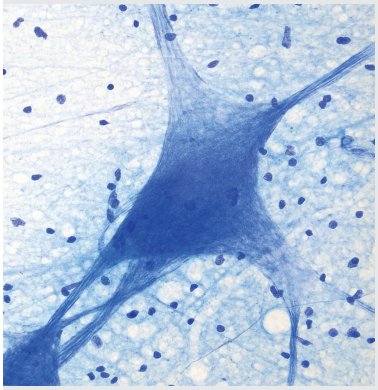
PediatricsNationwide.org/SIMPLE



New Fast, Reliable Model Tests Patient Response to Novel Treatments

It's well-known that treatments work for some patients and don't for others, and this can be a real challenge when it comes to rare neurogenerative disorders. Kathrin Meyer, PhD, and her lab established a faster, reliable *in vitro* model to investigate why.

PediatricsNationwide.org/NeuroModel

5 Keys to Managing Iron Deficiency in Children With Intestinal Problems

Iron deficiency is a prevalent concern among children with certain digestive problems, presenting various health challenges. A position paper from the NASPGHAN Intestinal Rehabilitation Special Interest Group delves into the identification and treatment of iron deficiency in children undergoing intestinal rehabilitation.

PediatricsNationwide.org/IronDeficiencyIntestinal

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