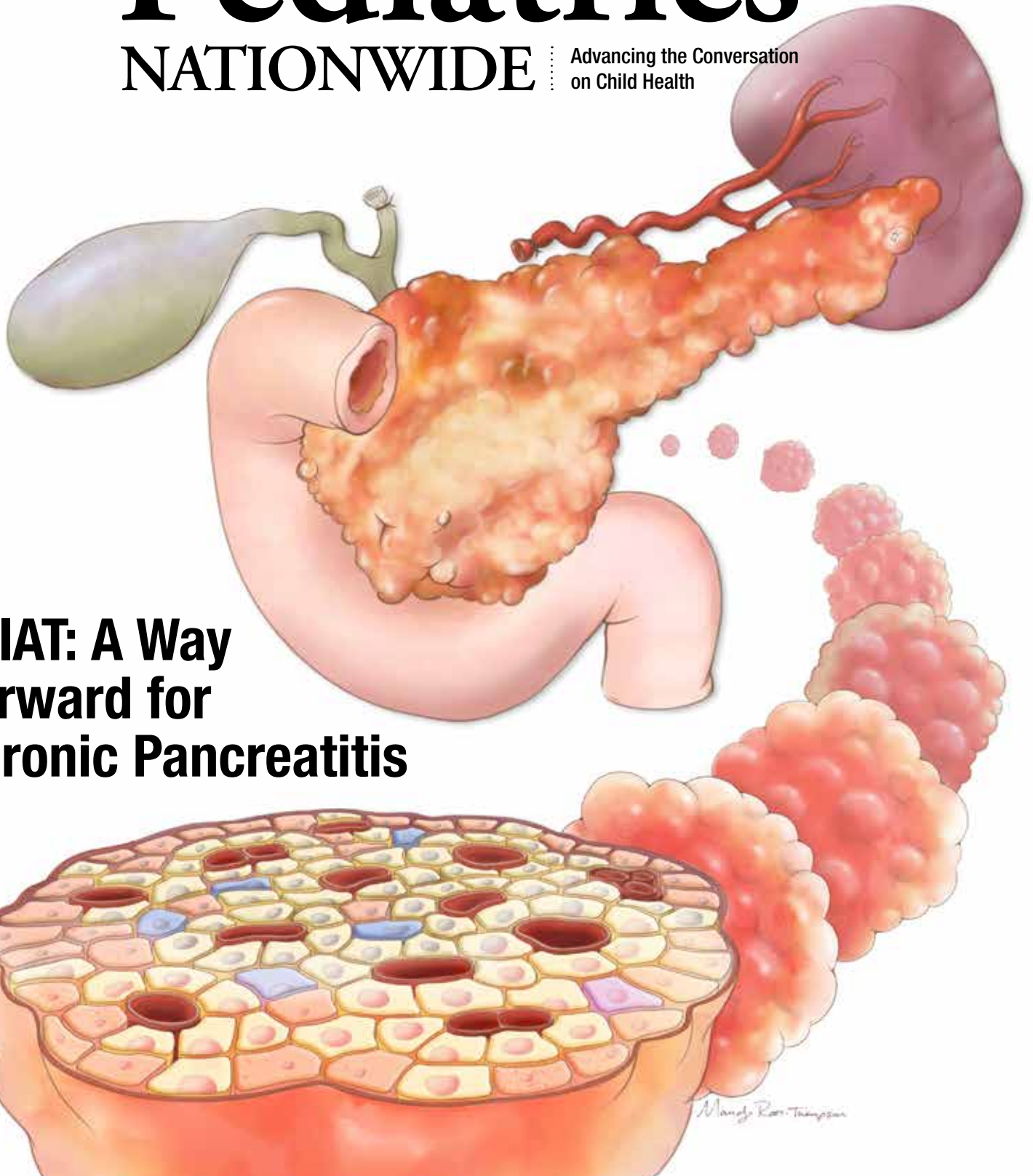


# Pediatrics

NATIONWIDE

Advancing the Conversation  
on Child Health



## TPIAT: A Way Forward for Chronic Pancreatitis

**INSIDE  
THIS ISSUE**

Integrating Behavioral Health  
and Primary Care Increases  
Access and Equity

New Initiative Aims to Bring  
Personalized Diagnosis and Treatment  
to Children With Solid Tumors

American Academy of Pediatrics Updates  
Guidelines for the Management of  
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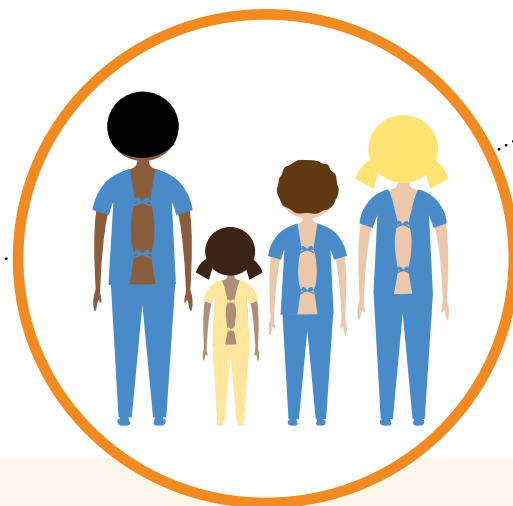
## 16 TPIAT: A Way Forward for Chronic Pancreatitis

Pancreatitis involves debilitating abdominal pain, usually with no obvious cause and no cure. Children are hospitalized for several days, even weeks with each episode. As damage to the pancreas accumulates, chronic pancreatitis can develop. For children with chronic pancreatitis, the pain is nearly constant and interferes with school, sports and social activities.

This issue's cover feature focuses on the changing landscape of treatments for chronic pancreatitis, including total pancreatectomy with islet autotransplantation (TPIAT).

### Pancreatitis Fast Facts

**~1 in 10,000** kids per year experiences a pancreatitis episode



**15-35%** of kids with an acute episode progress to recurrent disease

**5.8 in 100,000** kids have chronic pancreatitis

#### AMONG KIDS WITH CHRONIC PANCREATITIS:

**73%** have a genetic risk factor/mutation



**33%** have constant pain requiring opioids



**Up to 50%** are likely to require an operation in their lifetime



#### AMONG KIDS UNDERGOING SURGERY FOR CHRONIC PANCREATITIS:

**85-90%** experience a meaningful pain reduction



**Up to 50%** have pain recur after conventional operations



**90%** are opioid-free 2 years post-TPIAT



**41%** achieve insulin independence post-TPIAT



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“This is a new era in cancer care for all of us, and I am very grateful that we're part of a generation where we can build this testing infrastructure for kids around the country. I think it has been a long time coming and will level the playing field so all children have access to personalized diagnosis and therapy.”

— Maryam Fouladi, MD, MSc, FRCP, co-executive director of Pediatric Neuro-Oncology at Nationwide Children's Hospital

“Recommending that all newborns be tested with a device that measures bilirubin levels through the skin or by a blood test is a major update of the previous guidelines. Because kernicterus is so serious and so often preventable, we wanted to make sure that management was guided by a specific measure. This is an important advance in care.”

— Alex Kemper, MD, MPH, MS, division chief of Primary Care Pediatrics at Nationwide Children's Hospital

## Quality Improvement Scorecard Enhances Safety for Newborns

The collaborative program between academic and community hospitals improves neonatal care quality.



In a recent study published in *The Journal of Pediatrics*, researchers from Nationwide Children’s Hospital and affiliated level one and two community hospital nurseries implemented a quality improvement (QI) scorecard and found improvements in important perinatal outcomes.

“Roughly half of all newborns in the United States are delivered in low-volume perinatal centers, which continue to have higher infant mortality rates than their high-volume counterparts,” says Omid Fathi, MD, neonatologist at Nationwide Children’s main campus. “Incorporating tools from academic hospitals to lower volume health systems supports larger community health goals. That’s why we decided to work together to develop quality and safety initiatives and the scorecard.”

Partner institutions identified opportunities for improvement in neonatal care — including the need for standardizing delivery room practices, staff buy-in and debriefings for missed care opportunities. The centers prioritized perinatal exposures associated with survival and neurodevelopment — outcomes that are universally important to parents. As a result, the scorecard’s clinical metrics included normothermia upon and after admission, breastfeeding or pumping within one hour of birth, breast milk provided within 72 hours, and skin-to-skin care in the delivery room.

Baseline data was recorded for one year and included more than 3,000 infants. Then, they collected data for more than 8,000 infants from four community hospital

nurseries for four years. Each center reported significant improvements in at least two clinical outcomes after implementing the scorecard.

“The tools that came from this collaboration advance both community and academic health goals,” says Dr. Fathi, who was also the senior author of the recent study. “Our results suggest an actionable way to improve quality of neonatal care and reduce infant mortality, especially in areas at higher risk for racial and ethnic disparities.”

In addition to improved clinical outcomes from scorecard usage, at least one center documented improvements in each scorecard process measure: thermoregulation, use of oxygen and pulse oximetry in the delivery room, identification of infants at risk for sepsis and/or hypoglycemia, and breastfeeding success. Notably, three of the four centers improved rates of obtaining glucose checks for newborns with elevated hypoglycemia risk within 90 minutes.

Martin Hanawalt, MD, coauthor of the paper, hospitalist at Nationwide Children’s and medical director at OhioHealth Mansfield, emphasized the importance of engagement between community hospitals and academic centers and prioritizing pediatric care improvements in non-metro county health systems.

“At our hospital, the administration wanted to do [this program],” Dr. Hanawalt says. “But they’re also worried about adult patients and their emergency department. It can be hard to convince community hospitals that they need to do this sort of thing as well. Incorporating scorecard metrics that can be extrapolated to babies helps.”

Dr. Hanawalt says data collection is ongoing, and the program will continue to add metrics to the scorecard to improve community care.

“We’re collecting more data now on babies with neonatal abstinence syndrome [also referred to as neonatal opioid withdrawal syndrome (NOWS)], and I think there will be more metrics to report on in the future,” he adds.

Logan JW, Bapat R, Ryshen G, et al. Use of a quality scorecard to enhance quality and safety in community hospital newborn nurseries. *The Journal of Pediatrics*. 2022 Mar 28;S0022-3476(22)00283-00289.

— Emily Siebenmorgen

## Multimodal Molecular Profiles Offer Clinically Valuable Information to Oncologists

Expanding the profiling ordered for central nervous system (CNS) tumors may meaningfully impact diagnosis and treatment.

**P**rajwal Rajappa, MD, MS, a physician-scientist and principal investigator for the Steve and Cindy Rasmussen Institute for Genomic Medicine (IGM) at Nationwide Children’s Hospital, has long advocated for a more robust use of precision medicine approaches to improve clinicians’ understanding of CNS tumors. His latest research, published in *Neuro-Oncology Advances*, demonstrates the added clinical value of a multimodal approach to molecular profiling for pediatric patients with CNS tumors — some of the most histologically diverse and therapeutically challenging tumors in pediatric oncology.

The study included 53 pediatric patients with CNS tumors, all of whom underwent whole-exome sequencing (WES). A subset of tumors also underwent RNA sequencing (28 patients) and/or methylation array analysis (27 patients). This study is one of the first to examine the combined clinical utility of using multiple profiling methods in a large cohort of pediatric patients with CNS tumors.

“Whole exome sequencing was quite useful for identifying mutations, some of which were targetable, and bulk RNA sequencing revealed clinically relevant prognostic fusions,” says Dr. Rajappa, who directs the Translational Neuro-Oncology Laboratory at IGM. “Methylation profiling helped reclassify certain diagnoses, which had downstream treatment implications. Overall, we observed a meaningful clinical utility in combining a multimodal approach with each of the three next-generation sequencing platforms.”

In seven cases, RNA sequencing identified either the tumor driver or a targetable fusion, and in 23 cases it revealed potential treatment options based on outlier gene expression. Methylation profiling increased diagnostic confidence in eight cases and subclassification based on World Health Organization criteria in 10 cases.

WES revealed clinically important variant information in 36 out of the 53 samples, including 10 that would have gone undetected using only conventional targeted panels. Several children treated based on findings from the broad profiling experienced complete response to targeted treatment paradigms.

“Taken together, the data gave us a more comprehensive picture of the behavior and molecular characteristics of these disparate CNS tumor entities,” says Dr. Rajappa. “Multimodal profiling can be a valuable addition to the standard of care for children with some of the most difficult diagnoses.”

For initial clinical evaluation of CNS tumors, Dr. Rajappa recommends use of a panel of complementary assays, such as a targeted DNA or RNA panel and methylation profiling. If these do not yield information with respect to oncogenic drivers, he suggests incorporating WES and RNA-based fusion detection studies to increase the breadth of the sequencing efforts, given the clinical utility of these precision medicine approaches.

Rajappa P, Eng KW, Bareja R, Bander ED, Yuan M, Dua A, Bhanu Maachani U, Snuderl M, Pan H, Zhang T, Tosi U, Ivasyk I, Souweidane MM, Elemento O, Shoner A, Greenfield JP, Pisapia DJ. Utility of multimodality molecular profiling for pediatric patients with central nervous system tumors. *Neuro-Oncology Advances*. 2022 Mar 10;4(1):vdac031.

— Katie Brind’Amour, PhD

# Long-Term Pulmonary Symptoms Follow COVID-19 Infection in Children

Fatigue and shortness of breath may persist, even in the absence of abnormal test results.



So-called “long COVID” can result in lasting pulmonary sequelae in adults, but little is known about long-term outcomes in children and adolescents post-COVID-19. In February 2021, Nationwide Children’s Hospital initiated a multidisciplinary Pediatric Pulmonary Post-COVID clinic for children experiencing prolonged pulmonary symptoms after COVID-19 infection.

In the largest U.S. study to date of pediatric patients with long-term pulmonary sequelae following COVID-19, researchers conducted a retrospective analysis of all patients seen in the clinic between February 2021 and December 2021. They evaluated measures of lung function, including lung volumes, diffusion capacity, pre- and post-bronchodilator spirometry, and performance on a 6-minute walk test, and analyzed changes in pulmonary findings over time.

Despite a mostly mild, outpatient acute infection, virtually all patients presenting to the clinic experienced notable fatigue and shortness of breath, says Katelyn Krivchenia, MD, pediatric pulmonologist at Nationwide Children’s and co-lead author of the study published in *Pediatric Pulmonology*.

“Regardless of their prior physical function, most of them felt tired and short of breath,” she says. “We saw kids that used to run a 6-minute mile getting short of breath after walking up the stairs.”

The majority of these patients had no significant abnormalities on chest imaging, lung function testing

or physical exam. However, most patients consistently demonstrated tachycardia and heart rate variability during the 6-minute walk test, potentially suggesting autonomic dysfunction, as well as completing a lower-than-expected distance in the allotted time. At follow-up visits, 6-minute walking distance and tachycardia tended to improve, while heart rate variability, fatigue and shortness of breath persisted.

The researchers identified three clinical phenotypes in their cohort of patients. About one-third of patients responded positively to bronchodilator therapy, even if their initial spirometry testing was negative. Children in this group generally had a family or personal history of asthma. Another group of patients, about 12% of the cohort, had paroxysmal vocal cord movement disorder. And a final group exhibited symptoms even though no abnormalities could be found.

“We show that in this population, virtually everybody has normal testing results, in contrast to what we see in adults with long COVID,” says Dr. Krivchenia, who is also assistant professor of Pediatrics at The Ohio State University College of Medicine. This suggests the full panel of lung tests may not be necessary for pediatric patients.

The researchers also conclude that bronchodilator therapy may be worth starting sooner with pediatric patients, and clinicians should be aware of vocal cord dysfunction as a potential contributor to shortness of breath and fatigue in children with long COVID.

Dr. Krivchenia notes that more than 75% of the children seen in the clinic were not vaccinated against COVID-19, and some of them suffered re-infections.

“We found that long COVID is debilitating for some of these kids,” she says. “People think this disease is mild in pediatric populations, but we see kids that can’t go back to school, don’t graduate on time and can’t play their sport anymore.”

Palacios S, Krivchenia K, Eisner M, Young B, Ramilo O, Mejias A, Lee S, Kopp BT. Long-term pulmonary sequelae in adolescents post-SARS-CoV-2 infection. *Pediatric Pulmonology*. 2022 Jul 1. [Epub ahead of print]

— Mary Bates, PhD

# Understanding Pediatric Critical COVID-19 Disease Around the World

A large, multinational study found more children hospitalized with critical COVID-19 died than was indicated by previous studies.

Children under 18 represent around 22% of the population in the United States. Yet, just 15% of over 75 million U.S. COVID-19 cases reported to the Centers for Disease Control (CDC) and fewer than 0.2% of over 850,000 reported COVID deaths have occurred in this age group.

During the first year of the pandemic, even as doctors in the United States and United Kingdom began observing the appearance of a startling new condition, multisystem inflammatory syndrome in children (MIS-C), which appeared in kids who had been infected a few weeks prior, it was clear COVID-19 impacted kids and adults very differently — with kids rarely hit as hard.

Only a fraction of U.S. kids who were infected required hospitalization, and even fewer became critically ill, requiring respiratory, cardiovascular or renal support in the pediatric intensive care unit (PICU). Those children also had lower mortality rates compared to adults.

“Patients who got MIS-C maybe needed vasopressors and a ventilator for a couple days, but they often recovered rapidly,” says Todd Karsies, MD, a Critical Care Medicine physician at Nationwide Children’s Hospital.

Low mortality rates among U.S. children and an early focus on MIS-C in pediatric COVID-19 research in the United States, however, obscured the fact that globally, the story was more complicated.

Over 90% of pediatric COVID-19 deaths in the first year of the pandemic occurred in low- or middle-income countries (LMICs), and the highest mortality rates were among children under 1.

To better understand the epidemiology and outcomes of critical pediatric COVID-19 in PICUs in both highly resourced, high-income countries (HICs) like the United States and LMICs and begin assessing risk factors for death, over a dozen multinational scientists, including Dr. Karsies, launched the Critical Coronavirus

And Kids Epidemiology (CAKE) study, publishing their findings in *The Lancet Regional Health – Americas*.

“This study organically grew out of a different international project,” says Dr. Karsies. “Since December 2019, we’d already been collecting data from nearly 100 sites in 20 countries on kids who needed to be admitted to the ICU for bronchiolitis. When everything shut down for COVID-19, we were able to build on this existing infrastructure and hit the ground running quickly.”

Among 557 patients aged 18 or younger hospitalized at 55 sites in 18 countries with critical COVID-19 and/or MIS-C in between April 1 and December 31, 2020, the team found the mortality rate was much higher than reported by previous studies. Among critically ill children under 2, the mortality rate was upwards of 10%.

## FACTORS ASSOCIATED WITH HIGHER COVID-19 MORTALITY IN CHILDREN

### Lower respiratory tract symptoms (breathing problems)

#### Younger age

#### Illness other than MIS-C

And while 90% of pediatric mortality due to COVID-19 has been observed in LMICs, over 1,000 U.S. children have died with COVID-19. Typically, fewer than 200 children die each flu season.

“Kids are dying from COVID-19,” says Dr. Karsies. “We’re trying to better understand, based on the data that we have, which kids are at risk, which kids die, where and why these kids die, whether there are treatments that can reduce mortality, and what we need to focus future research on.”

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— Natalie Wilson

# Integrating Behavioral Health and Primary Care Increases Access and Equity

With mental health concerns on the rise, more primary care providers are integrating behavioral health services in their practices.



Written by Mary Bates, PhD



Despite increasing demand for behavioral health care, multiple barriers still exist that limit access for pediatric patients. In recent years, primary care settings across the country have responded by integrating mental health specialists into their practices. Now, a growing body of evidence suggests that integrating behavioral health services into pediatric primary care can reduce health disparities, improve outcomes and increase both patient and provider satisfaction.

In December 2021, the U.S. surgeon general released an advisory declaring the mental health challenges

facing children and teens a “national crisis.” The report noted that the COVID-19 pandemic has exacerbated an ongoing rise in depression, anxiety, self-harm and other behavioral health issues among youths. At the same time, there is a shortage of pediatric mental health specialists to meet the need.

Mental health disorders impact up to 40% of children and adolescents, but only 30% of them receive care, and on average, they experience a delay of 8 to 10 years between symptom onset and intervention.

“Primary care is one of the front doors to the mental health system. It’s the first place that most parents go when they have a concern about their child’s behavior or development.”

— Cody Hostutler, PhD, psychologist at Nationwide Children’s Hospital



The primary care office is often the place where behavioral health issues are first raised. About half of all pediatric primary care office visits involve behavioral or psychosocial concerns, says Cody Hostutler, PhD, a psychologist at Nationwide Children’s Hospital.

“Primary care is one of the front doors to the mental health system. It’s the first place that most parents go when they have a concern about their child’s behavior or development,” he says.

However, many pediatric providers feel that they don’t have the training or time to adequately manage behavioral health needs and have a hard time finding help.

To address these issues, some health systems have adopted integrated behavioral health strategies — systemic and physical structures where pediatricians and mental health specialists work together to care for children’s holistic health and development.

## Nationwide Children’s Integrated Approach

At Nationwide Children’s, efforts to integrate behavioral health and primary care took off in 2016. At that time, many of the hospital’s specialty medical clinics already had integrated psychologists. Dr. Hostutler was part of the team that spearheaded the move to a highly integrated model of behavioral health care in primary care settings.

“Presently, we have integrated behavioral health in just under half of our 14 primary care clinics, and we are working to place psychologists at each one,” says Alex Kemper, MD, MPH, MS, division chief of Primary Care Pediatrics at Nationwide Children’s. “As part of our well child checks, we focus on growth and development and promoting optimal outcomes, and behavioral health is central to that.”

For the integrated psychologists at Nationwide Children’s, about 20-25% of their daily appointments are scheduled follow-ups or further assessments. The bulk of their days are intentionally kept open, allowing them to jump in and assist with patients as needed.

Whitney Raglin Bignall, PhD, a psychologist at Nationwide Children’s Linden Primary Care Center, says that the emphasis on seeing patients and families on the day of their primary care appointment is a unique and important aspect of the hospital’s integrated model.

“Even though patients are coming in to see one of our primary care providers, there is an understanding that I

might see them that same day, too,” she says. “I review all the charts and read notes while they are in appointments because I am anticipating that I might get a chance to see that family that day.”

As a psychologist in a primary care center, Dr. Raglin Bignall’s work is varied but she says her goal is to leave every family with an understanding of the issue and the first few steps of a plan to move forward.

“A big part of our job is to take some of the stress off our pediatricians and other providers, while giving families some immediate strategies and a plan for the next step,” she says.

The work that integrated psychologists do at Nationwide Children’s can run the gamut. They are there to address serious mental health concerns, such as anxiety and depression, but also to help families with common issues like toilet training, pill swallowing, fear of vaccines and temper tantrums.

Even before concerns arise, Dr. Raglin Bignall and other integrated psychologists will pop into wellness visits for children as young as two months old to introduce themselves to families.

“It’s not just about behavioral health crises,” she says. “It’s about how we develop those relationships early and prevent problems later on.”

“Behavioral health integration is so much more than just therapy in the primary care setting,” agrees Dr. Hostutler. “At Nationwide Children’s, we are full partners in care, ready to jump in as needed to improve physical and mental health.”

## Models of Integrated Behavioral Health Care

The highly integrated approach to behavioral health at Nationwide Children’s falls at one end of a continuum of models of integrated care. These are typically organized into coordinated, co-located, and integrated models, depending on the level of integration of primary care providers and mental health specialists.

In coordinated models, mental health services are coordinated with primary care but are not provided in the primary care practice. Coordinated models often involve telehealth-delivered services such as providing information or updates to the primary care provider and facilitating referrals.



My job is so rewarding. I get to meet families and grow with them. And I get to work in this team where we think holistically about children's health. I work with schools and the community, as well – it's so much broader than just an office visit and it allows me to do a better job."

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



Co-located care refers to providing behavioral health services within the same clinic as a primary care provider but without significant collaboration between providers. In this model, the pediatrician and psychologist work in parallel at the same clinic, rather than being partnered.

Integrated models provide collaborative services within the primary care setting and involve the primary care provider and mental health specialist working together to care for patients.

Clinics can also use variations or combinations of these models to fit their specific needs. In addition to their highly integrated primary care clinics, Nationwide Children's also incorporates co-located therapy to its model so that patients needing more support can receive therapy within the primary care office on their own schedules.

### Benefits to Providers

Integrating behavioral health into primary care can allow pediatricians to see more patients and improve the overall efficiency of the clinic, says Dr. Kemper, who is also a professor of Pediatrics at The Ohio State University College of Medicine.

"If there is something complex or needing extra attention, the psychologist can go into the room and address that with the patient and the family while the pediatrician goes and sees other patients and comes back," he says.

Integration also allows primary care providers to focus on the services they feel more comfortable delivering. Pediatricians may be more likely to ask their patients about behavioral health concerns, knowing that they can be addressed by an integrated mental health specialist that same day.

Primary care providers also appreciate the opportunity that integration provides them to learn from their colleagues.

Working closely with mental health specialists allows pediatricians to acquire new strategies and build their skills, which can help them feel more confident in caring for their patients' mental health needs.

Integrated behavioral health providers benefit from working within these models of care, too, says Dr. Raglin Bignall.

"My job is so rewarding. I get to meet families and grow with them," she says. "And I get to work in this team where we think holistically about children's health. I work with schools and the community, as well — it's so much broader than just an office visit and it allows me to do a better job."

### Increasing Access and Equity

In addition to the benefits to providers, integration also affords opportunities for pediatricians and mental health specialists to better coordinate treatment, resulting in several advantages for patients and families.

"Usually, without having a behavioral health provider in the clinic, physicians have to put in a referral," says Dr. Raglin Bignall. "And especially in these times, there is a huge need and the wait lists are long. Families end up having to wait a long time to get help."

Families often prefer an integrated model because it gives them the chance to meet with a mental health specialist the same day they present with a concern.

"About 93% of the kids we see are seen on the same day they bring up their concerns to the physician," says Dr. Hostutler. "The wait time is a few minutes, not a few months. We say we provide the right service at the right time."

Scheduling behavioral health follow-ups within the primary care setting can also help reduce the stigma

of receiving mental health care. When a mental health specialist has been involved in wellness visits from infancy on, behavioral health becomes a standard part of raising a child and receiving medical care. Both patients and families may be more comfortable asking for and receiving mental health help in this context.

"Integration seems to be a more palatable, tolerable, accessible, less stigmatizing approach to treatment for a lot of people," says Dr. Hostutler. "By engaging in mental health treatment in collaboration with a primary care physician who knows the family and has their trust, and by doing it in a medical setting, more people are willing to engage in treatment."

At Nationwide Children's, integration has resulted in a tripling of the number of patients accessing behavioral health providers. At the same time, there has been a one-third reduction in referrals to behavioral health providers outside of the clinic.

"Integration triples access while reducing the number of kids referred out to a mental health professional in the community," says Dr. Hostutler. "The fewer referrals we send to providers in the community, the more availability they have and the shorter their waitlists."

Data from Nationwide Children's and at the national level suggest that behavioral health integration reduces barriers and improves equity in access to quality mental health care. Additionally, integration often leads to a reduction in emergency room visits and hospital stays for mental health crises, resulting in reduced costs. When behavioral health providers work collaboratively with primary care physicians, all parties benefit.

### Integrated Approaches for Any Clinic

Nationwide Children's is leading by example with their integrated primary care clinics. But clinicians at the hospital are also sharing their resources and experience with primary care clinics across the state. A team at Nationwide Children's, including Dr. Hostutler, works to scale behavioral health integration out into the community. They provide technical assistance to local primary care practices interested in integrating behavioral health care.

Dr. Hostutler emphasizes that "integrated care" encompasses a diverse set of services and there is no "one-size-fits-all" approach.

"There are some people who like to cook by recipe and then there are people who like to cook by ingredients,

based on what they have at hand," he says. "When we do our technical assistance to primary care clinics in the community, we cook by ingredient to develop personalized models. That is how we help them create a model of integration that best fits their clinic and their patients' needs."

A highly integrated model might seem preferable. In practice, the choice of model and how it is implemented will vary between clinics based on several issues, including patient demographics, payer mix, and access to community-based referrals for ongoing mental health care. For instance, if a clinic sees an overwhelming amount of substance misuse, it might make sense to specifically focus on screening and treating that issue. Or if a clinic is in an area where patients have fewer barriers to attending appointments and following through with referrals, a co-located model could work.

"There is no question that the integrated model improves health outcomes for patients and improves the quality of life for the families that we take care of," says Dr. Kemper. "Behavioral health integration is a no-brainer and once you see it in action, the benefits are remarkable."

LOOKING FOR HELP INTEGRATING BEHAVIORAL HEALTH INTO YOUR PRIMARY CARE PRACTICE?  
Reach out to to the Nationwide Children's support team here:  
NationwideChildrens.org/BHIntegration

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# New Initiative Aims to Bring Personalized Diagnosis and Treatment to Children With Solid Tumors

The National Institutes of Health's National Cancer Institute (NCI), Children's Oncology Group (COG), and Nationwide Children's Hospital are poised to change the direction of pediatric cancer diagnosis and care through a new initiative that is the largest of its kind in the United States. The Molecular Characterization Initiative offers tumor molecular characterization, also called biomarker testing, to children, adolescents, and young adults with solid tumors who are being treated at hospitals affiliated with COG. This state-of-the-art molecular characterization at the time of diagnosis helps COG-affiliated doctors select the best and most appropriate treatment for each patient.

"These organizations have a shared vision: children with cancer receiving a precise diagnosis based on the molecular

Collaboration among National Cancer Institute, Children's Oncology Group and Nationwide Children's Hospital will offer molecular characterization of childhood cancers.

*Written by Lauren Dembeck, PhD*

characteristics of their specific tumor. For each child, we hope to refine the initial diagnosis and potentially guide treatment," notes Douglas S. Hawkins, MD, Group Chair of COG. "With more than 200 member hospitals that treat children with cancer, COG provides myriad opportunities for innovative life-saving research. It doesn't matter where a family lives; if their child is diagnosed with cancer, they could have access to the Molecular Characterization Initiative."

The program is part of the NCI's Childhood Cancer Data Initiative (CCDI), which was launched in 2019 to foster data sharing and collection of new data among researchers who study childhood cancers. It was initially opened to patients diagnosed with central nervous system (CNS) cancer and in June expanded to include patients with soft tissue sarcomas and other

rare tumors. Initial enrollment in the CCDI Molecular Characterization Initiative is offered through "Project: EveryChild" (APEC14B1), a childhood cancer registry maintained by COG, as a grantee through an NCI-supported clinical trials group. Patients receive molecular characterization of their tumors free of charge through the voluntary program.

"We can help make molecular characterization available throughout the country so that it will be a standard of care that every child can get," says Maryam Fouladi, MD, MSc, FRCP, co-executive director of Pediatric Neuro-Oncology at Nationwide Children's and COG's central nervous system tumor disease committee leader. "An accurate molecular diagnosis can inform optimal treatment for every child."

The initiative is timely for children with CNS cancer. In 2021, the World Health Organization updated their classification of CNS tumors, and molecular characterization is now required for accurate diagnosis of CNS tumors and risk stratification of patients. The update also incorporates multiple newly recognized tumor types that are characterized by specific driver mutations and can be identified only by using biomarker testing.

For example, Dr. Fouladi explains, some childhood cancers, such as gliomas, can be misdiagnosed.

"We can apply molecular diagnostics to a child diagnosed with a high-grade glioma and find out that it is actually a low-grade glioma or an entirely different tumor, which may need very different treatments and have a very different outcome," she says. "Molecular diagnostics can really contribute to getting the correct diagnosis, offering the optimal treatment and, ultimately, improving the patient's outcome. It is not a luxury; it is a necessity for appropriate cancer care."

DNA and RNA from tumor and blood samples are analyzed to help make an accurate diagnosis and to

understand what is causing or driving each individual's cancer. Having a precise diagnosis based on the molecular characteristics of the patient's tumor can not only help doctors choose the most effective, but also the potentially least toxic treatment.

Some tumor types, such as medulloblastoma, require that doctors understand what subtype of tumor the patient has.

"The specifics of the biology of the tumor is critical for us to be able to treat a patient appropriately," says Dr. Fouladi, who is also professor of Pediatrics at The Ohio State University College of Medicine. "For example, by biologically defining the tumor of a child with medulloblastoma as high-risk, standard-risk or low-risk, we can study risk-stratified treatment approaches that consider reduction of irradiation and/or chemotherapy to diminish long-term neurocognitive, neuroendocrine, as well as chemotherapy-related side effects for low-risk patients to allow children to reach their full potential. Conversely, for children with biologically-defined high-risk medulloblastoma, we can study treatment approaches that intensify therapy to improve their survival."

Furthermore, for other cancers, knowledge of the molecular aberrations allows doctors to specifically target a given aberration with a targeted therapy, a drug that targets cancer cells without affecting normal cells, providing a less toxic treatment for those patients. The data from molecular characterization can also be used to determine whether a child is eligible for a clinical trial evaluating a new treatment explicitly designed for their tumor type.

The molecular data gleaned from the initiative will be added to NCI's Cancer Research Data Commons, providing access to these data to cancer researchers worldwide. Previously, comprehensive molecular characterization of tumors was available to some children

**Molecular diagnostics can really contribute to getting the correct diagnosis, offering the optimal treatment and, ultimately, improving the patient's outcome. It is not a luxury; it is a necessity for appropriate cancer care."**

– Maryam Fouladi, MD, MSc, FRCP, co-executive director of Pediatric Neuro-Oncology at Nationwide Children's Hospital





*The Biopathology Center supports cutting-edge research and positively impacts patient care through procurement, processing, banking and distribution of high-quality, clinically annotated biospecimens.*

being treated at larger institutions with internal resources to offer such state-of-the-art diagnostics or those who enrolled in certain clinical trials, and the resulting tumor biomarker data were stored exclusively at the hospital or institution where the child was treated, with limited sharing of data between institutions. Now, the data collected will be available in a central location so that researchers can better understand the molecular causes of childhood cancers and accelerate the development of new, more effective, and potentially less toxic treatments.

### **Nationwide Children’s Serves as the Sample-Processing Hub**

Nationwide Children’s provides two critical aspects of the CCDI Molecular Characterization Initiative: the Biopathology Center, which oversees the COG Biobank, and the Steve and Cindy Rasmussen Institute for Genomic Medicine (IGM), which performs the clinical molecular characterization assays. The IGM is funded to perform these assays through a subcontract with

Leidos Biomedical Research, Inc., current operator of the Frederick National Laboratory for Cancer Research.

The Biopathology Center receives tissue and blood from patients enrolling to the study and prepares specimens for molecular analysis by extracting nucleic acids and performing quality control on the analytes. These are then forwarded to the IGM, where multiple clinical characterization assays of the tumor and blood analytes and nucleic acids are conducted. The resulting data are analyzed and interpreted, and signed out as clinical results for return to the physicians who enrolled patients onto the CCDI Molecular Characterization Initiative. These results help refine the initial diagnosis, guide treatment decisions, and suggest potential clinical studies for that child. The IGM also deposits the data from these assays into NCI’s Cancer Research Data Commons for future studies, such as those exploring why some tumors become resistant to therapies that they initially responded to or what factors increase the risk of treatment-related side effects. Personal information

that could be used to identify a participant will be removed before data are added to the database.

“Because these results impact patient care, extracted analytes from tumor tissue and blood must be shipped to the IGM within five days,” explains Nilsa Ramirez, MD, director of the Biopathology Center at Nationwide Children’s. “Time is of the essence when a child’s physician is waiting on results. We aim to complete the entire process from receiving the specimens at our center through final analysis in the IGM within 21 days, which is an exceptional turnaround time for this process. We’re proud to be an essential part of this pioneering initiative.”

Both the Biopathology Center and IGM Clinical Laboratory are accredited under the College of American Pathologists Laboratory Accreditation Program and certified by CLIA (Clinical Laboratory Improvement Amendments) for clinical testing. The IGM Clinical Laboratory also is accredited by the New York State Department of Health, which is required for testing patients from New York.

“Executing multiple genomic tests to produce data that are interpreted through rapid and scalable computational analyses and lead to medically relevant results requires a highly integrated clinical environment,” says Elaine R. Mardis, PhD, co-executive director of the IGM and principal investigator of the initiative contract. “We are excited to be part of this incredibly worthy endeavor.”

The first completed results were provided on April 14, 2022, for a participant enrolled in March 2022. As many as 3,000 participants are expected each year.

“The CCDI Molecular Characterization Initiative is a transformative collaboration,” says Richard Wilson, PhD, executive director of the IGM. “We anticipate this project will fundamentally transform how we diagnose and treat children facing cancer.”

### **Transforming Clinical Trials**

The CCDI Molecular Characterization Initiative is already playing a key role in changing the way clinical trials on childhood CNS tumors will be conducted at Nationwide Children’s and elsewhere. For instance, physician Ralph Salloum, MD, of the pediatric neuro-oncology program at Nationwide Children’s, is the study chair for the Children’s Oncology Group ACNS2031 clinical trial for children with medulloblastoma, which is the most common malignant brain tumor in childhood. In the study, treatment will rely solely on the results of the initiative for risk stratification. All patients who would like to participate in the trial will have undergone molecular characterization prior to the enrollment. The study is slated to open in September 2022, in COG sites around the United States, Canada and Australia.

### **More Cancer Coverage to Come**

In late 2022 and 2023, the initiative will continue to expand to patients with other childhood cancers.

“The enormous collaborative effort to make the CCDI Molecular Characterization Initiative possible is very ambitious and very heartwarming. It has required the expertise of the clinicians, pathologists, and genomics specialists as well as the commitment of clinicians from institutions around the country all working together for a higher good. That’s what I think is the beauty of this initiative,” adds Dr. Fouladi. “This is a new era in cancer care for all of us, and I am very grateful that we’re part of a generation where we can build this testing infrastructure for kids around the country. I think it has been a long time coming and will level the playing field so all children have access to personalized diagnosis and therapy. It is really a dream come true.”

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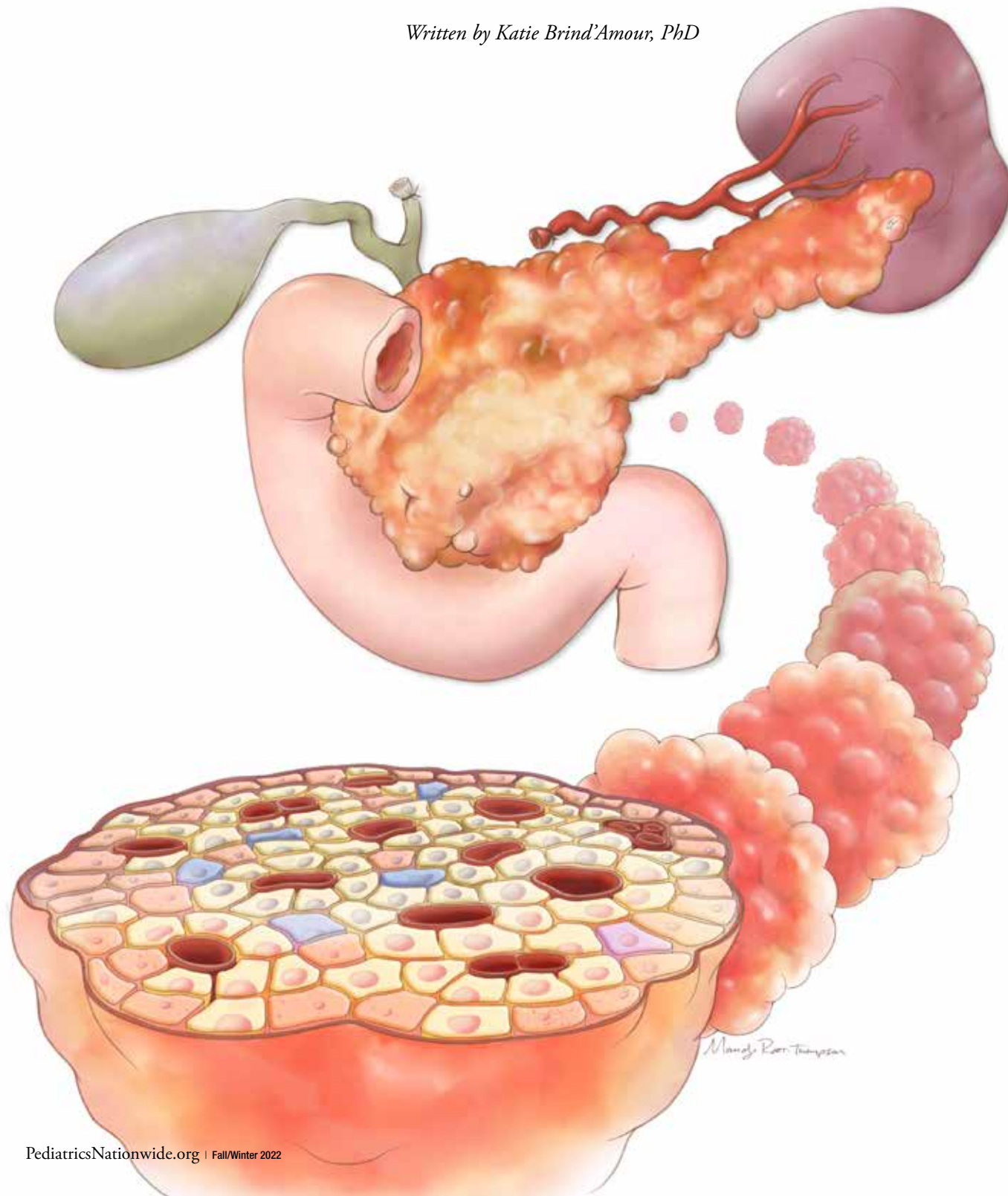




# TPIAT: A WAY FORWARD FOR CHRONIC PANCREATITIS

Nationwide Children's Hospital has assembled a veritable "dream team" of pancreatitis and pediatric transplant surgery experts to offer what they hope will become the world's preeminent pediatric center for complex pancreatic care.

Written by Katie Brind'Amour, PhD



Imagine your child suffering from a sudden, debilitating episode of abdominal pain. No obvious cause, no cure, just pain so severe it requires hospitalization for days — even weeks. Your child suddenly goes from an active, healthy kid to one who can't tolerate a single bite of food.

This nightmare, acute pancreatitis, affects about 1 in every 10,000 U.S. children per year. The condition used to be considered a disease of adulthood, tied to alcohol use, smoking, gallstones, high cholesterol and certain medications. But as diagnosis and data collection improved among children, clinicians have documented an increasing incidence of acute pancreatitis almost matching that in adults.

Now, imagine that your child is one of the 15-35% who have a second attack. Your child is hospitalized again, recovers again. Only to fall prey to another and then another episode of pancreatitis — now considered acute recurrent pancreatitis. Eventually, damage to your child's pancreas accumulates, and chronic pancreatitis (CP) develops. The pain is nearly constant and interferes with school, sports and social activities.

Your child can no longer lead a normal life, even with the use of round-the-clock pain medication.

"If you talk with families, you learn that this is such a frustrating, debilitating condition," says Oluyinka Olutoye, MD, PhD, surgeon-in-chief at Nationwide Children's Hospital. "Their kids aren't thriving, they're not growing, they're having persistent pain. They have tried everything, without success. For many families, this is almost a hopeless situation — they can't find the appropriate answers for their kids."

This tragedy is a reality for almost 6 in every 100,000 children in the United States, about two-thirds of whom require frequent opioid use for pain management. Pancreatic function may be lost over time as the organ

fights inflammation, blocked pancreatic ducts, scarring or other damage, resulting in the need for insulin or digestive enzyme medications in many children. Even with the best supportive care, about half of all patients with CP don't achieve adequate pain relief from medication or endoscopic procedures and eventually require surgical intervention.

## CP SURGERY: WHAT ARE THE OPTIONS?

Conventional pancreatic operations aim to relieve pain by correcting an anatomical or morphological problem such as a blocked duct, poor drainage or an inflammatory mass in the head of the pancreas. Options include the modified Puestow procedure (also called a longitudinal pancreaticojejunostomy), the Whipple (pancreaticoduodenectomy), and duodenum-preserving pancreatic head resections (the Beger, Berne and Frey procedures).

Unfortunately, it's not as simple as choosing one from among many good options. Most of these surgical procedures carry significant risks, and as many as half of those who undergo these conventional operations do not enjoy lasting pain relief. They also still face an elevated risk of diabetes, opioid dependence and pancreatic cancer.

"We think of surgery as a last resort, only after medical and endoscopic management have failed, and it's often not a miracle cure," says A. Jay Freeman, MD, MS, medical director of Pancreas Care at Nationwide Children's and a recent recruit from his role as director of the Advanced Pancreatic Care Program at Children's Healthcare of Atlanta. "Selecting an operation has a lot to do with what we think the underlying cause of a child's pain is. Ductal strictures or pancreatic lesions may be amenable to focused surgical approaches, but for hereditary pancreatitis and those with truly unrelenting pain, a lot of the conventional procedures haven't been hugely effective in the pediatric population."

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— A. Jay Freeman, MD, medical director of Pancreas Care at Nationwide Children's Hospital



This has increased the importance of imaging and interventional endoscopy in pre-surgical pancreatic care.

“What we want to do through a cohesive, multidisciplinary team is gather as much information as possible so that we have the best surgical outcomes — before we ever even operate,” says Muhammad Khan, MD, FASGE, director of advanced interventional endoscopy services at Nationwide Children’s. He is an expert in advanced abdominal imaging and endoscopic therapies and is fellowship-trained in endoscopic retrograde cholangiopancreatography and endoscopic ultrasound.

“That requires a robust genetic and molecular evaluation of patients, endocrinologic function evaluations and, of course, imaging and endoscopy is critical for virtually every child who progresses to surgery,” says Dr. Khan.

Procedures that preserve healthy tissue and provide resection and/or drainage approaches are considered appropriate options for some children with debilitating CP. Depending on the operation and underlying risk factors, as many as 85% of patients (based on adult data) who undergo duodenum-preserving pancreatic head resections experience meaningful reductions in pain. And nearly 3 in every 4 patients undergoing surgery found it helpful, according to a cohort of children in the INternational Study Group of Pediatric Pancreatitis: In search for a cuRE (INSPPIRE) project.

“Until we find a cure, there is certainly a place for these types of operations in the care of children with chronic pancreatitis,” says Jaimie Nathan, MD, FACS, chief of Pediatric Abdominal Transplant and Hepatopancreatobiliary Surgery at Nationwide Children’s and the most experienced board-certified pediatric surgeon in the country specializing in pancreatitis. “The key is making

sure that the right operation is selected for the right patient, at the right time in the treatment continuum.”

At most hospitals, however, care often follows a predictable trajectory, ending with conventional drainage and/or resection procedures. If those don’t work, patients are simply in pain and out of luck.

Thankfully, a position statement released this year by the Pancreas Committee of NASPGHAN (North American Society for Pediatric Gastroenterology, Hepatology and Nutrition), with Dr. Nathan as its lead author, now offers sophisticated guidance for the consideration of pancreas anatomy and morphology in the selection of a surgical procedure for pediatric CP.

**GO ONLINE TO**  
**[PediatricsNationwide.org/TPIAT-feature](https://PediatricsNationwide.org/TPIAT-feature) for a surgical decision tree developed by Dr. Nathan and team.**

The guidelines strongly urge clinicians to consider genetic risk factors, which may predispose children to more complicated disease, poorer surgical outcomes and medication-resistant pain. Once hereditary status is known, making the best decision requires advanced imaging and in-depth, multidisciplinary discussion of the child’s pancreas health, disease physiology and probable outcomes.

In most cases, none of the conventional operations are a good fit for a child’s disease. It used to be that conventional procedures would be tried anyway. But in 1989, adult surgeons started incorporating a more extensive procedure into their care of children with CP: the total pancreatectomy with islet autotransplantation, or TPIAT.

“If you use a non-TPIAT operation on a patient that had high likelihood of failing, you’ve burned bridges. They often muddle through, not relieved of their pain, staying on opioids or coping with chronic pain longer before they get to a salvage TPIAT, and in the interim they may develop central sensitization. At that point, the patient has also faced a much longer duration of disease, and you’ve missed the opportunity to maximize islet isolation yield and the potential for coming off exogenous insulin.”

— Jaimie Nathan, MD, chief of Pediatric Abdominal Transplant and Hepatopancreatobiliary Surgery at Nationwide Children’s Hospital



*Dr. Appakalai is among the world’s most experienced in processing human pancreases for clinical islet autotransplantation and allotransplantation. He has processed more than 1,500 pancreases, which have been utilized for clinical auto- and allotransplantation and for islet biology research initiatives. His research has been dedicated to methods to preserve and improve blood circulation to isolated islets after transplantation. Scan the QR code for an inside look at his lab.*



#### GETTING TO KNOW TPIAT

TPIAT was first developed for the treatment of debilitating pancreatitis in adults in 1977. The procedure involves complete removal of the pancreas together with the isolation of the pancreas’ insulin-producing islets, which are then introduced into the patient’s liver in the hope that they will continue their valuable work in a new home.

As the pediatric gastroenterology community became more aware of pancreatitis in children, the procedure gradually migrated into the list of surgical options for young patients at some institutions. The results were remarkable.

In an *Annals of Surgery* study of 75 pediatric patients, 90% experienced improvements in pain and had stopped taking opioids 2 years postoperatively. Improvements in quality of life were equally robust, with almost universal freedom from CP-related school absences and significant improvements in all domains on a standard quality of life tool. Forty-one percent achieved insulin independence, with high durability of response as of 10 years post-surgery.

However, very few surgeons in the country have extensive experience performing the procedure in children, and those that do often get patient referrals only after multiple other operations have failed.

“If they don’t have the anatomic features to consider non-TPIAT options, all you can offer is TPIAT,” says Dr. Nathan, who has cared for this population for more than 10 years and performed nearly 100 TPIATs since 2015.

A high percentage of children with acute recurrent and chronic pancreatitis do not have a dilated main pancreatic duct or an inflammatory head mass, which rules out the utility of surgical drainage procedures and partial resections, respectively.

“Even in children with a dilated duct or pancreatic head mass, if they have an underlying genetic risk factor, it’s unlikely that an operation other than TPIAT is actually still the optimal approach,” Dr. Nathan says.

Pancreatic inflammation, organ fibrosis, partial resections and drainage operations reduce the number of islets



Offering this advanced medical care and surgical service goes to the next level of achieving best outcomes for an important subgroup of patients who can't have their needs met by other means. Also having the ability to isolate the islets and advance autotransplantation science right here, though, is the key to making this truly unique."

— Oluyinka Olutoye, MD, PhD, surgeon-in-chief at Nationwide Children's Hospital



remaining in the pancreas. Delaying the use of TPIAT until after other operations have been attempted and failed may not be the best tactic.

"If you use a non-TPIAT operation on a patient that had high likelihood of failing, you've burned bridges," says Dr. Nathan. "They often muddle through, not relieved of their pain, staying on opioids or coping with chronic pain longer before they get to a salvage TPIAT, and in the interim they may develop central sensitization. At that point, the patient has also faced a much longer duration of disease, and you've missed the opportunity to maximize islet isolation yield and the potential for coming off exogenous insulin."

Despite complete resection, up to 1 in 10 patients may continue to experience pain after TPIAT, likely due to central sensitization (much like phantom limb pain after an amputation). And since the entire pancreas is removed, children also require pancreatic enzyme replacement therapy (PERT) for life. General complication rates are low, though — comparable to or better than conventional operations when TPIAT is done by an experienced surgeon.

As research continues, the goal is to refine the ideal point of intervention and the best population for the procedure. Some data support the use of TPIAT earlier in the treatment continuum than initially anticipated because of better pain relief (100%) and insulin independence rates (64%) among 3-to-8-year-olds compared to older children. This may reflect the fact that islet health is likely to be better earlier in the disease course — a critical factor for diabetes prevention — and sensitization is less likely to have developed.

The Prospective Observational Cohort Study of TPIAT (the POST Study), which Dr. Nathan led as the site

principal investigator at his prior institution and is now in the data analysis phase, hopes to determine whether patients with central sensitization, as assessed by quantitative sensory testing, have poorer long-term TPIAT outcomes. Additional research efforts at Nationwide Children's aim to further evaluate and improve outcomes for TPIAT patients.

"Offering this advanced medical care and surgical service goes to the next level of achieving best outcomes for an important subgroup of patients who can't have their needs met by other means," says Dr. Olutoye, who helped orchestrate the CP "dream team" recruitment and program development plans together with the medical leadership in gastroenterology at Nationwide Children's. "Also having the ability to isolate the islets and advance autotransplantation science right here, though, is the key to making this truly unique."

#### THE SCIENCE OF ISLET AUTOTRANSPLANTATION

The pancreas contains clusters of cells called islets, which collectively manage the body's blood glucose levels by secreting insulin. They make up only about 2% of pancreatic cells and depend on a network of vascular connections to monitor blood sugar and respond accordingly.

For TPIAT, the islets are isolated from the removed pancreas and the non-islet tissue via an enzyme digestion by a team of scientists in a Good Manufacturing Process (GMP) clean room. The goal is to maximize the number of healthy islets that can be re-implanted into the patient to prevent diabetes. The islets are then introduced into the liver via the portal vein. Upon arrival, the islets must re-establish a blood supply, which usually takes several weeks, before they can adjust blood glucose levels via insulin production.

"My research career has focused on manufacturing and optimizing pancreatic islet cell products for clinical transplantation studies, and specifically improving islet yield from every processed pancreas," says Balamurugan Appakalai, PhD, director of the Pancreatic Islet Cell Isolation Program and a principal investigator in the Center for Clinical and Translational Research in the Abigail Wexner Research Institute at Nationwide Children's. "We have established advanced islet manufacturing protocols for clinical islet autotransplantation."

To achieve consistent success in clinical outcomes, an islet isolation team must learn to recognize key variables of a pancreas, such as fibrosis and patient age. They must also understand the principles of the isolation procedure well enough to adapt it for each individual organ.

Dr. Appakalai and his team are working to improve the survival of transplanted islets after separation from the native pancreas, focusing on providing blood supply to transplanted islets immediately after infusion into the liver. His team also works with stem cell approaches to generate insulin-producing cells in the lab.

"I am grateful that there is such a strong and growing clinical utility for my work," says Dr. Appakalai, who has processed more than 1,500 pancreases. "And working with a collaborative, science-friendly team of endocrinologists, gastroenterologists, surgeons and radiologists will help us continue to improve the success of our science at the bedside and at the bench."

The team's on-site GMP islet facility is the only one of its kind at a pediatric hospital in the United States, and will also process pancreases for TPIAT performed



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— Balamurugan Appakalai, PhD, director of the Pancreatic Islet Cell Isolation Program in the Abigail Wexner Research Institute at Nationwide Children's Hospital



at other institutions — providing the opportunity for the operation to be offered at centers that do not have a local islet isolation facility.

#### A Bright Future for CP Care

As research continues to confirm that pediatric TPIAT is safe and effective at providing lasting pain relief for children with advanced CP, this procedure is poised to offer a very promising alternative to conventional operations. Coupled with improvements in islet isolation and transplantation technology, it appears likely that TPIAT will soon become more commonplace in the surgical management of pediatric CP.

"TPIAT isn't a service that you dabble in," says Dr. Olutoye. "You have to commit as an institution to recruit the experts in the field, and to not just provide the service but be poised to advance the field with the level of medical care, imaging resources, surgical expertise, pain management, and the scientific and clinical research efforts that these patients deserve. This is a crucial need for these families, so if we can help them achieve best outcomes, we are invested in it 100%."

The growing team and pancreatitis-related offerings have already made Nationwide Children's the epicenter for advanced treatment of pediatric CP, TPIAT and islet transplantation research. But the capabilities of the "dream team" have important benefits for other patients, as well, both in terms of broadened research capacity and expanded clinical care offerings.

"The growth of the pancreas care program means that we can offer comprehensive care and screening after acute pancreatitis episodes to identify important complications early," says Cheryl Gariepy, associate division chief of

# Total Pancreatectomy With Islet Autotransplantation: The Basics

1. The pancreas, spleen, gallbladder and majority of the duodenum are removed. The pancreas is delivered to the islet isolation team.

2. The islet isolation team injects an enzyme solution into the pancreas. The tissue and enzymes are placed in a Ricordi chamber where the islets are separated from the other cell types.

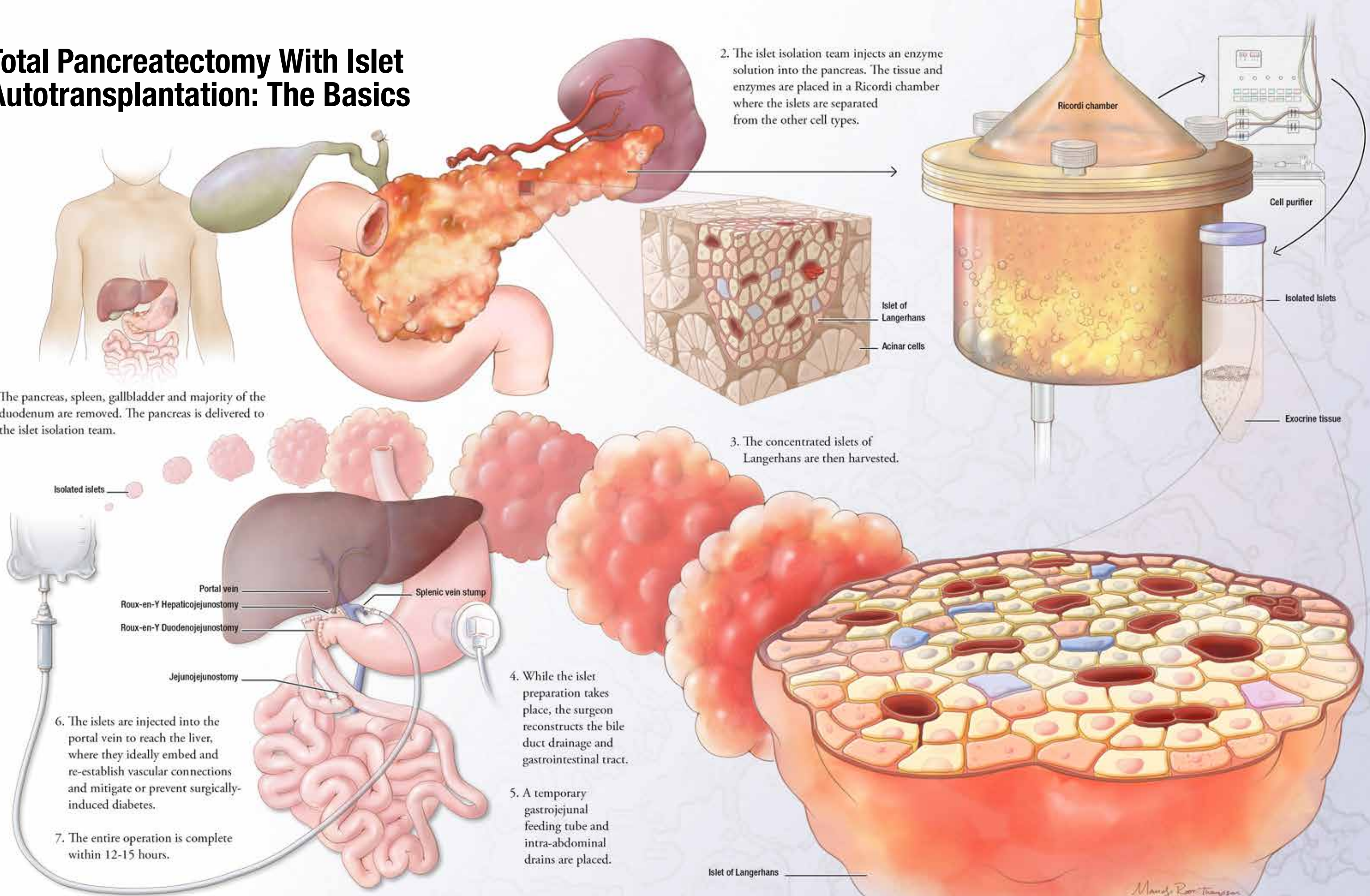
3. The concentrated islets of Langerhans are then harvested.

4. While the islet preparation takes place, the surgeon reconstructs the bile duct drainage and gastrointestinal tract.

5. A temporary gastrojejunal feeding tube and intra-abdominal drains are placed.

6. The islets are injected into the portal vein to reach the liver, where they ideally embed and re-establish vascular connections and mitigate or prevent surgically-induced diabetes.

7. The entire operation is complete within 12-15 hours.





The growth of the pancreas care program means that we can offer comprehensive care and screening after acute pancreatitis episodes to identify important complications early. It also means that a team of providers with internationally recognized expertise will be able to offer all of the most advanced services and procedures to children with pancreatic disease in one place.”

— Cheryl Garipey, associate division chief of Gastroenterology, Hepatology and Nutrition at Nationwide Children’s Hospital



Gastroenterology, Hepatology and Nutrition at Nationwide Children’s. She is a long-time principal investigator for INSPPIRE and a key member in helping Nationwide Children’s gain recognition as a National Pancreas Foundation Center of Excellence for both clinical care and academic research. “It also means that a team of providers with internationally recognized expertise will be able to offer all of the most advanced services and procedures to children with pancreatic disease in one place.”

The team’s surgeons and clinicians will also collaborate on all solid organ transplants, as well as clinical care and outcomes for children with other pancreatic, liver, biliary tract and gastrointestinal disorders. Dr. Khan is also busy expanding the interventional endoscopy component of the program with novel treatments for the entire gastroenterology department’s patient population, carried out in a custom-built interventional endoscopy suite.

“We have great support to build a leading global program with an interdisciplinary pancreatic pain clinic, state-of-the-art imaging, the nation’s most robust surgical offerings and a collaborative team of experts that can offer a truly holistic approach to pain management and pancreatic care,” says Dr. Freeman. “That makes a big difference in a patient’s experience when they seek out treatment for a rare and challenging disease, and I am excited to be part of this.”

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## HOW ONE FAMILY IN APPALACHIA CHANGED THE MEDICAL FIELD’S UNDERSTANDING OF PANCREATITIS

More than 30 years ago, a teenager from Kentucky named Kevin Slone had his first attack of acute pancreatitis. Doctors at the Cleveland Clinic urged his father, Bobby Slone, to try to document whether other people in the family had similar stomach problems.

Bobby Slone took the homework to heart, documenting incidences of similar symptoms across multiple generations of his family tree. The family’s health issues were so pervasive in their home region of Appalachia that it was already a well-known condition: “Slone’s Disease.”

When Kevin was again admitted for pancreatitis, this time to the University of Kentucky, a staff gastroenterologist who had long been laboring to uncover potential genetic causes for pancreatitis jumped at the opportunity to meet the Slones. Thanks to the family’s pre-documented medical history and willingness to coordinate a reunion for the collection of blood samples, the Midwest Multicenter Pancreatic Study Group identified the first genetic marker for hereditary pancreatitis, on chromosome 7q35.

Since their 1996 publication in *Gastroenterology*, findings on hereditary pancreatitis and genetic risk factors for pancreatic disease have been steadily growing. Now, clinicians and genetic counselors have a strong appreciation for hereditary causes, which are a much more common factor among children with pancreatitis than among adults.

In fact, the INSPPIRE cohort uncovered genetic mutations among nearly half (48%) of children with acute recurrent pancreatitis, and among nearly 3 in 4 (73%) of those with chronic pancreatitis.

“We have gotten to the point in advanced pancreatitis care that understanding whether there is a genetic component can meaningfully alter the care plan for patients,” says Dr. Freeman, who recommends obtaining a genetic screen for children after a second episode of acute pancreatitis, or whose first episode occurs prior to 6 years of age. “Children with a hereditary or genetic cause are predisposed to have recurrent pancreatitis episodes and potentially an increased inflammatory signal, which makes them more likely to develop chronic pain and sensitization.”

Primary care providers can typically order small (four-gene) panels, but specialized pancreas care centers often offer eight- or even 12-gene panels that will give a more comprehensive result regarding a hereditary component of disease. Known genetic mutations that carry increased risk of pancreatitis include variations in the PRSS1, CFTR, CTRC, SPINK1, CPA1, CEL, CEL-HYB and CLDN2 genes. The PRSS1, SPINK1, CTRC and CFTR mutations are particularly common in children with chronic pancreatitis.

“Having a genetic component to pancreatic disease makes it more likely that pain won’t be well managed by conventional operations,” says Dr. Nathan. “That knowledge is essential to making an informed decision about surgery and the overall care plan.”

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## American Academy of Pediatrics Updates Guidelines for the Management of Neonatal Hyperbilirubinemia

Nationwide Children’s physicians collaborate on updates to testing, treatment and follow-up recommendations for preventing hazardous hyperbilirubinemia and possible brain damage.

Written by Emily Siebenmorgen

The American Academy of Pediatrics’ (AAP) recommendations for managing hyperbilirubinemia in infants 35 gestational weeks and older are among its most accessed sets of clinical practice guidelines. A team led by Alex Kemper, MD, division chief of Primary Care Pediatrics at Nationwide Children’s Hospital, has updated the 2004 guidelines in response to research developments.

Although nearly all newborns will have some degree of jaundice, relying on appearance is an unreliable way to determine which newborns are at risk for developing high concentrations of bilirubin. If not treated, elevated bilirubin levels could lead to kernicterus, a type of permanent brain damage associated with significant movement disorder, hearing loss and other problems. Measuring the bilirubin concentration of all newborns before discharge to guide follow-up and treatment, when necessary, is central to preventing the high levels of bilirubin that can lead to kernicterus.

“Recommending that all newborns be tested with a device that measures bilirubin levels through the skin or by a blood test is a major update of the previous guidelines. Because kernicterus is so serious and so often preventable, we wanted to make sure that management was guided by a specific measure. This is an important advance in care,” Dr. Kemper explains.

The new guidelines are accompanied by a technical report, which was led by Jonathan Slaughter, MD, MPH, neonatologist and principal investigator at the Center for Perinatal Research in the Abigail Wexner Research Institute at Nationwide Children’s. The technical report explains the risk of adverse outcomes from phototherapy, one of the main ways to lower bilirubin concentrations, is extremely low. Since the 2004 guidelines, evidence regarding the risk of kernicterus has also emerged allowing the guidelines to slightly increase the thresholds for a patient’s bilirubin levels before recommending phototherapy treatment.

“

Recommending that all newborns be tested with a device that measures bilirubin levels through the skin or by a blood test is a major update of the previous guidelines. Because kernicterus is so serious and so often preventable, we wanted to make sure that management was guided by a specific measure. This is an important advance in care.”

– Alex Kemper, MD, MPH, MS, division chief of Primary Care Pediatrics at Nationwide Children’s Hospital



“Data from the last 10-plus years show phototherapy is safe and effective when needed and used appropriately,” Dr. Slaughter says. “But, we also know phototherapy can be hard on families and can sometimes interfere with breastfeeding. Even moving the phototherapy thresholds a little bit substantially changes the number of babies who need to remain in the hospital.”

In addition to tolerance for slightly higher bilirubin levels, the new treatment recommendations take additional consideration for a patient’s background before administering phototherapy or more aggressive care.

“The new guidelines better take into account factors like gestational age, risk of developing hyperbilirubinemia, and the risk of developing neurologic problems,” Dr. Slaughter adds.

This update also introduces the term “escalation of care,” formalizing procedures to lower a patient’s bilirubin levels once they reach 2 mg/dL below the threshold for an exchange transfusion, a risky treatment for rapidly lowering bilirubin concentrations by removing blood with elevated bilirubin and replacing it with fresh donor blood.

“Exchange transfusions are rare, and we want to prevent the need for such care when at all possible.

“

The new guidelines better take into account factors like gestational age, risk of developing hyperbilirubinemia, and the risk of developing neurologic problems.”

– Jonathan Slaughter, MD, MPH, neonatologist and principal investigator at the Center for Perinatal Research in the Abigail Wexner Research Institute at Nationwide Children’s Hospital



Escalation of care is a medical emergency that requires aggressive care to prevent the need for an exchange transfusion. This includes the need to be in a neonatal intensive care unit, intensive phototherapy, and IV hydration,” Dr. Kemper says. “With escalation of care, you want to do everything you can to avoid an exchange transfusion.”

The guidelines emphasize the importance of educating parents on jaundice, hyperbilirubinemia and kernicterus prevention.

“We want to empower families to understand what they can do to prevent hazardous levels of bilirubin. The new guideline emphasizes the importance of arranging follow-up care and making sure that parents understand these plans and what they should look for in the meantime,” Dr. Kemper says. “We are excited because the revised guideline helps pediatricians better target care based on risk and fully engages families in preventing a very serious health outcome.”

Kemper AR, Newman TB, Slaughter JL, Maisels MJ, Watchko JF, Downs AM, Grout RW, Bundy DG, Stark AR, Bogen DL, Holmes AV, Feldman-Winter LB, Bhutani VK, Brown SR, Panayotti GMM, Okechukwu K, Rappo PD, Russel TL. Clinical Practice Guideline Revision: Management of Hyperbilirubinemia in the Newborn Infant 35 or More Weeks of Gestation. *Pediatrics*. 2022 Aug 5; e2022058859.

Slaughter JL, Kemper AR, Newman TB. Technical Report: Diagnosis and Management of Hyperbilirubinemia in the Newborn Infant 35 or More Weeks of Gestation. *Pediatrics*. 2022 Aug 5; e2022058865.

# What's the Relevance of Emotional Intelligence in Medicine?

By Mike Patrick, MD, and Erica Banta, MBA, LDSS

The practice of clinical medicine requires an intelligent mindset. Strong cognitive intelligence (IQ) is required to develop and maintain a substantial knowledge base and to call upon the critical thinking skills needed to synthesize a hundred points of data into a meaningful clinical picture, correct diagnosis and appropriate management plan. But another type of intelligence is equally important: emotional intelligence (EQ). Emotional intelligence powers our feelings, responses and engagement with colleagues and patients. It is a stronger predictor of success than IQ and (unlike IQ) it can be developed over time.

Emotional intelligence is rooted in four quadrants: self-awareness, self-management, social awareness and relationship management.

## Personal Competence

The first two quadrants form the basis of one's personal competence. During the day, feelings — both positive and negative — come in and out of our consciousness. When we experience feelings that are perceived as negative, it is useful to reflect on their source.

Why are we having these feelings? The source may be readily apparent, or it may take some digging to understand their significance. Perhaps we are frustrated with the morning commute or disappointed that our schedule is too full... or too light. We might even be angry because a particular patient has failed to show up for an appointment again or because we have provided the same feedback to an employee over and over without resolution of a particular problem.

By identifying the source of our feelings, we can begin to process them in a healthy way. This, in turn, will boost our professionalism, our mood and the influence we have on those whose paths we cross in the course of our work.

Our feelings influence our behaviors. Upon entering the brain, sensory information passes through the

limbic system on its way to the frontal cortex. This pathway attaches emotions to the data. The frontal cortex then processes the sensory and emotional data and sends messages back to the body, which take the form of behavior. This behavior is manifest as spoken words and changes in our non-verbal body language such as posture, gestures, facial expressions and eye contact.

When emotions are left unchecked, the thinking part of the brain is likely to place critical importance on them. This may result in a sharp word or body language that is incongruent with professionalism in clinical and learning environments. This can decrease our effectiveness as we engage with others and negatively impact the morale of our team.

However, if we practice self-awareness and understand where our feelings come from and why we feel them, the frontal cortex can take this additional information into account and respond in a more effective and constructive way. Instead of a sharp word about the patient who chronically misses an appointment, we may come to understand their transportation challenges, which motivates us to connect the family to reliable transportation resources.

## Social Competence

The final two quadrants create one's social competence. Social awareness is the ability to understand the emotions, needs and concerns of other people, pick up on emotional cues, feel comfortable socially and recognize the power dynamics in a group or organization. Social awareness can also encapsulate the skill of treating people according to *their* emotional reactions, which can also be known as empathy.

Hearing what the other person is "really" saying is a key component of social awareness. When we are active listeners, we stop talking and pause the inner monologue in our own minds. Active listening can prevent a misdiagnosis and help to build relationships with patients, families and even colleagues.

## self-awareness

- knowledge of self
- accurate self-assessment
- self-confidence

## self-management

- emotional self-control
- integrity
- adaptability

## social awareness

- empathy
- service orientation
- organizational acumen

## relationship management

- building influence
- facilitating team performance
- managing conflict

Creating and maintaining good working relationships can heavily impact the patient experience and is rooted in social awareness. These relationships can be, and often are, mirrored by students in a learning environment. Clinicians who are also teachers have a responsibility to demonstrate positive relationships with other doctors, nurses, support staff and others.

Relationship management is the ability to develop and maintain good relationships, communicate clearly, inspire and influence others, work well in a team and manage conflict. It is the culmination of the previous three quadrants in that it takes into consideration awareness of one's own self and emotions and combines the skill of empathy and listening to manage interactions.

Leadership and influence can be direct effects of positive relationship management. Cooperation, collaboration and better decision-making are unequivocal results of the influence that stems from intentionally practicing relationship management. When teams are operating at their best, with trust and solid relationships at the foundation, those who lead and teach can quickly assess the strengths and opportunities of those around them, and the barriers of finding expedited solutions begin to break down.

In all relationships (personal and professional) conflict and disagreements are inevitable. Two people cannot possibly have the same needs, opinions and expectations at all times. However, resolving conflict in healthy constructive ways can strengthen trust between people. When conflict isn't perceived as threatening or punishing, it fosters freedom, creativity and safety in relationships.

Once we know how to manage stress, stay emotionally present and aware, communicate nonverbally and actively listen, we will be better equipped to handle emotionally charged situations and conflicts, enabling us to catch and defuse many issues before they escalate.

Emotional Intelligence has been an important topic in the business and organizational leadership spaces for decades. The propensity to actively use the skills of EQ can be a great predictor of organizational success. It is equally important in health care. Administrators, clinicians, professors and other medical professionals can leverage the tenants of EQ to understand and manage their own stress and emotions, build better relationships, foster higher-performing teams and reinforce positive patient outcomes.

The need for EQ is higher today than ever. Self-awareness and relationship building are now the currency of a health care economy that has the human at the center.



Mike Patrick, MD, emergency medicine physician and medical director of Digital Health at Nationwide Children's Hospital (left)

Erica Banta, MBA, LDSS, director of Talent Management at The Ohio State University (right)

## Connections

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A growing body of evidence supports telebehavioral health delivery for children, adolescents and their families, as outcomes are comparable to in-person treatment delivery. Despite evidence of efficacy, regulatory and financial concerns and technology barriers continue to impede widespread uptake of telebehavioral health.

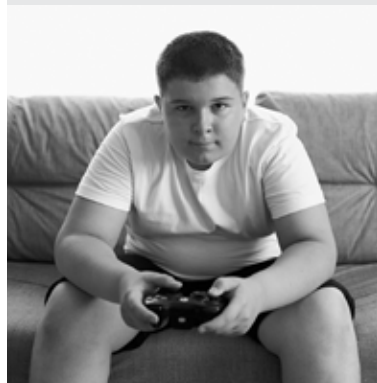
[PediatricsNationwide.org/telebehavioral-health](https://www.PediatricsNationwide.org/telebehavioral-health)



#### Do Symptom Scores and pH Impedance Correlate in Infants Treated for Gastroesophageal Reflux?

Current diagnostic criteria for gastroesophageal reflux disease are based on symptoms, leading to subjective and provider-dependent diagnoses. In his recent publication, Sudarshan Jadcherla, MD, and his team evaluate symptom and pH-impedance metrics, finding weak to non-existent correlations between the two. These findings support the call for establishing objective criteria for diagnosis and treatment of GERD in infants.

[PediatricsNationwide.org/symptoms-pH-impedance-correlation](https://www.PediatricsNationwide.org/symptoms-pH-impedance-correlation)



#### Weight Changes Among Youth in Early COVID-19 Pandemic

Changes in schedules, food choices and increases in screen time were a major part of life for children during the early months of the COVID-19 pandemic. Ihuoma Eneli, MD, and her team recently published the change in weight category for >4,500 low-income youth during the first 3 to 6 months of the pandemic. Significant weight gain was observed among the cohort.

[PediatricsNationwide.org/COVID-19-weight-changes](https://www.PediatricsNationwide.org/COVID-19-weight-changes)

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## The Collaboratory for Kids and Community Health: A hub for innovative ideas to improve the health of children and their neighborhoods

Building on its work developing models that focus on the “whole child” and population-level wellbeing for all children, Nationwide Children's Hospital has launched The Collaboratory for Kids and Community Health. It gives providers, researchers, policy makers, health care systems and community partners a resource for sharing best practices in this area.

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