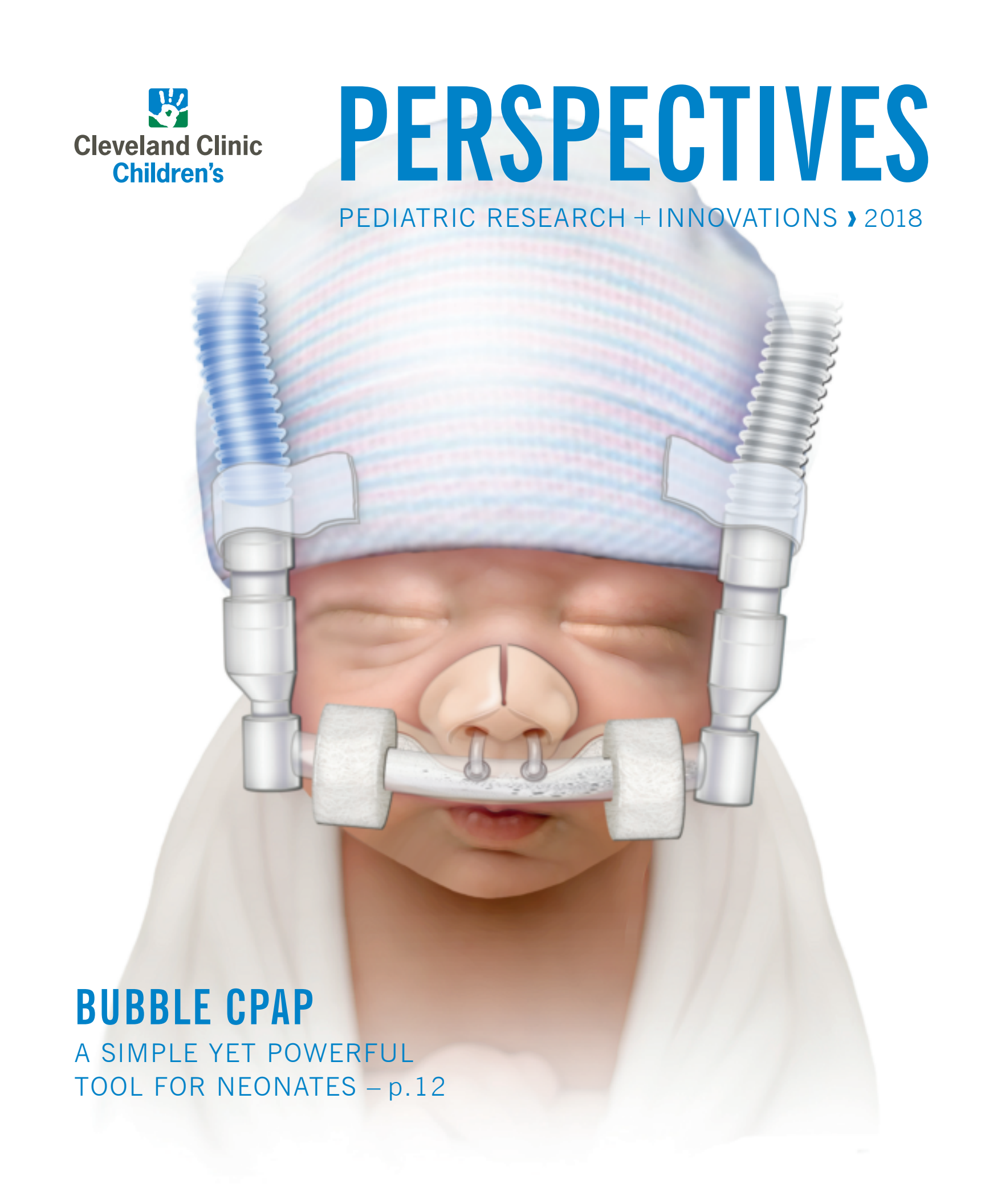
Cleveland Clinic Children's

PERSPECTIVES

PEDIATRIC RESEARCH + INNOVATIONS › 2018



BUBBLE CPAP

A SIMPLE YET POWERFUL TOOL FOR NEONATES – p.12

Cleveland Clinic Children's provides comprehensive medical, surgical and rehabilitative care for infants, children and adolescents. Our more than 300 pediatric physicians accommodate more than 692,000 outpatient visits and 13,490 inpatient admissions per year at Cleveland Clinic Children's hospital and outpatient facilities on our main campus, at the Cleveland Clinic Children's Hospital for Rehabilitation campus, and at regional hospitals, family health centers and other locations throughout Ohio. Cleveland Clinic Children's & Pediatric Institute offers integrated care and access to cutting-edge research across a variety of pediatric medical and surgical specialties. It is backed by the full resources of Cleveland Clinic, a nonprofit academic medical center ranked the No. 2 hospital in the country by *U.S. News & World Report*.

INSIDE

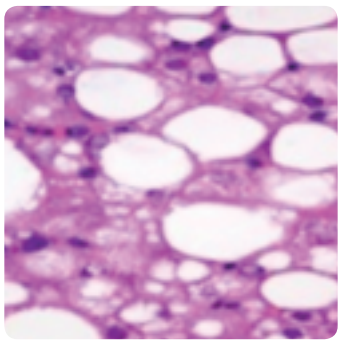
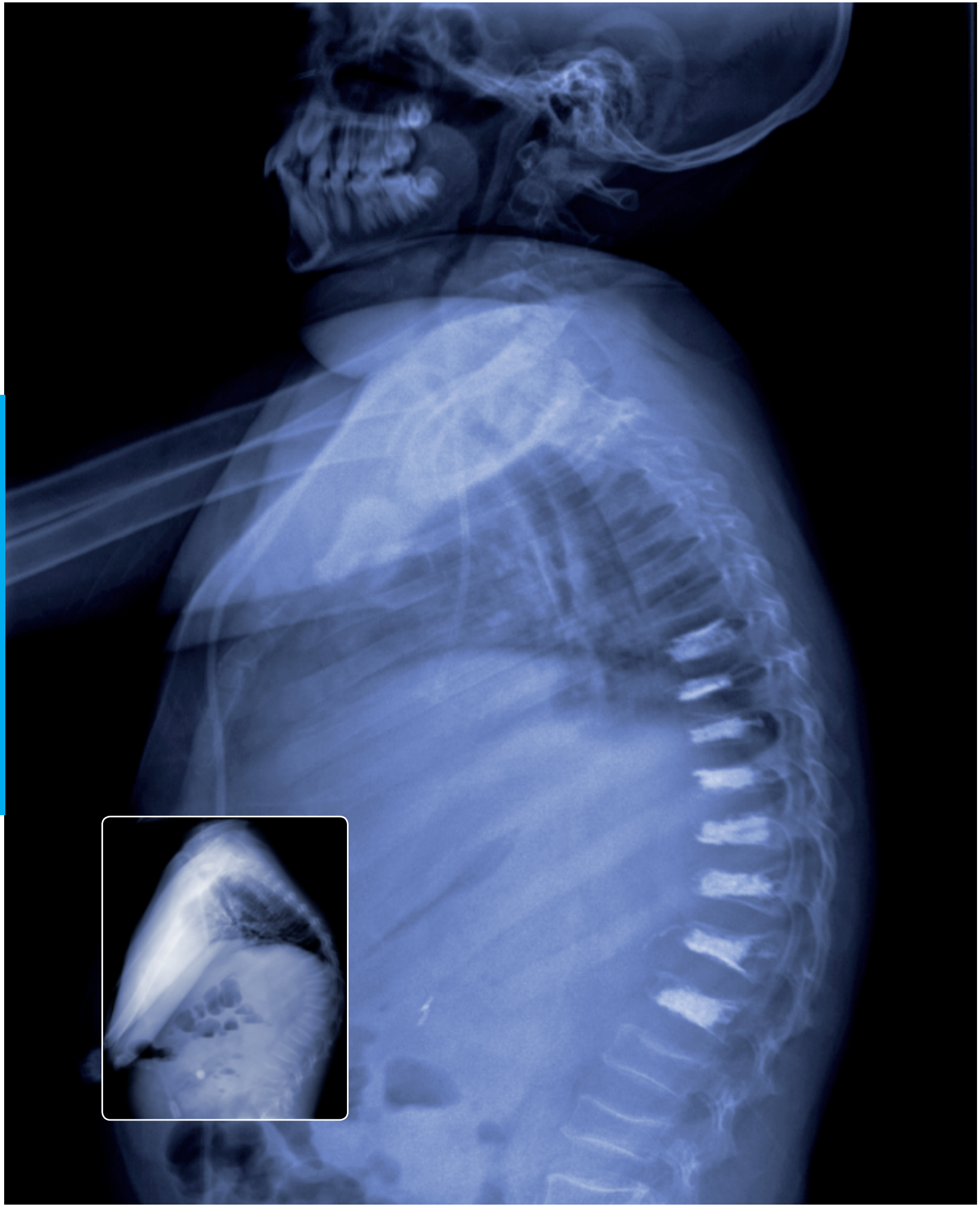


IMAGE OF THE ISSUE ❯

A 13-year-old male presented with severe thoracic and lumbar back pain and respiratory distress following prolonged high-dose steroid use. The patient underwent four-level balloon kyphoplasty in two stages, separated by one week. His kyphotic deformity and pain improved dramatically postoperatively, allowing him to sit without pain within one month and walk independently within two months. Inset image: Prior to procedure, there were numerous vertebral compression fractures in the lower thoracic and upper lumbar regions.



BY THE NUMBERS

2017 YEAR IN REVIEW Cleveland Clinic Children's & Pediatric Institute is one of 27 clinical and special expertise institutes at Cleveland Clinic designed to offer highly integrated care and conduct innovative research across multiple settings. Our patients come to us from around the country and around the world, and we are proud to develop innovative care plans and provide the very best care possible. The depth and breadth of our care and expertise can be seen in our annual numbers.

692,000+
Outpatient visits

Inpatient admissions
13,400+

Emergency department visits
85,000+

40+
Community locations

Surgeries
10,700+

389
Total beds

DEAR COLLEAGUES

RITA PAPPAS, MD

Here at Cleveland Clinic Children's, we have been busy reimagining things with the opening of our new 120,000-square-foot outpatient center, unifying outpatient pediatric services on our main campus and offering the very latest in technological advances and collaborative pediatric care in one location. Our September opening was exciting.

We are also excited to bring you this annual publication, which has been reimagined once again this year. In this beautiful piece, our team came together to share some of our most newsworthy stories, innovations and research of the past year.

Cleveland Clinic Children's physicians treat many of the most complex medical cases in the U.S. and around the world, with patients traveling to us for access to multiple specialists. Annually, our staff of more than 300 full-time pediatricians and pediatric specialists manage over 692,000 pediatric visits to our hospitals, family health centers and other locations across Northeast Ohio.

We are dedicated to medical, surgical and rehabilitative care of infants, children and adolescents, and we work to excel at providing specialized care supported by comprehensive research. This year's publication highlights some of our most timely and relevant activities in pediatric care today, with the following features …

- Chair of Pediatric Cardiology Elizabeth Saarel, MD, discusses the safety of sports for athletes with implantable cardioverter defibrillators based on long-term results of a prospective multinational registry.
- Neonatology Chairman Hany Aly, MD, details the efficacy of the bubble CPAP for our neonatal patients.
- Praveen Selvakumar, MD, pediatric gastroenterologist, covers the prevalence and seriousness of a newly suspected disease for young people in the U.S. — nonalcoholic fatty liver disease (NAFLD) in lean adolescents.
- In the Center for Pediatric Neurosciences, Manikum Moodley, MD, joined Mary Rensel, MD, of adult Neurology, to highlight the testing that resulted in the first-ever FDA-approved drug to treat pediatric-onset multiple sclerosis.
- Ethan Benore, PhD, Head of the Center for Pediatric Behavioral Health, highlights physical and occupational therapy outcomes and changes in the functional abilities of adolescents.

This book includes these features and more. Thank you for your interest in our work and for your support. I hope you find these articles insightful and inspirational, and I invite you to provide your feedback and share your insights — because we must continue to reimagine healthcare every day if we want all our young patients to have the very best chance for a healthy life.

Best Regards,

Rita M Pappas

Rita Pappas, MD | Cleveland Clinic Children's Interim Chair | pappasr@ccf.org

A NEW HOME FOR CHILDREN'S

On Sept. 24, Cleveland Clinic Children's fulfilled a decades-long dream of moving pediatric ambulatory services to a new facility on its main campus in downtown Cleveland. This expansion unites primary and specialty outpatient care in one convenient, coordinated environment that is better equipped to manage Cleveland Clinic Children's 692,000+ annual patient visits. The 120,000-square-foot state-of-the-art structure is outfitted with the latest technology and designed to provide the best possible outcomes in terms of safety, quality, patient satisfaction and value. It features 50 exam rooms, 20 private infusion rooms, four procedure rooms, and hundreds of physicians, nurses, therapists and administrative staff working side by side to provide the most comprehensive and integrated medical, surgical, developmental and behavioral care for pediatric patients.

"This is an exciting new chapter in the history of Cleveland Clinic Children's," says Rita Pappas, MD, Interim Chair of Cleveland Clinic Children's.

Read more:
clevelandclinicchildrens.org/newhome

FOCUSING ON FUNCTIONAL IMPROVEMENT FOR CHRONIC PAIN

BY ETHAN BENORE, PHD, AND HEIDI KEMPERT, PTA

Featuring weights and elastic cords, the spider cage (also known as the universal exercise unit) is used to treat children with a variety of conditions, including cerebral palsy, hemiplegia, brachial plexus injury, post-brain injury or surgery. The apparatus helps children improve strength and balance.

FOCUSING ON FUNCTIONAL IMPROVEMENT FOR CHRONIC PAIN

BY ETHAN BENORE, PHD, AND HEIDI KEMPERT, PTA

TAKEAWAYS

The primary focus in pain rehabilitation should be on functionality.

Self-report measures are as important as objective measures in understanding the success of a pain rehab program.

While objective measures target physical gains, subjective measures allow for assessment of psychological constructs important to rehabilitation.

Children with chronic pain often face severe impairment in physical functioning as they withdraw from typical life activities, becoming deconditioned and fearful of more pain. This study demonstrates the utility of both subjective and objective measures in identifying changes in physical functioning during an intensive pediatric chronic pain rehabilitation program.

In chronic pain rehabilitation, it is important to have a primary focus on functional improvement as the leading outcome — not pain reduction. While past studies have demonstrated the importance of measuring adolescents' self-perception of their abilities within physical and occupational therapy, these tools often are not easily utilized or have not been examined in a pediatric chronic pain population. In this study it was hypothesized that adolescents completing an intensive interdisciplinary pain rehabilitation program would report functional gains from admission to discharge, and that perceived gains in physical ability would be associated with objective physical activities. Further, it was hypothesized that gains in functioning would be associated with pain reduction.

Seventy-eight children and adolescents with chronic pain who participated in the three-week intensive interdisciplinary pain rehabilitation program completed self-report measures. These included the Lower Extremity Functional Scale (LEFS) and the Upper Extremity Functional Index (UEFI). In addition, adolescents were objectively monitored for repetitions of selected physical activities for one-minute intervals. Assessments were taken at admission and discharge.

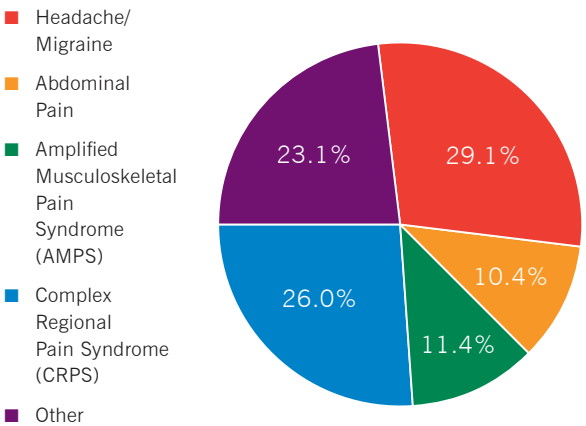
Results indicate significant gains in all measures of functioning during the program (all participants < 0.01). Over half the children also reported clinical gains (> 9 points) on the LEFS and UEFI. Small but significant correlations between self-report and objective outcomes suggest they are measuring similar yet distinct factors. Further, while children reported a mild reduction in pain over the three weeks, regression statistics do not support that pain reduction was directly related to changes in physical functioning alone. It is likely that cognitive or environmental response to rehabilitation is involved.

Using subjective and objective measures provides a feasible and meaningful way to track progress in chronic pain rehabilitation. While objective measures target purely physical gains, subjective measures allow for assessment of psychological constructs important to rehabilitation, such as self-efficacy. These functional improvements appear independent of pain ratings and should be valued as a separate outcome in pain rehabilitation.

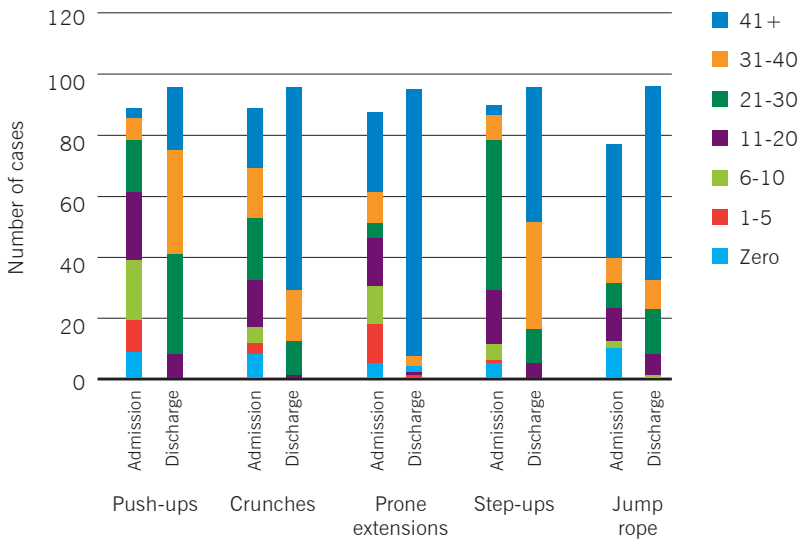
These findings increase our understanding of rehabilitation practices and provide opportunities to promote clinical improvement in pediatric pain. The use of self-reported measures along with objective measures can help therapists better understand a patient's level of impairment

GROUP DIFFERENCES AT BASELINE AND DISCHARGE					
	Admission Mean (SD)	Discharge Mean (SD)	% Clinical change	Change statistic	*P* Value
Lower Extremity Functional Scale (LEFS)	43.1	39.2	70.5%	– 9.08 [a]	< 0.001
	(15.46)	(14.41)			
Upper Extremity Functional Index (UEFI)	56.2	68.1	55.1%	– 8.439 [a]	< 0.001
	(14.57)	(10.73)			
Push-ups [b]				– 6.576 [b]	
Crunches [b]				– 5.842 [b]	
Prone extensions [b]				– 5.622 [b]	
Step-ups [b]				– 6.786 [b]	
Jump rope [b]				– 2.640 [b]	
Pain	6.7 (2.09)	5.5 (3.41)		2.879 [a]	0.006
a Paired *t*-test.					
b Wilcoxon signed ranks test; see figure below at right for data distribution.					

PERCENTAGE OF CASES BY DIAGNOSIS



PERFORMANCE ON OBJECTIVE MEASURES OF PHYSICAL FUNCTIONING FOR PARTICIPANTS IN PEDIATRIC CHRONIC PAIN REHABILITATION, AT ADMISSION AND DISCHARGE



from chronic pain — and track their improvement over time. In addition, these measures may be used clinically to facilitate patient education and improve patient insight into aspects of rehabilitation therapy. Further research should include evaluation of follow-up data to assess maintenance of functional gains to further inform and improve pain rehabilitation programs.

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Ms. Kempert (kemperh@ccf.org; 216.448.6253) is a physical therapy assistant in the Pediatric Pain Rehabilitation Program.

BUBBLE CPAP FOR PREVENTION OF CHRONIC LUNG DISEASE IN PREMATURE INFANTS

BY HANY ALY, MD, FAAP, MSHS

TAKEAWAYS

The incidence of chronic lung disease in babies differs significantly among institutions.

CPAP has been found to have multiple physiologic advantages.

A recent meta-analysis shows early use of CPAP had a marginal benefit for the composite outcome of survival without chronic lung disease when compared to prophylactic surfactant with intubation.

The AAP Committee on Fetus and Newborn recently acknowledged the deficiency of data on efficacy of ventilation systems.

The discovery of surfactant was one of the most significant events in the history of neonatology. Certainly, surfactant saved the lives of premature infants who were otherwise considered nonviable. However, the prevention of chronic lung disease (CLD) did not progress, and it became clear that a significant portion of the help surfactant provides to the premature lung is counteracted by mechanical ventilation.[1]

The incidence of CLD differs significantly among institutions even after adjusting for centers' distributions of birth weight, race and sex. This wide variability could not be explained by biological factors, and therefore, respiratory management was considered key to creating or preventing CLD. The lowest incidence of CLD in literature has been reported from centers that use bubble CPAP (b-CPAP) as early as possible, preferentially in the delivery room and as the primary mode for respiratory support of all premature infants in respiratory distress.[2]

We have previously demonstrated the reproducibility of b-CPAP use. In a center that had 33 percent of its very low birth weight (VLBW) infants develop CLD, the implementation of a b-CPAP program was associated with a reduction of CLD to 6 percent.[3] However, the reduction of CLD rates did not occur immediately — it required significant time to develop staff experience and to achieve the full effect of b-CPAP. In a follow-up study, we demonstrated the consistency of outcomes over 12 years with a CLD rate of 5 percent.[4]

How the apparatus works

The bubble CPAP apparatus is simple; it is composed of a breathing circuit with an inspiratory limb delivering a heated, humidified gas mixture to the infant and an expiratory limb immersed underwater in a container to create the desired pressure (see Figure). Gas flow generates bubbles under the water that cause oscillations of the water level and subsequently of the pressure delivered to the patient. Therefore, the patient on b-CPAP receives an oscillating rather than a constant pressure. This oscillation effect may add to the efficacy of b-CPAP in volume recruitment.

CPAP has multiple physiologic advantages. In spontaneously breathing premature infants, it eases respiratory efforts by stenting the airway and the diaphragm. It maintains alveoli inflation, increases the functional residual capacity of the lung, and optimally matches ventilation with perfusion. Compared with mechanical ventilation and tracheal intubation, CPAP minimizes volutrauma and subsequent biotrauma. CPAP induces a favorable strain that stimulates lung growth when administered to animals over a prolonged time.[5]

Multiple randomized controlled trials were launched to compare the efficacy of early nasal CPAP to mechanical ventilation. These trials did not specify b-CPAP, but rather used any type of CPAP and did not offer details of competency-based training to ensure its efficacious use. Despite these reservations, trials confirmed the feasibility of applying CPAP early in life to

LEFT: The bubble CPAP apparatus provides continuous positive airway pressure via a humidified gas source that connects to the infant's airway through nasal prongs. As gas exits the tubing submerged in a bottle of water, bubbles are created that produce small airway pressure oscillations.

premature infants, including those at the extreme premature age of 24-25 weeks, without change in mortality and CLD.

When these trials were considered collectively in a recent meta-analysis, early use of CPAP had a marginal benefit for the composite outcome of survival without CLD when compared to prophylactic surfactant with intubation. These findings do not reconcile with recurring reports on substantial reduction of CLD in neonatal units that used b-CPAP.

Two factors could explain the reduced CLD in b-CPAP units. The first is the type of CPAP and the type of nasal prongs. The second is the competency of the caregiver using b-CPAP at the bedside. Therefore, b-CPAP strategy is a complete bundle of care that requires clear practice guidelines and a training process. In an effort to help neonatal units reproduce b-CPAP success, we offer a hands-on training program that familiarizes staff with b-CPAP components, indications for use, method of application, checkpoints for maintenance, troubleshooting of problems, weaning methods and criteria for b-CPAP failure.[2]

No studies have compared CLD in infants supported with b-CPAP versus infants supported with other CPAP devices. Data are scarce on short-term endpoints, including work of breathing and oxygenation that favored b-CPAP. Nonetheless, numerous studies have compared the short-term outcomes of using CPAP, biphasic nasal CPAP, nasal intermittent positive pressure ventilation, and high-flow nasal cannula while using various types of facial and nasal interfaces.

The American Academy of Pediatrics Committee on Fetus and Newborn recently acknowledged the deficiency of data on the efficacy and safety of these modalities. Of note, none of these noninvasive modalities could mimic the success of b-CPAP in reducing CLD. In the absence of data on CLD reduction, the extrapolation that all CPAP and noninvasive techniques is as efficacious as b-CPAP are realistically unfounded.[1]

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NONALCOHOLIC FATTY LIVER DISEASE IN LEAN ADOLESCENTS: A NEW DISEASE TO WORRY ABOUT?

BY PRAVEEN SELVAKUMAR, MD

TAKEAWAYS

Lean NAFLD, or nonfatty liver disease, is the term for the disease in people with no significant obesity.

Because there is no evidence of this in the pediatric population, Cleveland Clinic Children's set out to study NAFLD in adolescents aged 12-18 years.

Metabolic syndrome components such as low HDL-C, hypertriglyceridemia and insulin resistance are more frequent among lean adolescents with suspected NAFLD compared with lean healthy adolescents.

With the rising epidemic of obesity, nonalcoholic fatty liver disease (NAFLD) has become the most common cause of chronic liver disease in children and adolescents in the United States.

NAFLD is defined as hepatic steatosis in the absence of alternative causes such as significant alcohol intake, viral hepatitis or medications. Contrary to the belief that NAFLD is almost always associated with obesity, it has been recently recognized that fatty liver disease can occur in people with no significant obesity, termed "lean NAFLD" or "nonobese NAFLD."

The prevalence of lean NAFLD in adults varies widely, ranging from 3 to 30 percent depending on the study population, diagnostic modality and body mass index (BMI) cutoffs used to define lean subjects.[1] Most of the evidence on lean NAFLD is based on Asian population or community-based adult studies. Evidence is lacking on lean NAFLD in the pediatric population. Therefore, we aimed to estimate the population-based prevalence of NAFLD among lean U.S. adolescents (12-18 years) and to assess the characteristics and risk factors of NAFLD in this unique population.[2]

Study design

Our team performed a retrospective data analysis of adolescents aged 12-18 years with BMI < 85th percentile who were enrolled in the National Health and Nutrition Examination Survey (NHANES) database during the 2005-2014 cycles. NHANES is a cross-sectional survey of the U.S. civilian, noninstitutionalized population conducted by the National Center for Health Statistics (NCHS) to assess the health and nutrition status of adults and children.

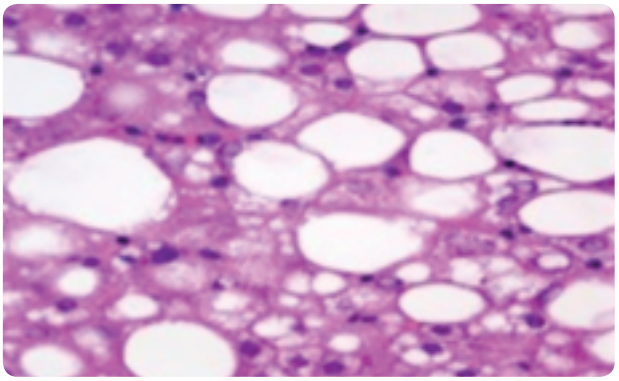
This program conducts an annual survey of a nationally representative sample of about 5,000 persons from different counties in the U.S.

A BMI cutoff of less than the 85th percentile for specific age and gender was used to define lean adolescents. Suspected NAFLD was defined as alanine aminotransferase (ALT) > 25.8 U/L for boys and > 22.1 U/L for girls, as proposed by the SAFETY study.[3] Components of metabolic syndrome such as hypertriglyceridemia, low high-density lipoprotein cholesterol (HDL-C), hypertension, prediabetes/diabetes and insulin resistance were also assessed. We excluded subjects with viral hepatitis (B or C), those using hepatotoxic medications and those missing ALT to define NAFLD.

Lean NAFLD does exist in American adolescents

The study analyzed 1,482 lean adolescents, corresponding to the weighted U.S. population of over 18 million. The estimated prevalence of suspected NAFLD in lean adolescents for each of five cycles during 2005-2014 was 6.9 percent, 8.8 percent, 8.1 percent, 5 percent and 11.5 percent, respectively. Therefore, the mean estimated prevalence of suspected NAFLD among lean U.S. adolescents during 2005-2014 was 8 percent. Fortunately, we didn't find any trend in lean NAFLD in contrast to NAFLD in obese patients, which studies have shown has increased significantly in the past two decades.

PREVALENCE OF SUSPECTED NAFLD AMONG LEAN AMERICAN ADOLESCENTS WAS 8%			
Factors	Healthy lean adolescents (%)	Adolescents with lean NAFLD (%)	*P* value
Hyper-triglyceridemia	3.9	10	0.028
Low HDL-C	6.8	15.5	0.016
Insulin resistance	20.4	29.9	0.053
Insulin resistance increased the risk of having suspected NAFLD fourfold			



ABOVE: Simple steatosis under the microscope. NAFLD comprises a disease spectrum that ranges from simple steatosis to nonalcoholic steatohepatitis (NASH), which can progress to liver fibrosis and eventually end-stage cirrhosis.

Characteristics of lean NAFLD in American adolescents

For a better understanding, we compared the lean American adolescents with and without NAFLD. Interestingly, metabolic syndrome components such as low HDL-C (15.5 percent vs. 6.8 percent; *P* value 0.016), hypertriglyceridemia (10 percent vs. 3.9 percent; *P* value 0.028) and insulin resistance (29.9 percent vs. 20.4 percent; *P* value 0.053) are more frequent among lean adolescents with suspected NAFLD compared with lean healthy adolescents. In addition, non-Hispanic black lean adolescents had lower rates of suspected NAFLD than did their Caucasian counterparts. More important, lean adolescents with suspected NAFLD had approximately four times higher odds of having insulin resistance compared with lean healthy controls.

Importance of recognizing lean NAFLD in adolescents

Lean NAFLD is an evolving concept with much of the information yet to be understood, such as clinical and prognostic implications, especially in children. Regardless, lean NAFLD most likely represents a distinctive phenotypic spectrum of NAFLD. The complex interplay of visceral instead of general obesity, high fructose or cholesterol consumption, gut microbiota, and genetic predisposition might play a role in the development of NAFLD in lean subjects, but the contribution of each factor might be different from that of obese NAFLD.

In the absence of traditional obesity, hepatic steatosis in these lean subjects could be under-recognized. Hence, it is important to be aware of this unique phenotype of NAFLD and to identify lean patients at risk for NAFLD, as they might have the same or even worse outcomes compared with obese patients with NAFLD.

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SPORTS FOR YOUNG PATIENTS WITH IMPLANTABLE CARDIOVERTER DEFIBRILLATORS: REFINING THE RISK

BY ELIZABETH SAAREL, MD

Mya Beattie, age 14, has long QT syndrome. In September 2016, following syncope, she had a single chamber implantable cardioverter defibrillator implanted. Today she continues to play volleyball.

SPORTS FOR YOUNG PATIENTS WITH IMPLANTABLE CARDIOVERTER DEFIBRILLATORS: REFINING THE RISK

BY ELIZABETH SAAREL, MD

TAKEAWAYS

In 2006, an international investigation was done on patients who received ICDs for prevention of sudden cardiac death.

Final long-term results published in 2017 confirm the safety of participation in sports for even the youngest patients with ICDs.

The potential benefits of sports participation for young patients with ICDs were found to outweigh the risks in most cases.

Despite a dearth of research, published guidelines in the United States and Europe (based on expert opinion) have recommended against competitive sports participation in activities more strenuous than bowling or golf (Class IA) for patients with pacemakers or implantable cardioverter defibrillators (ICDs).[1,2]

For the benefit of our young patients, we were recently able to change opinions and the U.S. guidelines about sports participation for children and young adults with ICDs.[3] This change was based on research done at Cleveland Clinic and Cleveland Clinic Children's along with other international centers.[4,5]

In 2006, a prospective multicenter registry was launched to study the safety of sports participation for patients with ICDs. This international investigation included patients from ages 10 to 60 years who received ICDs for primary or secondary prevention of sudden cardiac death. Investigators from Cleveland Clinic pushed to include young patients in this groundbreaking study.

Diagnoses include inherited arrhythmia syndromes, inherited or acquired cardiomyopathies, congenital heart disease and valvular heart disease. The first published results from this registry indicated that athletes with ICDs can engage in vigorous and competitive sports without physical injury or failure to terminate the arrhythmia despite the occurrence of both inappropriate and appropriate shocks,[4] and the final long-term results published in 2017 confirmed the safety of participation for even the youngest patients with ICDs.[5] Patients' choice of athletics included running, alpine hiking, swimming, skiing, snowboarding, rock climbing, basketball, football, baseball, gymnastics and other sports, both at the college (Division I, II and III) and high school varsity and junior varsity levels.

Previous research supporting safety

In previously published work, we included 21 pediatric and adult congenital heart patients with ICDs who regularly participated in competitive or vigorous sports. These data also indicated no mortality and no increase in morbidity after four years.[6] Patients' choice of athletics included all of the above-listed sports.

Similar to patients in the Multinational Sports Registry, 20 of these patients did not have an increased incidence of ICD therapies during athletics, either inappropriate or appropriate, and there was no increased rate of damage to the ICD system during organized sports. Of note, most of the patients with ICDs were on beta blocker therapy to prevent inappropriate ICD shocks due to sinus or supraventricular tachycardias, and most underwent formal exercise testing to screen for arrhythmia prior to sports participation. One teen with congenital heart disease did experience two appropriate ICD shocks for treatment of ventricular tachyarrhythmias during basketball and did decide to withdraw from competitive athletics.

When questions arise about sports participation, it is our practice to counsel patients and families about the risks, including the potential for increased rate of ventricular tachyarrhythmias and damage to the pacemaker or ICD system. Counseling is patient-specific, with the underlying cardiac disease, type of device, indication for implant, position of leads and pulse generators, underlying heart rhythm, patient age, and type of athletic activity considered when estimating risk.

Weighing the benefits

The potential benefits of sports participation for young patients include decreased risk for obesity, metabolic syndrome, coronary and peripheral artery disease, stroke and diabetes.[7] There are additional benefits of exercise, including a positive effect on general mental health, decreased risk for depression and overall improvement in well-being, all of which affect quality of life.[8] Ultimately, the importance of sports participation to each patient's quality of life must be estimated by the individual and his or her family.

In summary, the risk of sports participation for our patients with implanted cardiac devices may include an increased tachyarrhythmia burden, injury after loss of consciousness from cardiac device function or malfunction, and permanent damage to the implanted device system during sports. Sports that evoke a high potential for serious injury to self or others if a patient were to experience syncope, including those involving motor vehicles, should be discouraged. In the future, our estimates of risk should be guided by research rather than opinion. The risks of sports participation must be weighed against the benefits, including potential for improved quality of life, for all young patients with implanted cardiac devices.

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Cleveland Clinic
Children's

ENHANCING CARE FOR PEDIATRIC MS: CHILDREN'S HOSPITAL WORKS WITH ADULT MS CENTER

BY MANIKUM MOODLEY, MD, FCP, FRCP, AND MARY RENSEL, MD, FAAN

TAKEAWAYS

Working with adult care physicians sheds light on care for pediatric-onset multiple sclerosis (POMS).

Cleveland Clinic study supports associations between MS and environmental triggers, including vitamin D deficiency and obesity.

For the first time there is an FDA-approved treatment for children with multiple sclerosis.

Pediatric-onset MS is now being diagnosed in increasing numbers of children, yet its pathogenesis and optimal management regimens remain elusive.

To contribute greater insight into these questions, we undertook a study to describe the pediatric-onset multiple sclerosis population seen at Cleveland Clinic over a recent 13-year period in terms of clinical characteristics and outcomes of treatment as patients progressed into adulthood.

With its protean clinical manifestations and lack of biological markers, pediatric-onset MS (POMS) is easy to misdiagnose. In children, correct diagnosis is an even greater challenge because MS is uncommon, and various genetic and neurometabolic disorders also produce active neurological impairment and white matter changes on a brain MRI.

Disorders that may be mistaken for MS in children include:

- Acute disseminated encephalomyelitis (ADEM)
- Neuromyelitis optica (NMO)
- Leukodystrophies
- Mitochondrial defects
- Metabolic disorders (organic and aminoacidemias)
- Obscure vasculopathies, collagen vascular diseases

Diagnostic implications in children

Correct diagnosis of metabolic and genetic diseases is critical in children because of the many implications not only for their immediate care but also for determining long-term prognosis and the need to identify at-risk family members.

In addition, early diagnosis and prompt treatment may prevent or delay the development of disability. The potential to treat MS with disease-modifying agents has also changed the prognosis for MS significantly.

In this Cleveland Clinic study, we retrospectively identified all patients who presented to Cleveland Clinic and received a diagnosis of MS between 2002 and 2015, and had their first attack before age 18. Of the 64 patients who met the initial inclusion criteria, four were excluded because of ongoing uncertainty of the MS diagnosis. For the 60 remaining patients, epidemiological, clinical, neuroimaging, laboratory and outcome data were collected and analyzed, as was detailed information on therapeutic management.

Mean age at presentation was 15.7 years, ranging from 2.5 years to 19 years. The two-and-a-half-year-old patient is one of the youngest POMS patients ever reported.

Consistencies with the existing literature

Many findings from this patient sample were consistent with prior reports of POMS, including general findings in terms of presenting symptoms, MRI findings and laboratory test results. Notable specific findings that confirmed previous literature reports of POMS included:

- A 2-to-1 female predominance within the cohort, particularly among patients over age 12.

LEFT: Dr. Rensel and Dr. Moodley in collaboration on a case.

Approximately 30 percent of patients with POMS will have disease breakthrough on first-line therapies, hence the need for second-line agents.

- A high rate of vitamin D deficiency (63 percent).
- A high rate of overweight/obesity (49 percent), with a higher mean annualized relapse rate among overweight or obese patients.

These data lend support to proposed associations between MS and environmental triggers such as vitamin D deficiency and obesity.

Divergence from the existing literature

A number of additional findings from this cohort differed from prior reports in notable ways:

- A higher proportion of patients had a family history of MS (32 percent) compared with previously reported POMS cohorts (6 to 21 percent).
- The most common type of clinical finding on examination was oculomotor findings (in 50 percent of patients), in contrast to the dominance of motor dysfunction in prior reports.
- One particular oculomotor finding — abnormal saccadic eye movements — was highly prominent, observed in 35 percent of patients, despite being relatively rare in the prior POMS literature.
- The average duration between first and second attacks was 14.9 months, which is longer than the norm in previous POMS reports.
- A significant number of patients with relapsing disease were switched from first- to second-line disease-modifying therapies (DMTs), and this practice increased over the 13-year study period.

As anticipated, our study identified beta interferon as the most frequent choice of first-line DMT, followed by glatiramer acetate. While interferon continued to be effective for many patients throughout the follow-up period, other patients required higher-efficacy medications due to the low efficacy of the interferon therapy. A significant number of patients moved to higher-efficacy medications at early ages, requiring second-line DMTs that until recently were only approved for use in adult MS.

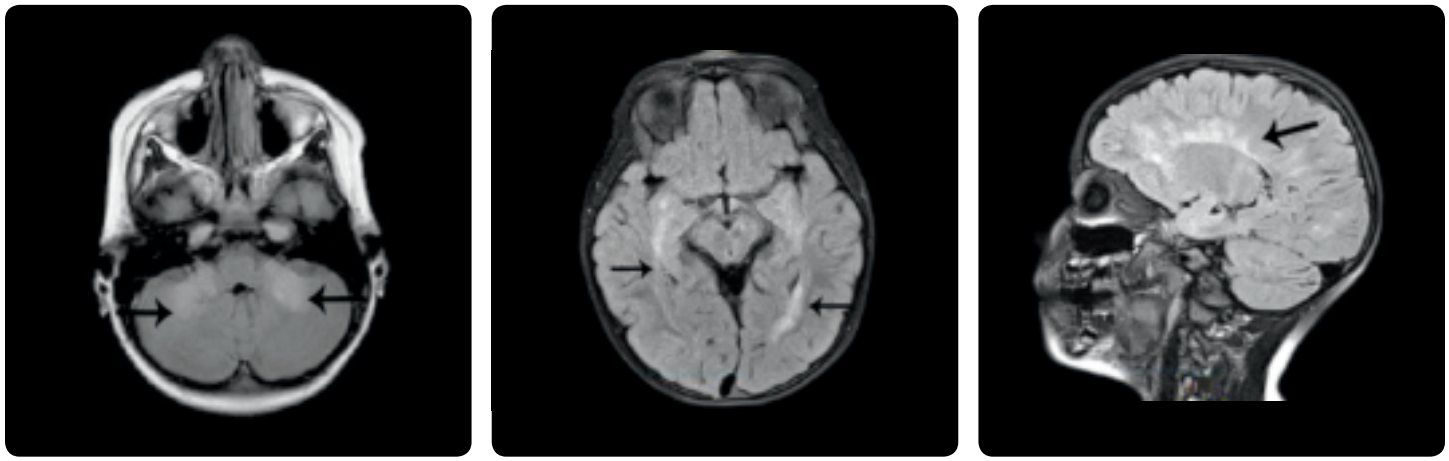
Use of three second-line DMTs was reported in the study: fingolimod, dimethyl fumarate and natalizumab. Of the 17 patients receiving one of these second-line DMTs at the end of follow-up, seven had started them before age 21, all without significant side effects.

Emerging research questions

The study authors identify use of these second-line DMTs in treatment-refractory patients as a priority for future POMS research. Trials of fingolimod, dimethyl fumarate and natalizumab in POMS are underway, and they will be critical for a more controlled assessment of these agents' efficacy, adverse effects and optimal dosing in pediatric patients.

Approximately 30 percent of patients with POMS will have disease breakthrough on first-line therapies, hence the need for second-line agents. For the first time, we have an FDA-approved treatment specifically for children and adolescents with MS (May 2018). As multiple sclerosis can have a profound impact on a child's life, this approval represents an important and needed advance in the optimal care of pediatric patients with MS. Gilenya® was first approved by the FDA in 2010 for the treatment of relapsing MS in adults. In May 2018, the FDA-approved Gilenya (fingolimod) to treat relapsing MS in children and adolescents age 10 years and older.

An additional research priority spotlighted in the paper is evaluation for neurocognitive dysfunction. Despite a lack of formal assessment for it in this study, cognitive and/or memory dysfunction was identified by patients and their caregivers as a prominent presenting symptom, the researchers note.



ABOVE: Images of a two-and-a-half-year-old girl with MS. Sagittal MRI showing extensive corpus callosum white matter lesions with finger-like projections (Dawson fingers), typical lesions for MS.

Our institution has adopted routine neuropsychometric testing for patients with POMS, but such testing was not always performed earlier in the study period, when understanding of cognitive impairment in POMS was still in its infancy. It's now well-known that brain growth and cognition are adversely affected in POMS. Future studies should focus on rigorous evaluation of testing measures to determine whether there's an association between early neuropsychological dysfunction and relapse trajectory.

Additional emerging research questions in POMS include the role of remote infection with Epstein-Barr virus (EBV), low serum vitamin D levels and exposure to maternal smoking. Ongoing studies are looking at the impact of EBV on host immune function and at vitamin D-related functions in patients with MS.

Conclusion

Although MS is typically considered a disease of adults, pediatric healthcare providers must be aware of the clinical features and evaluation of this disease, as up to 5 to 10 percent of all MS patients have their first clinical symptoms in childhood. A heightened awareness of this disease and an earlier diagnosis will allow for early and timely initiation of disease-modifying therapy, which may impact a patient's risk for long-term disability.

With increased national and international recognition of POMS and advances in clinical and basic science research, clinicians and researchers understand better the epidemiology, pathobiology, clinical features, cerebrospinal fluid and radiologic features of this chronic disease.

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NEWSWORTHY

REDUCING THE CHANCES FOR RELAPSE IN DSRCT PATIENTS

Pediatric oncologist Peter Anderson, MD, PhD, is using a drug called ONC201, which he believes has promise in the adjuvant setting and the potential for use in preventing relapse of desmoplastic small round cell tumor (DSRCT), a rare and aggressive form of sarcoma with the greatest incidence in children, adolescents and young adults.

"We have one patient who has said this is the best she has felt in more than three years, and she continues to respond, more than six months on the well-tolerated ONC201 drug," says Dr. Anderson.

According to Dr. Anderson, getting a consultation from an expert who is familiar with the principles of therapy for DSRCT is one of the most important steps in treating a rare tumor such as DSRCT. Cleveland Clinic Children's is facilitating this process by offering HIPAA-secure virtual visits to patients who live not only in Ohio, but in other states and Canada. This program helps DSRCT patients know options and how to control side effects of therapy.

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PARENT SATISFACTION AS AN OUTCOME TO EVALUATING CHRONIC PAIN TREATMENT

Chronic pain is debilitating and affects children's independent functioning. But

Gerard Banez, PhD

chronic pain also affects the whole family. A study by Ethan Benore, PhD, and Gerard Banez, PhD, examined the relationships between parental behavior and cognition and treatment outcomes in children in Cleveland Clinic Children's intensive interdisciplinary pain rehabilitation program.

The study examined data from 670 consecutive referrals of children with chronic pain who were enrolled in a clinical database registry from 2009 to 2014. Both children and parents completed measures of physical and psychosocial functioning as well as pain-related severity ratings at three separate time points.

The findings indicate that both children and parents benefit from intensive pain rehabilitation, and that child-parent dyads tend to respond in tandem. Benefit for the parents may further benefits for the child. This study underscores the need to actively include parents in the rehabilitation process. Future research focusing on specific treatment components targeting parenting and rehabilitation programming may ultimately lead to a greater quality of life for all.

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3D PRINTING TECHNOLOGY HELPS CRITICALLY ILL BOY AVOID HEART TRANSPLANT

Sultan, 10, of Saudi Arabia was born with a congenital heart defect that impaired the circulation of blood in his heart. After his third open heart surgery to repair the defect, he developed a life-threatening complication. Doctors in Sultan's home country told his parents that he would likely die without a heart transplant. Devastated but determined, his parents turned to specialists at Cleveland Clinic Children's to help save their son's life.

Hani Najm, MD, Chair of Pediatric and Congenital Heart Surgery, immediately began mapping out a plan with his team. Dr. Najm, who has performed over 5,000 open heart surgeries throughout his career, believed that Sultan's heart could be saved without transplantation.

A 3D model of Sultan's heart was created to help Dr. Najm's team plan for his complex procedure. The surgery, called double switch, reroutes blood flow from

one side of the heart to the other. Dr. Najm performed the lifesaving surgery in November 2017. Sultan is now celebrating a second chance at life and has returned home with his family.

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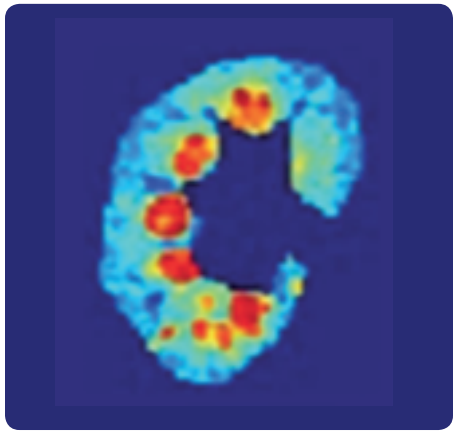
QUANTITATIVE MRI ASSESSMENTS OF ARPKD PROGRESSION AND RESPONSE TO THERAPY

A research team including pediatric nephrologist Katherine Dell, MD, published a study potentially setting the stage for quantitative MRI techniques in clinical studies to stage and measure progression in human autosomal recessive polycystic kidney disease (ARPKD).

A quantitative image analysis of high-resolution (noncontrast) T2-weighted MRI techniques was applied to study cystic kidney disease progression and response to therapy in the PCK rat model of ARPKD.

The authors report that serial imaging over a two-month period demonstrated that renal cystic burden, total cyst volume and (to a lesser extent) total kidney volume detected cystic kidney disease progression, as well as the therapeutic effect of octreotide, a medication shown to slow kidney and liver disease progression in this model. All three MRI measures correlated significantly with histologic measures of renal cystic area; the correlation of RCB and TCV was stronger than that of TKV.



ARPKD

This research is significant because ARPKD is associated with significant mortality and morbidity, and no disease-specific treatments are currently available. With the use of sensitive measures of kidney disease progression, new therapies may one day be developed.

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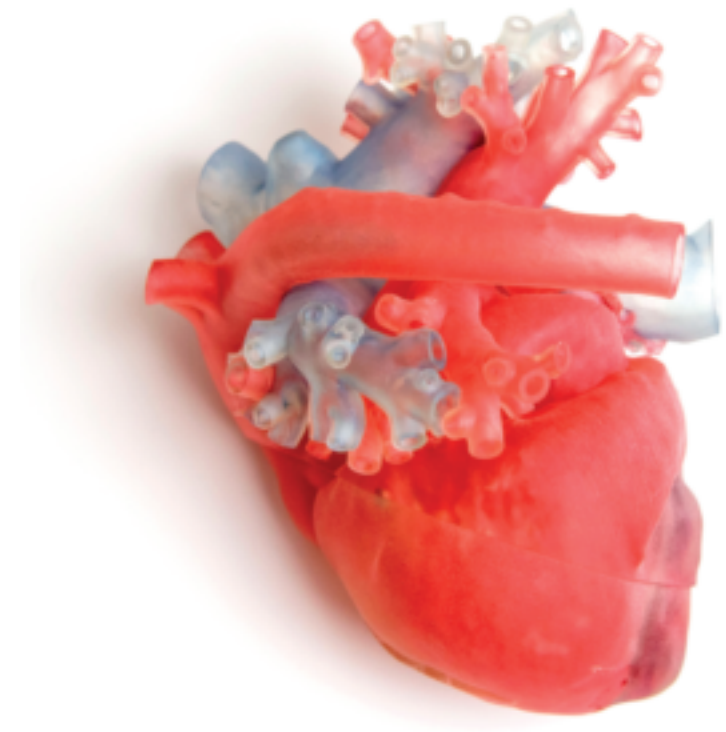
VIPS II STUDY HOMES IN ON PEDIATRIC ARTERIAL ISCHEMIC STROKE

Arterial ischemic stroke (AIS) in childhood is rare and often unrecognized, occurring in about 2.4 per 100,000 U.S. children annually. Recurrence poses a particular challenge: One month after an initial event, about 7 percent of children have another stroke, with the recurrence rate climbing to about 12 percent after one year. In the presence of an arteriopathy, however, this risk is increased fivefold versus an "idiopathic stroke," with the highest risk of recurrence within the first three months after the index stroke.



3D model of a heart

Better understanding of the potential etiology of recurrence risk is the focus of the second Vascular Effects of Infection in Pediatric Stroke (VIPS II) study currently underway at Cleveland Clinic and 16 other centers in the U.S., Canada and Australia. VIPS II follows the first VIPS trial, which found that the greatest predictor of stroke recurrence is arteriopathy. One common and unique pattern of arteriopathy seen in children involves a focal narrowing of the distal internal carotid artery, or proximal middle cerebral artery, known as focal cerebral arteriopathy of childhood, notes pediatric

cerebrovascular specialist Neil Friedman, MBChB.

"We learned in VIPS I that abnormal blood vessels pose the greatest risk for a recurrent arterial ischemic stroke in children, but we really don't understand the underlying basis very well," says Dr. Friedman, Director of Pediatric Neurosciences at Cleveland Clinic and a co-investigator in both VIPS I and VIPS II. Using cutting-edge testing techniques on blood samples and throat swabs from patients, VIPS II investigators anticipate better defining the roles of infection and inflammation on arteriopathy to help inform treatment decisions following an initial AIS.

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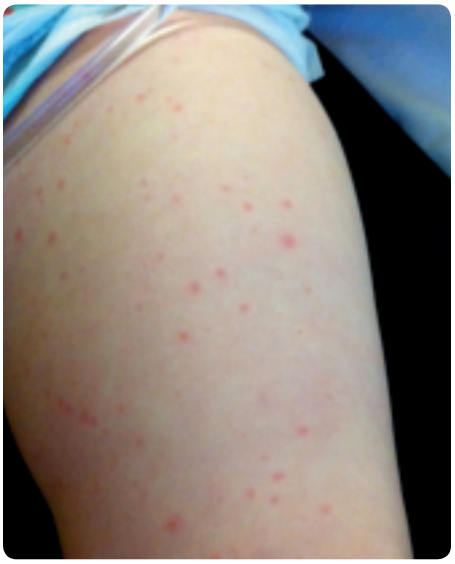
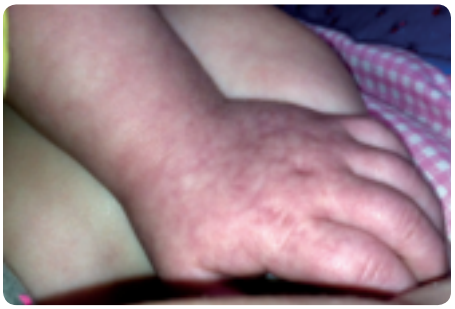
CANAKINUMAB TREATMENT FOR GENETIC RECURRENT FEVER SYNDROMES

Andrew Zeft, MD, MPH, Head of the Center for Pediatric Rheumatology and Immunology, was a co-investigator in a study of canakinumab to control and prevent flares in patients with colchicine-resistant familial Mediterranean fever, mevalonate kinase deficiency and tumor necrosis factor receptor-associated periodic syndrome (TRAPS). While molecular mechanisms differ, excessive interleukin-1β production in these diseases is a common mediator. This multicenter international trial randomly assigned patients at the time of a flare to receive 150 mg of canakinumab subcutaneously or placebo every four weeks. Patients received an add-on injection of 150 mg of canakinumab if they didn't have a resolution of their flare. The goal was a complete response, with





Rash symptoms from HIDS (hyper-IgD syndrome), a form of mevalonate kinase deficiency

resolution of flare and no recurrent flare until week 16.

This novel approach of grouping separate diseases with different genetic causes on the basis of a common targetable pathogenic mediator provided evidence of a common pathogenic role of interleukin-1β in colchicine-resistant familial Mediterranean fever, mevalonate kinase deficiency and TRAPS. The study also concluded that the medication showed that the inhibition of interleukin-1β was successful in controlling and preventing flares in patients with these diseases.

"This trial design was chosen to address the rarity of the diseases." says Dr. Zeft. "There was a need for a randomized, controlled trial to look at the hypothesis of a key common mediator."

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APPLYING ADULT TECHNOLOGY TO CHILDREN TO DIAGNOSE RCC

An otherwise healthy 12-year-old girl had acute appendicitis that was incidentally diagnosed with two solid enhancing right renal neoplasms via CT. After laparoscopic appendectomy, the patient underwent a renal mass biopsy, which showed an animated oncocytic renal epithelial neoplasm, and was then referred to Cleveland Clinic for further management. Cleveland Clinic pediatric urologist Audrey Rhee, MD, and a team at Cleveland Clinic Children's cared for the young girl. While physical examination revealed a healthy girl with no evidence of cutaneous lesions or lung or urinary issues, the patient's family history was notable for renal malignancy. A 99mTc-sestamibi single-photon emission computed tomography/X-ray computed tomography was then used, leading to a diagnosis of a hybrid oncocytic/chromophobe tumor (HOCT). The patient underwent a successful robotic partial nephrectomy, and she was discharged two days after surgery.

The final pathology showed two HOCTs measuring 2.8 cm and 2.0 cm in the largest dimension, with negative surgical margins. This case highlights that pediatric renal cell carcinoma (RCC) is a rare malignancy with genetic underpinnings and biologic behavior that differ from those of adult RCC. 99mTc-sestamibi SPECT/CT demonstrates high sensitivity in differentiating oncocytoma and HOCT from other solid renal neoplasms.

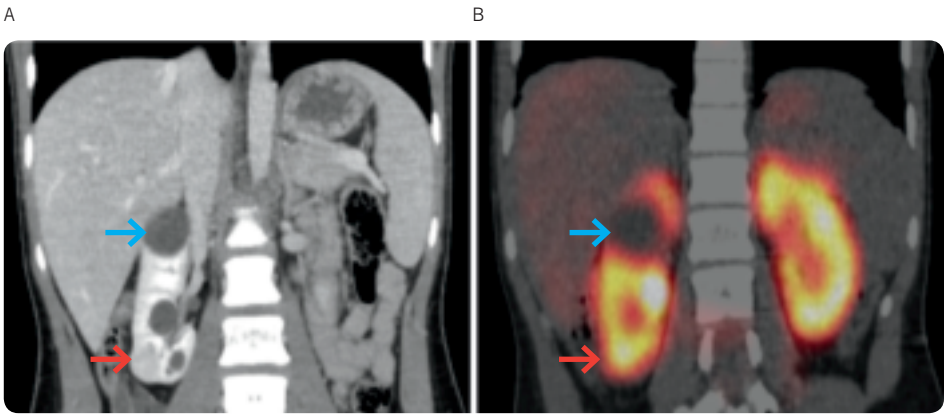

FIGURE. (A) Coronal contrast-enhanced computed tomography demonstrating a second smaller, 2.0 cm solid enhancing renal mass in the lower pole of the right kidney (red arrowhead), as well as an upper pole renal cyst (blue arrowhead). (B) On 99mTc-sestamibi single-photon emission computed tomography/X-ray computed tomography, the lower pole mass accumulated radiotracer in a fashion consistent with a benign renal oncocytoma or a hybrid oncocytic/chromophobe tumor (red arrowhead). In contrast, the upper pole cyst appears as a photopenic defect (blue arrowhead).

VELOSANO

In July 2018, Cleveland Clinic hosted its fifth annual VeloSano Bike to Cure weekend. VeloSano (meaning "swift cure" in Latin) is a year-round, community-driven fundraising initiative with 100 percent of the dollars raised going directly to support cancer research at Cleveland Clinic. Each year, researchers and physicians go through a competitive peer-review process to win a Pilot Award for their research projects. The focus of these one-year grants is to build on and transition recent advancements in cancer genetics and epigenetics and basic and translational tumor immunology.

On the 2018 VeloSano ride: Rabi Hanna, MD, with his patient Maisie Nowlin, who survived severe aplastic anemia. Dr. Hanna is Department Chair, Pediatric Hematology and Oncology, and Director, Pediatric Bone Marrow Transplant.

This year, 36 physicians and employees of Cleveland Clinic Children's participated in the bike ride, including Rabi Hanna, MD, Chair, Department of Pediatric Hematology and Oncology, and Director, Pediatric Bone Marrow Transplantation, Cleveland Clinic Children's (pictured below with a patient). In 2016, Dr. Hanna's Hodgkin lymphoma immunotherapy research project was awarded a $100,000 Pilot Award.

BY THE NUMBERS

VeloSano started in 2014

$ raised to date
$12.5 million

Number of Cleveland Clinic Children's projects funded
4

Amount of money gifted for Children's research projects
$335,000

Money raised by riders from Cleveland Clinic Children's
$81,845

SELECTED CLINICAL STUDIES

Consider offering your patients enrollment in a leading-edge clinical study. You can obtain further information by contacting the principal investigator. To learn more about these and other active Cleveland Clinic Children's studies, please send a message to pedsresearch@ccf.org.

AUTISM

Neurocognition in PTEN Hamartoma Tumor Syndrome (PTEN)

Cleveland Clinic is one of three sites in the country (including Stanford and Boston University) to be conducting research to evaluate the potential safety and efficacy of everolimus and its potential neurocognitive benefits. Participants will be treated with everolimus or placebo for six months to get a better understanding of *PTEN* and new forms of treatment. After unblinding, those who received placebo will be crossed over to everolimus. This trial is sponsored by the National Institutes of Health, the *PTEN* Research Foundation and the Zacconi Family Foundation.

Eligibility

Male and female outpatients between 5 and 45 years of age with a pathogenic *PTEN* mutation confirmed by clinical genetic testing; IQ greater than 50 (either verbal or nonverbal) and performance below the age-adjusted population mean on at least one standardized measure. Must have adequate bone marrow function, liver function and renal function and be medically stable with no active medical problem.

Principal Investigator
Rabi Hanna, MD

Sub-Investigator
Charis Eng, MD, PhD

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CARDIOLOGY

GORE® CARDIOFORM ASD Occluder Clinical Study

The Gore ASSURED Clinical Study is a 36-month study evaluating the safety and efficacy of this device for the treatment of transcatheter closure of ostium secundum atrial septal defects (ASDs). The trial will include 125 subjects in the pivotal phase and up to 335 subjects in the continued access phase. Sponsored by W. L. Gore & Associates, Inc.

Eligibility

Participants can be children or adults with an appropriate atrial septal defect, with no other existing cardiac conditions.

Principal Investigator
Tom Fagan, MD

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ENDOCRINOLOGY

A Safety, Tolerability and Efficacy Study of TransCon hGH in Children with Growth Hormone Deficiency

Sponsored by Ascendis Pharma A/S, this is a global 26-week trial of the long-acting growth hormone product TransCon hGH. It will be administered once a week to male and female participants with growth hormone deficiency (GHD). The trial will include participants from the U.S., Canada, Australia, New Zealand and elsewhere.

Eligibility

Participants should be 6 months to 17 years old with a diagnosis of GHD prior to the initiation of daily hGH therapy; Tanner stage < 5 at visit 1; open epiphyses (bone age ≤ 14 years for females or ≤ 16 years for males).

Principal Investigator
Roy Kim, MD, MPH

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NEUROLOGY

A Trial to Evaluate the Safety and Efficacy of Elamipretide in Subjects with Primary Mitochondrial Myopathy Followed by an Open-Label Extension (MMPOWER-3)

This is a multicenter phase 3 trial sponsored by Stealth BioTherapeutics Inc. It is evaluating the safety and efficacy of daily subcutaneous injections of elamipretide in patients with primary mitochondrial myopathy. It will be followed by an open-label treatment extension.

Eligibility

Patients must be at least 16 years old and diagnosed with PMM and enrolled in Study of Patients with Primary Mitochondrial Disease (SPIMM-300).

Principal Investigator
Sumit Parikh, MD

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ONCOLOGY

Phase 2 Study of ONC201 in Neuroendocrine Tumors

The objective of this study is to find out whether the new drug ONC201 can make tumors smaller or go away completely and/or can prevent cancer metastases. Disease burden at study entry will be compared at six weeks and three months, and patients without progression at three months will continue treatment and have imaging again at six, nine and 12 months. Metabolic response will also be compared. This phase 2 study of ONC201 in PC-PG (pheochromocytoma-paraganglioma) and other neuroendocrine tumors will determine whether inhibition of DRD2 (a member of the dopamine receptor family) is safe in neuroendocrine cancers, including PC-PG.

Eligibility

Subjects must have unresectable, recurrent, locally advanced, or metastatic neuroendocrine tumor or metastatic PC-PG (cohort A) or have unresectable, locally advanced or metastatic tumors and have failed or are refractory to available therapy (cohort B); or have well-differentiated neuroendocrine tumors that have relapsed or are refractory to at least two systemic therapies. Subjects must also have normal organ and marrow function and one or more detectable lesions.

Principal Investigator
Peter Anderson, MD, PhD, Cleveland Clinic Cancer Center

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ORTHOPAEDICS

Improving ACL Reconstruction Outcomes: CBPT

The purpose of this study is to look at the efficacy of cognitive-behavioral-based physical therapy (CBPT) for patients following ACL reconstruction (ACLR). The hypothesis is that it will improve knee function, return to sport and quality of life outcomes. There are two treatment groups, one receiving telephone-based CBPT for ACLR and one receiving telephone-based education, with the education group expected to demonstrate greater improvement at 12 months post-surgery. Sponsored by Vanderbilt University Medical Center.

Eligibility

Patients should be 14 to 35 years of age with no previous surgery to either knee; time from injury to surgery 12 months or less; and active participation in a sport on a weekly basis prior to injury.

Principal Investigator
Kurt Spindler, MD

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PULMONOLOGY

Safety and Efficacy of 2 Treatment Regimens of Aztreonam for Inhalation Solution in Children with Cystic Fibrosis and New-Onset Pseudomonas Aeruginosa Infection (ALPINE2)

The primary objective of this study, being supported by Gilead Sciences, is to evaluate the safety and efficacy of a 14-day course versus a 28-day course of aztreonam for inhalation solution (AZLI) in CF participants with new-onset pseudomonas aeruginosa (PA) respiratory tract infection.

Eligibility

Participants should be 3 months to 18 years old with a diagnosis of cystic fibrosis as determined by the 2008 CF Consensus Conference criteria; documented new-onset of positive respiratory tract culture for PA within 30 days of screening; forced expiratory volume in one second (FEV1) greater than 80 percent predicted (for subjects 6 years of age or older who can reliably perform spirometry assessments); and clinically stable with no evidence of acute significant respiratory symptoms that would require administration of antibiotics, oxygen or hospitalization.

Principal Investigator
Nathan Kraynack, MD

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RESEARCH IS PART OF OUR DNA

KATHERINE DELL, MD, VICE CHAIR OF RESEARCH, CLEVELAND CLINIC PEDIATRIC INSTITUTE

ABOVE: Dr. Dell shares a moment with a patient.

Research is an essential component of providing the best care for our pediatric patients, and "investigation of our patients' diseases" remains a core component of Cleveland Clinic Children's mission. This issue of *Perspectives in Pediatric Research and Innovations* highlights some of the important clinical and translational research being conducted by my colleagues across a spectrum of pediatric specialties. Recent published reports provide new information, including:

- Self-reported functional outcomes and parent satisfaction with our intensive interdisciplinary pain treatment program, which focuses on nonpharmacologic interventions for pediatric chronic pain in adolescents.
- Epidemiologic, clinical and diagnostic testing results and outcomes of a single-center cohort of patients with pediatric-onset multiple sclerosis (POMS), a rare but increasingly prevalent condition.
- Higher than expected prevalence of nonalcoholic fatty liver disease (NAFLD) in lean adolescents, a group traditionally thought to be at low risk for the disease.

We continue to expand our portfolio of clinical trials in our search for the most advanced treatments. Notable studies that opened this past year (see pp. 28-29) involving novel medications or new applications of existing medications include:

- A phase 2 study of a different medication for refractory neuroendocrine tumors.
- Two studies of medications to treat life-threatening infections in patients with cystic fibrosis.
- A randomized control trial of the mTOR inhibitor, everolimus, for the treatment of autism.

We look forward to building on the expanding research programs in our new outpatient facility. Please join us on this continuing journey.

ConsultQD

To stay up to date on the latest research and innovation at Cleveland Clinic Children's, be sure to visit our ConsultQD physician website at **consultqd.clevelandclinic.org/pediatrics**.

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ABOUT CLEVELAND CLINIC

Cleveland Clinic is an integrated healthcare delivery system with local, national and international reach. At Cleveland Clinic, more than 3,600 physicians and researchers represent 140 medical specialties and subspecialties. We are a main campus, more than 150 northern Ohio outpatient locations (including 19 full-service family health centers and three health and wellness centers), Cleveland Clinic Florida, Cleveland Clinic Lou Ruvo Center for Brain Health in Las Vegas, Cleveland Clinic Canada, Sheikh Khalifa Medical City and Cleveland Clinic Abu Dhabi.

In 2018, Cleveland Clinic was ranked the No. 2 hospital in America in *U.S. News & World Report*'s "Best Hospitals" survey. The survey ranks Cleveland Clinic among the nation's top 5 hospitals in 12 specialty areas, and the top hospital in heart care for the 24th consecutive year.

Perspectives in Pediatric Research and Innovations is written for physicians and should be relied on for medical education purposes only. It does not give a complete overview of topics covered and should not replace a physician's independent judgment about the appropriateness or risks of a procedure for a given patient.

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