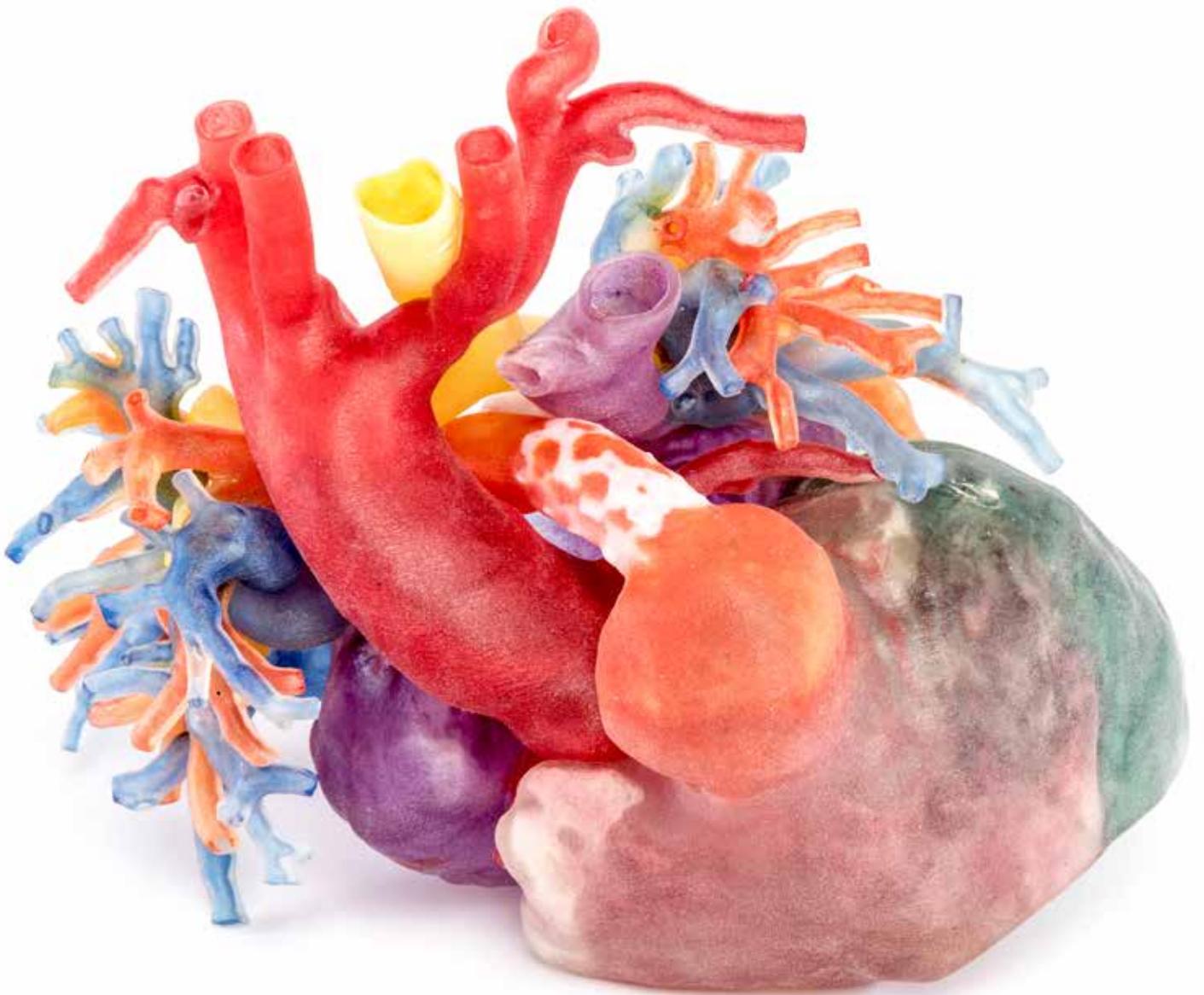




Cleveland Clinic Children's

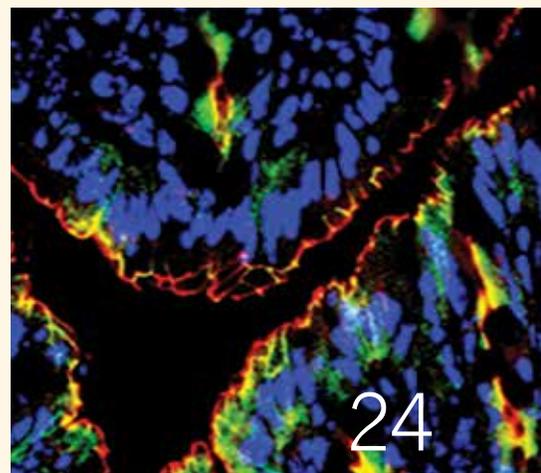
Pediatric Research Perspectives

2016-2017



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in Congenital Heart Disease p.8

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ON THE COVER. The Department of Pediatric Cardiology, in collaboration with the Lerner Research Institute, has developed 3-D-printed models based on a patient's existing contrast-enhanced cardiac MRI or CT scan.

Dear Colleagues,

We are considering not only our duty to the patient of today, but no less our duty to the patient of tomorrow.

– George Crile Sr., MD, Co-founder, Cleveland Clinic

Cleveland Clinic's Founders pledged to commit significant resources to "the investigation of disease" when the organization was dedicated in 1921. Cleveland Clinic Children's remains dedicated to that commitment, through impactful studies reflecting the full range of pediatric specialties. We have been proud to share our findings through *Pediatric Perspectives* over the years. Now, to emphasize that purpose, we have renamed our publication *Pediatric Research Perspectives*.



Here are some of the articles featured in our newly renamed publication:

- Volumes and experience matter, in research and clinical outcomes. Cleveland Clinic performs more surgeries for ulcerative colitis (UC) than any center in the world. Pediatric gastroenterologist Marsha Kay, MD, and colorectal surgeon Tracy Hull, MD, have drawn on the vast trove of data they've derived to study the long-term outcomes of proctocolectomy with ileal pouch anal anastomosis — the most common surgery for severe UC. Their findings (page 12) support the benefits of early and aggressive treatment, and remind us to be alert to the symptoms of this disease.
- Few readers will fail to be enlightened by the observations of Ellen Rome, MD, whose timely article (page 4) offers insights on gender dysphoria and anorexia nervosa in transgender youth based on her systematic analysis of her extensive experience with this historically understudied population.
- Until now, the management of autism has been complicated by the absence of an objective and quantitative diagnostic tool. But Thomas W. Frazier, PhD, pediatric neurologist Sumit Parikh, MD, and colleagues have achieved a high rate of accuracy in diagnosing autism using an index based on remote eye gaze tracking to various stimuli (page 18).
- I would also draw your attention to By the Numbers (page 38), a quick overview of our annual statistics. Our more than 300 pediatricians and pediatric specialists handled more than 900,000 patient visits last year, along with 18,455 inpatient admissions. We are proud to have earned the confidence of so many patients, families and referring physicians.

There is an additional statistic not mentioned in that overview that we can never forget: One-third of the people in the world are children. These are our constituents. Maintaining their health and well-being drives the research you'll read about here and everything we do. Thank you for your interest in our work and for your support.

Respectfully,

A handwritten signature in black ink, appearing to read "G. Piedimonte". The signature is stylized and written over a light blue horizontal line.

Giovanni Piedimonte, MD

Chairman, Pediatric Institute | Physician-in-Chief, Cleveland Clinic Children's
President, Cleveland Clinic Children's Hospital for Rehabilitation
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Effects of Treating Gender Dysphoria and Anorexia Nervosa in Transgender Youths: Lessons Learned

By Ellen S. Rome, MD, MPH

When taking a history, many pediatricians have become adept at asking the HEADDSSS questions about Home, Education, Activities, Drugs (and cigarettes and alcohol), Depression, Suicide, Safety and, of course, Sex. Primary care clinicians have increased their skills in asking, “Are you attracted to guys, girls or both? Have you had sex with guys, girls or both? Oral, vaginal, anal? Has anyone ever done anything to you sexually that made you uncomfortable?”

These questions used to make some clinicians squeamish, but they are now taught as mainstream, bread-and-butter teenage health to all medical students and residents — and have been embraced as normative questions for this age group. What must also be remembered is that not all youths experience gender identity, or an individual’s internal sense and subjective experience of gender, which may or may not be the same as the sex assigned at birth.

Understanding anorexia in youths with gender dysphoria

Some youths have gender dysphoria, in which they feel uncomfortable with their assigned gender identity; they may feel they have the wrong body parts. Add to this discomfort insufficient coping strategies and/or supports, and some youths find their way to maladaptive coping strategies, ranging from looking for love in all the wrong places with sexual risk-taking, self-medication with alcohol or drugs, or disordered eating.

The astute clinician, periodically during follow-up visits, should ask the HEADDSSS questions again; they do not have to be one-stop shopping at the initial visit, then forgotten.

Several cases in the literature document male-to-female (MtF) patients with disordered eating and gender dysphoria, with each noting a drive to be more feminine as a motivator for their symptoms.¹⁻⁵ In a recent case report,⁶ Cleveland Clinic Children’s team described a 16-year-old patient with a female sex assigned at birth who presented with symptoms consistent with anorexia nervosa. Over the course of treatment, this female-to-male (FtM) young person wanted to eradicate any feminine curves, stating, “I dislike my curves, my breasts, my hips, my face. I wish I had more defined muscles in my arms and a more angular face.” Over the next 10 months, with individual therapy and parental support, he began hormone therapy with testosterone cypionate at 50 mg/week. At age 19, five months after starting testosterone, he underwent bilateral mastectomy.

Once medical treatment for his gender dysphoria began, his anxiety and disordered eating decreased substantially as he began to identify himself as a transgender male. In college, he began to advocate for transgender inclusivity, expanded his peer group and initiated a romance with a female. After doing well for a number of months with a BMI of 19 kg/m², he relapsed with weight loss resulting in a BMI of 17.9 kg/m² during a self-identified time of school stress and exercise restrictions during his postoperative course.

Digging deeper with HEADDSSS and beyond

This case was the first to describe FtM gender dysphoria resulting in anorexia nervosa, with description of a course inclusive of hormonal therapy and treatment. This young person initially presented as a “typical anorexic” patient — as a Caucasian young lady in mid-adolescence. His therapy addressed his gender dysphoria only at his own request during treatment for his eating disorder, in which he felt safe enough to disclose this sensitive issue.

To get at this information earlier, the astute clinician, periodically during follow-up visits, should ask the HEADDSSS questions again; they do not have to be one-stop shopping at the initial visit, then forgotten. After establishing confidentiality, the discussion

can be framed with an opening statement such as, “My agenda is to have you lead a healthy and happy life, and that includes developing a healthy sexuality over your lifetime. Do you see yourself as a male, female, transgender or other? Are you attracted to guys, girls, both or none of the above?” These questions can be added to the ones in the original HEADSSS lineup. Another option is to add survey questions that a teen can answer confidentially. This two-step approach helps clarify assigned gender (the gender ascribed to the individual at birth) as well as gender identity. Survey questions can include the following:

| What sex were you assigned at birth, on your original birth certificate (check one): | |
|--|--|
| <input type="checkbox"/> | Male |
| <input type="checkbox"/> | Female |
| How do you describe yourself? (check one) | |
| <input type="checkbox"/> | Male |
| <input type="checkbox"/> | Female |
| <input type="checkbox"/> | Transgender |
| <input type="checkbox"/> | Do not identify as male, female or transgender |

Eating disorder treatment involves acute and chronic medical stabilization, nutritional improvement, and psychological skills-building to improve coping strategies and resiliency. Use of a hierarchical approach can help prioritize care, addressing the life-threatening issues of suicidality plus acute medical stabilization first, and moving on to refeeding plus psychological growth. When considering hormonal treatment in the gender dysphoric individual with or without an eating disorder, the Standards of Care of the World Professional Association for Transgender Health suggest that hormonal suppression should occur only when the adolescent has reached Tanner 2, or early puberty.⁷ These early pubertal changes can be the harbinger of disordered eating in both transgender and cisgender youth (cisgender means their assigned biologic gender matches their internal view of gender identity).

The team’s ongoing research explores the long-term outcomes of youths and young adults with eating disorders with and without gender dysphoria. Males in the cohort lost more weight prior to presentation than females; they also required more hospital days to resolve acute medical instability. Adolescent and young adult males with eating disorders admitted for acute medical stabilization tended to report a heterosexual gender identity more frequently than LGBTQ; their prevalence of LGBTQ appeared similar to that of other adolescent population profiles. Readmission rates and remission were similar between males and females.

Gender dysphoria is not universally linked with eating disorders, yet it can provoke an eating disorder as a maladaptive coping strategy in a vulnerable patient. Pediatricians can serve as a front-line screen for body discomfort, gender dysphoria, and disordered eating attitudes and behaviors.

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Hope for Pediatric Chronic Pain Through a Cost-Effective, Interdisciplinary Approach

By Ethan Benore, PhD; Gerard Banez, PhD; and Jenny Evans, PhD

Chronic pain in children is a tremendous problem across the United States. Due to the constant sensation of pain, children develop additional struggles with school attendance, peer relationships and activities of daily living — all of which reduce their quality of life. There is a significant financial burden of pediatric chronic pain as well. These children undergo extensive medical or rehabilitative treatments — in addition, parents often miss work to help provide this care. Current estimates are that chronic pain in children costs \$19.5 billion annually in the United States.¹

Despite the burden and cost of pediatric chronic pain, there is hope. Multiple treatment centers have published outcomes supporting the clinical effectiveness of intensive interdisciplinary pain management.² These programs typically occur over several weeks, either within a hospital setting or in a day hospital or outpatient process.

Cleveland Clinic's approach

The Pediatric Pain Rehabilitation Program at Cleveland Clinic Children's is one such program that has demonstrated successful management of chronic pain, extending out two to four years.³

The program typically occurs over three weeks (two weeks inpatient, one weekday hospital treatment). On average, patients receive three hours of physical/occupational therapy (PT/OT) each day (> 15 hours/week), as well as recreational and art therapies (six hours/week), psychology (> six hours/week), parent psychoeducation/support group (three hours/week), and school (> 7 hours/week). The treatment approach also provides interdisciplinary collaboration and cotreatment. The program's primary goal is to enhance daily functioning (i.e., return to school and activities) despite the presence of chronic pain.

The cost of managing pain

These clinical outcomes do not come without their own cost. The added cost of intensive rehabilitation for pediatric pain in Cleveland Clinic Children's program is approximately \$31,720

(on average). Based on the current healthcare environment and the struggle for affordable care, the financial value of intensive rehabilitation for pediatric chronic pain has yet to be determined. The team's research sought to demonstrate the value of our program from a financial standpoint.⁴

To evaluate the cost-effectiveness of our program, researchers used the 2011 household component event files from the Medical Expenditure Panel Survey. Data were used to estimate the healthcare costs of our patients, including lost revenue from missed work. Using patient and family reports of missed school and work and access to medical care, estimated annual costs for all medical care related to chronic pain in the year prior to admission. Patients were reassessed patients one year following discharge from the program using these same variables.

What the study found

The table displays the significant change in healthcare utilization following intensive pain rehabilitation. All measures significantly improved at $P < .05$, with the exception of ED visits, which were minimal at baseline. The number 1 in the "1-Year Post-Discharge" Median column represents the estimated annual cost of healthcare related to these services for pediatric chronic pain, as well as costs for the following year (including for the intensive program). Annual expenditures dropped from \$74,217 to \$15,378 (see figure). The cost savings over the first year are estimated at \$27,118, but importantly, these reduced expenditures indicate how or on what basis?³

The value of healthcare services is based not only on clinical outcomes, but on the financial "value added" of these services. This study demonstrates one method for assessing the financial value of these services. While there are limitations in the method,² it is the team's belief that patients, insurers and healthcare providers benefit from a process to assess cost-effectiveness of clinical programs. In the current climate that emphasizes affordability and transparency, analysis of cost-effectiveness should be an objective of all those working to improve the quality of children's healthcare.

Table: Healthcare Utilization in the Previous 30 Days, at Preadmission and 1-Year Post-Discharge

| | Preadmission | | 1-year post-discharge | | Change | | | | | |
|-----------------------------|--------------|------|-----------------------|-------|--------|------|--------|-------|------|------|
| | Mean | SD | Median | Range | Mean | SD | Median | Range | p* | r** |
| Days hospitalized | 2.1 | 7.18 | 0 | 0-3 | 0.2 | 0.80 | 0 | 0-6 | .006 | -.22 |
| Specialty physician visits | 1.7 | 2.12 | 1 | 0-12 | 0.8 | 1.45 | 0 | 0-10 | .000 | -.28 |
| PT/OT visits | 3.0 | 4.50 | 1 | 0-22 | 1.6 | 3.34 | 0 | 0-20 | .000 | -.29 |
| Psychology visits | 1.5 | 1.81 | 1 | 0-8 | 1.2 | 2.04 | 0 | 0-16 | .031 | -.17 |
| Emergency Department visits | 0.4 | 1.73 | 0 | 0-12 | 0.2 | 1.43 | 0 | 0-4 | .058 | -.14 |
| PCP visits | 0.7 | 0.92 | 0 | 0-5 | 0.4 | 0.76 | 0 | 0-5 | .048 | -.15 |
| Parent workdays missed | 5.9 | 9.90 | 1 | 0-30 | 0.6 | 2.11 | 0 | 0-15 | .000 | -.45 |

*Significance of change using Wilcoxon signed-rank test of differences
 **Pearson's r represents the effect size

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Dr. Evans is a former postdoctoral fellow in Cleveland Clinic's Pediatric Behavioral Health Center.



Figure. Financial burden of pediatric chronic pain both the year prior to and the year following intensive pediatric chronic pain rehabilitation. The cost of pain rehabilitation is included.

3-Dimensional Printing in Congenital Heart Disease

By Patcharapong Suntharos, MD, and Hani Najm, MD

Three-dimensional models have long been a great resource to help medical professionals understand unique anatomy in detail. The advancement of 3-D printing now allows clinicians to print a 3-D model of an actual, real-life patient's structure.¹ This is an exceptional tool, especially for congenital cardiologists and cardiothoracic surgeons who require precise detail of complex anatomy when planning for percutaneous or surgical interventions.

Three-dimensional imaging to a 3-D printed model

The Department of Pediatric Cardiology, in collaboration with the Lerner Research Institute, has developed 3-D-printed models based on patients' existing contrast-enhanced cardiac MRI or CT scans. The images of either the whole heart or part of the cardiac structure of interest were imported into Mimics software (Materialise, Leuven, Belgium). Using Mimics, cardiac structures were manually segmented. The mask was converted into a 3-D volume and compared slice by slice to the MRI DICOM images to verify accuracy and make corrections as needed (Figure 1).

Next, the 3-D volume was exported as an STL file and imported into Magics (Materialise) for 3-D print preparation. In Magics, a 2-3 mm wall was added by offsetting the lumen. Additional engineered features, such as lines to indicate anatomical orientation or a unique text identifier, were also added to the digital model. The final STL file was printed with a Stratasys Connex 350 using TangoPlus FLX930 resin (Stratasys, Minneapolis, and Rehovot, Israel). After printing, standard part cleaning was performed to remove support material.

Application in complex congenital interventional cardiology

Transcatheter pulmonary valve implantation (TPV) is one of the most complex transcatheter procedures performed in pediatric and adult patients with congenital heart disease. The Melody[®] Transcatheter Pulmonary Valve (Medtronic Inc., Minneapolis), approved for TPV in the United States, is indicated for implantation in a dysfunctional right ventricle (RV) to pulmonary artery (PA) conduit. However, the majority of patients who will benefit from TPV do not have an RV-PA conduit. This valve, along with the Edwards SAPIEN XT valve (Edwards Lifesciences Corp., Irvine, California), currently approved for TPV and the Edwards

SAPIEN 3 valve, used for transcatheter aortic valve replacement, have been used off-label in native right ventricular outflow tracts (RVOTs).

Due to the complexity of the RVOT, 3-D printed models were used to help in planning this complex procedure. After printing the model of the patient's actual RVOT, the RVOT stenting procedure was simulated under fluoroscopy in the pediatric cardiac catheterization laboratory using the model (Figures 2 and 3).

In 2015, four models were printed: two for patients with tetralogy of Fallot (TOF) post-transannular patch repair (native RVOT), one in a patient with partial AV canal and pulmonary stenosis post-pulmonary valvotomy, and one in a patient who had TOF with anomalous left coronary artery crossing the RVOT with dysfunctional RV-PA conduit and regurgitant native hypoplastic pulmonary valve (double-barrel-type repair). All four patients (ages 19 to 64) underwent successful TPV without complication (three with the Edwards SAPIEN valve and one with the Melody valve). In the team's experience, the 3-D-printed models were extremely helpful in planning the procedure, especially in determining the stent and valve size and optimal anatomic position.

Novel surgical technique can be achieved with application of 3-D technology

Ethan is a 9-year-old boy with heterotaxy syndrome, a complex congenital heart disease — situs inversus, complete common AV canal, total anomalous pulmonary venous return (TAPVR), left superior and inferior venae cavae to the left-sided atrium, two good-sized d-loop ventricles with the aorta arising from the right ventricle remote from the ventricular septal defect, and pulmonary atresia with multiple major aortopulmonary collateral arteries (MAPCAs). He underwent TAPVR repair with anastomosis of the pulmonary venous confluence to the right side of the common atrium when he was approximately 1 month old, and subsequently his MAPCAs were repaired using a 12 mm aortic homograft-valved conduit connected to the right ventricle in December 2007. Since the second surgery, he has had nine cardiac catheterization procedures, mainly to alleviate significant pulmonary artery branch stenoses and augment pulmonary artery blood flow. However, he still had profound cyanosis despite multiple percutaneous interventions.

Figure 1.



Figure 2.



Figure 3.

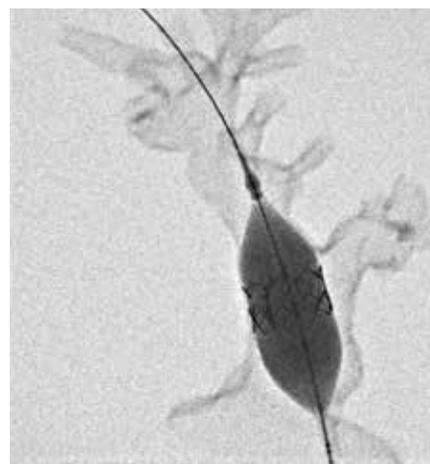


Figure 4.



Figure 5.



Figure 1. Software used to import the patient's cardiac MRI/MRA and convert the data to 3-D model.

Figure 2. A 3-D printed model of a right ventricular outflow tract, main pulmonary artery and both branches.

Figure 3. A stored fluoroscopic image of simulated Edwards SAPIEN valve placement procedure in the right ventricular outflow tract printed model.

Figure 4. Ethan's 3-D printed heart model.

Figure 5. Ethan with his "own heart model" in his hands.

In July 2016, faced with a deeply cyanosed child, the team needed to innovate a procedure that would improve his hypoxia. Standard imaging modalities were limited in this regard.

Using the 3-D model of his heart allowed examining the feasibility of performing a procedure to improve his oxygen saturations. The surgeon's ability to hold Ethan's heart replica model and make an incision in it demonstrated the feasibility of performing the novel procedure. This provided a significant jump in the team's ability to predict surgical outcomes. That procedure was executed in real life exactly as planned on the 3-D replica (Figures 4 and 5).

The surgical procedure resulted in an excellent outcome. Ethan is now doing very well, with oxygen in the low 90s, a level he has never achieved before.

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The Need for Culture-Appropriate Carb Counting for Children with Diabetes

By Sumana Narasimhan, MD

Aliyah* was only 8 years old. She was always a happy, healthy little girl who loved to play with her brothers and sisters — and then run back inside to snack on whatever her mom had cooked up.

Her family had recently moved to the U.S. from Saudi Arabia. She enjoyed eating pizza and was not quite sure about pasta yet. Her mother cooked most of the meals in her family and followed age-old recipes passed on by word of mouth, using fragrant spices and fresh ingredients not always found in mainstream cookbooks.

Aliyah's world was turned upside down this year when she started going to the bathroom a lot and losing weight and was finally diagnosed with Type 1 diabetes. When Aliyah's family met the diabetes team at Cleveland Clinic Children's, her mother's main concern was "How do I cook traditional foods for her anymore?"

The continued importance of accurate carbohydrate counting

Technological advances and pharmaceutical discoveries have revolutionized the treatment of Type 1 diabetes. New insulin analogs, advanced delivery systems such as the insulin pump, and continuous glucose monitors have made glucose sensing and the insulin titration much easier. Accurate dosing of insulin based on blood sugar and carbs consumed is critical to optimally managing Type 1 diabetes.

Mealtime insulin dosing still relies on accurate carbohydrate counting — specifically, on the patient being able to estimate the grams of carbohydrate expected to be eaten during a meal. In the past, carbohydrate counting was taught as "exchanges," each exchange equaling 15 grams of carbohydrate. While easy, this method compromises on accuracy. Newer insulin regimens require accurate dosing with little room for "guesstimation" or rounding.

How culture plays an important role

In Aliyah's case, Dr. Narasimhan and medical student, Hamza Nasir, faced a dilemma when her mother posed her question about carbohydrate counting for ethnic foods. Plenty of Arabic language translations of diabetes education materials were found, as well as a few research articles that provided examples of cuisine-specific nutritional information. But finding easy-to-read, cuisine-specific carbohydrate counting materials online was difficult.

Although it seems that carbohydrate counting resources would be easily accessible, most readily available food lists are for cuisines eaten in Europe or North America. Translations tend

to be nonspecific and do not address carbohydrate counting or portion sizes. Resources published in different countries are sometimes only in the native language and not verified for accuracy. Extensive ethnic food resources are available, but they tend to focus on the nutritive value of ingredients, rather than on appropriate meals or food choices for those with particular conditions or dietary limitations. Further, these resources tend to be in the form of research articles, lacking patient-friendly advice.

Because most traditional foods are prepared from a multitude of raw, indigenous ingredients using variations of recipes passed on through generations, portioning and carbohydrate counting become arduous tasks for families who are still coming to terms with a new diagnosis of Type 1 diabetes in their toddler or child.

A solution is sorely needed

In today's global village, clinicians increasingly encounter cultural diversity in their practices. It is imperative that diabetes associations look into providing easily accessible tools online in different languages for carbohydrate counting of ethnic foods.

A centralized database consolidating information about ethnic foods' carbohydrate counts would be ideal. This would help ease the of carb counting, allowing children with Type 1 diabetes to achieve optimal glycemic control while enjoying traditional home-cooked meals.

**Patient name has been changed to protect privacy.*

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Examining the Cost of Imaging and Audiometric Testing for Pediatric Hearing Loss

By Samantha Anne, MD, MS

Hearing loss affects nearly 15 percent of children between ages 6 and 19 years. Diagnosing hearing loss and evaluating a child once hearing loss is confirmed involves an array of testing, including audiometric testing, radiologic testing and genetic testing, among others. The pediatric otolaryngology section at Cleveland Clinic has been investigating the costs of these hearing evaluations in this patient population.

Tympanometry and OAEs vs. full audiometry

Evaluating a child with suspected hearing loss requires a reliable, reproducible and accurate audiometric test. Young children, especially those younger than 3 years, have been shown to have high rates of incomplete or failed testing attempts (manuscript in submission). One option for screening healthy children with no risk factors for hearing loss is to use otoacoustic emissions (OAEs) instead of pure-tone audiometry, and further screen children who have failed OAEs with tympanometry to evaluate middle ear status.

A study to determine the cost of combined tympanometry and otoacoustic emissions versus a comprehensive audiogram in the pediatric population found that testing with tympanometry and OAEs would save nearly \$70 compared with full audiometry.¹

Testing with tympanometry and OAEs would save nearly \$70 compared with full audiometry.

Which imaging study is best?

Once hearing loss is diagnosed, the child may undergo genetic testing, ophthalmologic examination, electrocardiogram and various laboratory testing, based on the index of suspicion in each case. In terms of radiologic evaluation of hearing loss, which test is best is still debatable. Consideration must be given to need for sedation, radiation and specific information attained from each technique.

A study completed in the department evaluated the cost of CT versus MRI, as well as differences in the need for sedation and the duration of sedation. MRI and CT give slightly different information; both are used based on individual institution's preference. The study found that magnetic resonance imaging of the brain, internal auditory canal/cerebellopontine angle (MRI IAC/CPAs) is, in general, twice as costly as computed tomography of the temporal bone (CTTB) and almost 40 percent of patients need sedation to complete MRI IAC/CPA.²

More study is needed

Cost is just one variable to consider in the evaluation of pediatric hearing loss. Further studies are needed to determine the best audiometric testing method that accurately and reliably tests young children. In addition, once a child is diagnosed, the type of testing used to investigate the cause of hearing loss will be determined on a case-by-case basis.

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Long-Term Follow-Up of Ileal Pouch Anal Anastomosis in Pediatric and Young Adult Patients with Ulcerative Colitis

By Marsha Kay, MD, and Tracy Hull, MD

For pediatric patients with ulcerative colitis, management of the disease is important for both controlling symptoms and preventing negative consequences such as malnourishment that can hamper growth and development. When medical management fails to relieve symptoms or there is a risk of dysplasia (precancerous changes in the lining of the colon), surgery is an effective option.

The surgery of choice is proctocolectomy with ileal pouch anal anastomosis (IPAA). This procedure removes the colon and rectum and creates a pouch from the ileum to hold stool. Pouch types include the more common J-pouch, which is easier to construct, and the S-pouch, which is used for patients with anatomical challenges and is technically more demanding to construct.

Research has been limited on long-term outcomes of IPAA in pediatric patients. To learn more about how patients fare over time and to have more data to guide surgical decisions, the Departments of Pediatric Gastroenterology and Colorectal Surgery conducted a study on long-term surgical outcomes in pediatric patients who were treated at Cleveland Clinic, which performs more surgeries for ulcerative colitis (UC) than any institution in the world.

The study surveyed 157 pediatric surgical patients who underwent IPAA from 1982 to 1997 and participated in an initial follow-up survey in 2002.¹ The most common indication for surgery was failure of medical management. Researchers reached 74 patients, with a median age of 38 years (39 male and 35 female) and a median age at surgery of 18 years, making it the largest and longest follow-up study in pediatric patients to date.

Study results

Participants reported a variety of complications over the average 20-year time period following the surgery; the most common was pouchitis (inflammation of the pouch), which was reported by 45 percent of participants. This condition is a well-known and common complication of pouch procedures occurring in patients of all ages, with a known increase in frequency with longer term follow-up. Pouchitis is primarily treated with medical therapy, and patients are usually able to retain their pouch.

Other complications included fistulae (30 percent), strictures (16 percent), obstruction (20 percent), pouch failure (14 percent) and change of diagnosis to Crohn's disease (28 percent). More female patients than male patients reported obstruction, which may be due to anatomical differences. Pouch failure was significantly associated with a change in diagnosis to Crohn's disease and having an S-pouch. However, most patients (60 percent) later diagnosed with Crohn's disease were able to keep their pouch. None of the participants reported the development of dysplasia.

Fertility issues are a potential concern for women with inflammatory bowel disease (IBD) who undergo IPAA — infertility rates for this group are two to three times higher than for women with IBD who are treated with medical management.² In this study, half of the 21 women who had children reported having some difficulty during pregnancy or difficulty conceiving, but the survey data did not analyze the specific issues involved. No males in the study reported fertility issues.

At follow-up, nearly half of the participants reported taking medications to control stooling frequency, which increases with an IPAA procedure, and 19 percent were on antibiotics, which is the initial treatment of choice for pouchitis. Some of the patients were on biologics and immunomodulators at follow-up, likely reflecting the group that had a change in diagnosis to Crohn's disease with long-term follow-up.

Despite the complications, participants were overwhelmingly positive about their surgery: 79 percent were very satisfied and 14 percent were somewhat satisfied with how they were doing at long-term follow-up.

Advances in diagnosis and treatment

Over the past two decades, there have been significant advances in the diagnosis and treatment of UC. Cleveland Clinic uses the latest technologies such as wireless capsule endoscopy and MRE (magnetic resonance enterography) to aggressively evaluate the small intestine and better distinguish between UC (which does not involve the small intestine) and Crohn's disease, so that patients can receive the appropriate treatment for their condition.

New medications, such as the biologic agents infliximab and adalimumab (initially available in 1998 and 2002, respectively), have dramatically improved quality of life for UC patients and have significantly decreased the need for surgery.

Surgical techniques have also advanced: IPAA can be performed laparoscopically, which shortens recovery time and reduces scar tissue, potentially making infertility less of an issue for women. J-pouches can be constructed in more patients, which reduces the chances of pouch failure. Clinicians also are better able to manage complications during the perioperative period, which may reduce the incidence of long-term complications. Cleveland Clinic pediatric gastroenterologists and colorectal surgeons work as a team to evaluate patients and select appropriate candidates for surgery. Patients who have had IPAA procedures have done very well.

Early diagnosis and treatment important

Patients with UC who are diagnosed and aggressively treated during the early stage of their disease typically achieve better outcomes due to earlier initiation of medical therapy, although some patients with severe disease at onset may still require surgery. Pediatricians should be alert to possible UC symptoms such as abdominal pain, diarrhea including nocturnal bowel movements and fecal urgency, blood in stools, weight loss, and unexplained fevers, especially if there is a family history, and refer patients for a consultation with a pediatric gastroenterologist.

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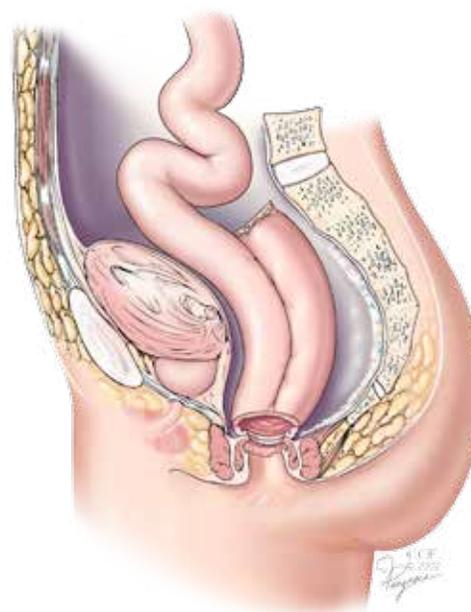
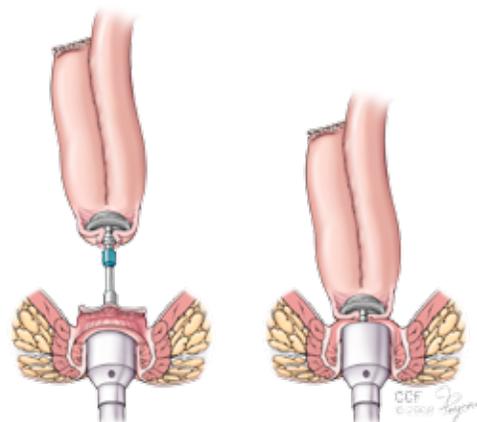
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Figures 1 & 2. A J-pouch is constructed using two loops of small intestine measuring approximately 6 inches in length. After pouch construction is complete, the pouch is capable of holding about two-thirds of a pint of fluid. The pouch is filled with sterile saline to ensure it is completely watertight. After testing, the pouch is placed into the pelvis where the rectum used to be and attached to the upper portion of the anal canal. This is the primary pouch procedure done at Cleveland Clinic.

Bone Marrow Transplantation as a Cure for Sickle Cell Disease Also Benefits Patients with Thalassemia

By Rabi Hanna, MD

Sickle cell disease and thalassemia are associated with significant morbidity and mortality. Although medical management has significantly improved rates of survival and quality of life, patients with these diseases still face substantial challenges.

Patients with sickle cell disease often require multiple hospital admissions for extended periods of time due to excessive pain crises, acute chest syndrome or, occasionally, stroke. Transplantation for sickle cell provides the only chance of cure for these patients: Overall, 90 percent end up being cured of their disease when bone marrow is obtained from an HLA-matched family member. Successful BMT improves quality of life by eliminating hospitalizations, and may reduce long-term healthcare costs. Over a life span, the cost of transplantation is far less than that of multiple hospital admissions for high-risk patients.

Ideal scenario: HLA-matched donors

The best scenario is for BMT to be performed with an HLA-matched donor, either an HLA-identical sibling or an HLA-matched unrelated donor. With a matched donor, BMT for sickle cell has a 90 percent cure rate and a greater than 95 percent survival rate.¹ Any sickle cell patient with an HLA-matched family donor is eligible for transplantation at Cleveland Clinic.

Overall, 90 percent of patients are cured of their disease when bone marrow is obtained from an HLA-matched donor.

Because sickle cell affects a disproportionate number of blacks due to socioeconomic reasons, a low percentage of these patients have HLA-matched family donors.^{2,3} Fortunately, many qualify for Cleveland Clinic's haplo-identical donor transplantation program. This program uses bone marrow from HLA half-matched (haplotype) donors — usually biological parents and half-matched siblings — or umbilical cord blood.

Cleveland Clinic's haplo-identical donor transplant program is a huge step forward in increasing access to BMT for these patients. The protocol was built on the success of haplo-identical BMT in providing lifesaving therapy for patients with hematological malignancy. However, the same protocol yielded a high graft-rejection rate in patients with sickle cell. To overcome this, the team added another phase called 'preconditioning therapy' and increased the intensity of conditioning therapy by adding an additional medication, thiotepa, to the chemotherapy regimen.

Limitations for half-matched donors

Cleveland Clinic offers haplo-identical transplantation for sickle cell disease through an institutional protocol and, soon, through participation in a national phase 3 clinical trial (BMT Clinical Transplant Network Protocol #1507). This study will be open to adult and pediatric patients. Adult patients must meet NIH criteria for severe sickle cell, and pediatric patients (< 15 years of age) should have documented stroke.

This study will aim to decrease the risk of graft rejection in haplo-BMT, hopefully making it more accessible to patients with sickle cell disease. The team is encouraged by the low incidence of severe and chronic graft-versus-host disease with haplo-BMT.

BMT for other hemoglobinopathies

Unlike patients with sickle cell disease, who produce malformed red blood cells that cause complications such as pain crises, acute chest syndrome and stroke, patients with major thalassemia produce defective blood cells that are immediately hemolyzed, rendering them ineffective. Patients suffer from severe anemia and iron overload in organs such as the liver, heart and pancreas. Patients with thalassemia have shorter life spans due to these long-term complications.



Bone marrow transplantation results in a high rate of cure and restores quality of life for patients with sickle cell disease and thalassemia.

BMT is currently the only potential cure for thalassemia, and Cleveland Clinic has transplanted many patients with the disease — all from Middle Eastern countries, where the disease is more prevalent than in the United States.

The team has gained experience in transplanting these patients using the haplo-BMT protocol with post-transplant high-dose cyclophosphamide. Results are encouraging so far.

In the future, Cleveland Clinic envisions haplo-BMT being applied to other benign hemoglobinopathies in which blood production is inadequate or ineffective, such as inherited bone marrow failure syndromes. BMT is a potential lifesaving treatment for many blood disorders.

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Infants Presenting with a Febrile UTI: Is There a Benefit to Delaying Renal Imaging?

By Prabi Rajbhandari, MD, and Raed Bou Matar, MD

Urinary tract infection (UTI) is one of the most commonly encountered diagnoses for urgent care and emergency room visits. In 2011, the American Academy of Pediatrics (AAP) revised its guidelines for the evaluation and treatment of UTI in infants ages 2 to 24 months. A renal and bladder ultrasound (RBUS) was recommended as the initial screening modality in infants who present with their first febrile UTI.¹

In this context, RBUS aims to detect anatomic abnormalities requiring further intervention. The guidelines also recommend delaying RBUS until after the acute infection has subsided. The latter recommendation was primarily based on expert opinion, with the aim of minimizing the likelihood of detecting transient dilation of the collecting system caused by bacterial endotoxins. According to two animal studies performed during the 1960s and 1970s, bacterial endotoxins released during an acute UTI induce transient ureteral smooth muscle relaxation that, in turn, results in ureteral dysfunction and transient hydronephrosis.^{2,3} No similar experimental data are available in humans. Moreover, no clinical studies to date have systematically examined the value of delaying renal imaging in infants with UTI.

Findings did not support the current AAP recommendations to delay RBUS in infants with febrile UTI until the acute illness has subsided.

In day-to-day practice, planning for RBUS later during the course of the illness carries a potential risk of this valuable study being delayed weeks to months or not done at all, particularly in less compliant families or those who, for any reason, are lost to subsequent follow-up.

Early versus late renal bladder ultrasound

The primary objective of this study was to investigate whether, in children ages 2 to 24 months presenting with their first febrile UTI, obtaining RBUS early (< 10 days from presentation) versus late (\geq 10 days from presentation) is associated with an altered rate of persistent, minor anatomic abnormalities on repeat imaging. In addition, minor abnormalities detected on RBUS were correlated with the presence of vesicoureteral reflux (VUR) on voiding cystourethrogram (VCUG), and such correlation was also compared between the early versus late groups.

To answer this question, researchers performed a retrospective chart review of all patients 2 to 24 months of age who presented to Cleveland Clinic outpatient clinics between January 2009 and December 2013 with their first febrile UTI. Febrile UTI was defined by a temperature of \geq 100.4°F, with an abnormal urinalysis plus growth of > 50,000 colonies of a known uropathogen on urine culture. Patients were grouped based on timing of their first RBUS: early and late (< 10 versus \geq 10 days). The two groups were then compared based on clinical variables, including RBUS and VCUG results.

Delaying RBUS did not impact the likelihood of abnormal imaging

RBUS results were available for 201 patients who were included in the study. Initial RBUS was abnormal in 77 infants (38.3 percent), which included minor abnormalities (pyelectasis/pyelocaliectasis/mild hydronephrosis) in 49 patients (24 percent). Twenty-five infants with minor abnormalities (51 percent) underwent a repeat RBUS, of which 13 (27 percent) had persistent findings on repeat imaging. VCUG was done in 144 infants (71 percent), of which 65 (32 percent) had \geq grade II VUR. Among patients with minor abnormalities, 24 (49%) had \geq grade II VUR. The two groups did not

differ in terms of persistent minor abnormalities on repeat RBUS (42 percent versus 33 percent, $P = 0.99$) or VUR detection rate on VCUG (53 percent versus 41 percent, $P = 0.49$).

Should the published recommendation to delay RBUS be modified?

The findings of this study suggest that in infants presenting with their first febrile UTI, minor abnormalities seen on RBUS obtained early versus late during the course of the illness carried a similar likelihood for being persistent on repeat imaging and for associated VUR. As this was a retrospective study, additional research is needed to better delineate the optimal timing of RBUS during the course of a febrile UTI in infants. However, findings did not support the current AAP recommendations to delay RBUS in infants with febrile UTI until the acute illness has subsided.

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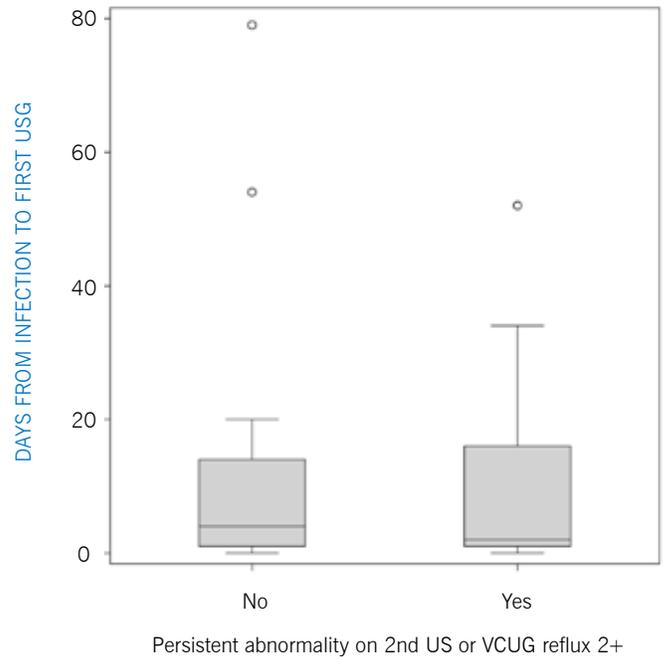


Figure. Boxplot showing no difference in kidneys with persistent minor abnormality on repeat RBUS or grade II VUR versus those kidneys without persistent abnormalities in timing of initial RBUS. The lower and upper lines of the box indicate the 25th and 75th percentiles of the data, and the center line in the box indicates the median. The plots extend the range of the data up to 1.5 times the length of the box, and further outliers are represented by circles.

Eye Gaze-Based Autism Risk Index Shows Promise as First Objective Diagnostic Tool

By Thomas W. Frazier, PhD, and Sumit Parikh, MD

An old adage holds that the eyes are the window to the soul. But for children with suspected autism spectrum disorder (ASD), new research suggests that the eyes promise to be even more — the key to the first objective and quantitative tool for diagnosing ASD.

Cleveland Clinic recently developed an objective measure of autism symptom level — named the “autism risk index” (ARI) — based on remote eye gaze tracking to various stimuli. In April 2016, the team published a paper in the *Journal of the American Academy of Child and Adolescent Psychiatry* reporting results of initial and replication studies that showed the ARI to have high diagnostic accuracy in differentiating children with ASD from similar children with non-ASD developmental disorders. These findings suggest that the eye gaze-based ARI could prove to be a useful quantitative and objective measure of risk for ASD in at-risk settings.

Rationale and hypothesis

The Autism Center’s efforts to develop the ARI stemmed from the reality that current methods for diagnosing ASD — direct clinical observation, interviews and parent reports — are highly subjective. Spurred by the recognition that abnormal eye gaze and social attention patterns are core features of ASD and by recent

studies supporting the potential discriminative value of eye gaze tracking in ASD, the team hypothesized that children with ASD gaze longer at nonsocial targets and less at social targets relative to children with non-ASD disorders. So members set out to develop and replicate a measure of ASD symptom level based on eye gaze tracking to social and nonsocial visual stimuli.

The team opted to collect eye gaze data using remote eye tracking, a promising technology that avoids the use of the headgear or disruptive monitoring associated with other methods (such as EEG or MRI). Remote eye tracking is unobtrusive and akin to watching TV, with the eye tracker mounted to the frame of a 19-inch LCD monitor that presents visual stimuli to young subjects (see top image).

Study design

Two samples were evaluated from children ages 3 to 8 who had been referred for evaluation by their pediatricians and were later diagnosed, based on clinical consensus, as having either ASD or another (non-ASD) developmental disorder. (Consensus diagnosis was based on multidisciplinary evaluations that included administration of the Autism Diagnostic Observation Schedule [ADOS-2] and the Social Responsiveness Scale [SRS-2].)

Blinded researchers conducted the seven-minute evaluations at the LCD monitor, during which the eye tracker recorded how long children looked at prespecified regions of interest (ROIs) as they were presented with literature-based social stimuli (e.g., faces) and nonsocial stimuli (inanimate objects and geometric shapes) (Figure). Looking times were recorded for each prespecified ROI and averaged across ROIs to generate a composite risk index (i.e., the ARI). Area-under-the-curve (AUC) analyses evaluated classification accuracy relative to consensus clinical diagnoses for both the initial study (N = 45) and the replication study (N = 34).

Drs. Frazier and Parikh and colleagues hypothesized that children with ASD gaze longer at nonsocial targets and less at social targets relative to children with non-ASD disorders.



Researchers conduct eye-gaze tracking for each child, using an LCD monitor with a remote eye tracker.

ADVANTAGES OF THE AUTISM RISK INDEX

- › The index promises easier acceptance of an ASD diagnosis by parents wary of relying on clinical impressions alone.
- › Remote eye tracking is unobtrusive and well-suited to young children.
- › Assessment is rapid, can be largely automated, requires limited technical expertise and does not require ongoing verification of interrater reliability.
- › The technology is highly scalable, and hardware costs are likely to be modest.
- › The index can be easily used in conjunction with other clinical measures.

Key results

In both the initial and replication study samples, the ARI demonstrated high diagnostic accuracy, with AUC values for sensitivity versus specificity as follows:

- Initial sample, AUC = 0.91 (95% CI, 0.81-0.98)
- Replication sample, AUC = 0.85 (95% CI, 0.71-0.96)

The index dramatically outperformed the SRS-2 instrument in diagnostic accuracy and showed a strong correlation with ADOS-2 severity score ($r = 0.58$ and $r = 0.59$ for initial and replication samples; $P < .001$), which is the gold-standard measure of ASD symptom severity.

The team concluded that combining eye tracking measurements into a risk index has strong potential clinical value for objectively enhancing ASD diagnosis, grading symptom severity and even gauging symptom changes in response to treatment.

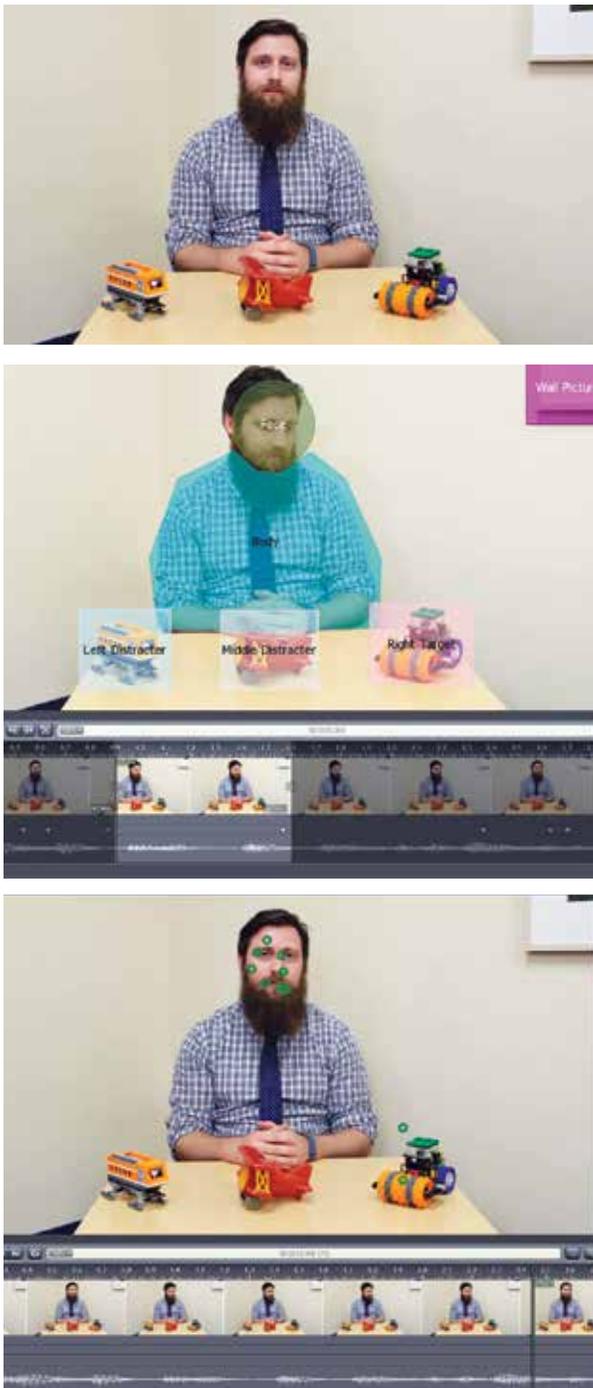


Figure. Example screenshots of some of the joint attention stimuli used in the replication study. Top image shows the stimulus alone; middle image shows the stimulus with temporal regions of interest designated; bottom image shows attention to the social regions of interest (green circles) in healthy controls. (Top two images reprinted from Frazier et al.¹ with permission from Elsevier.)

Next steps: More replication, refinement, commercialization

Before these findings can be turned into a clinical tool, the team needs to replicate the approach again in a larger sample. In this next step, fine-tuning the ARI algorithm to make it more accurate and sensitive to ASD is also planned. The original approach was conservative — i.e., all prespecified ROIs were included, regardless of direction and validity level — and it is expected that more sophisticated machine-learning methods can greatly enhance the ARI's accuracy.

After this replication, the final ARI will be taken and its performance will be examined across multiple sites in the U.S. to ensure that it performs as expected. The team will also begin collecting data from a larger sample of healthy children to see whether the ARI can be helpful not only for diagnosis but also for screening in general population settings. Simultaneously, steps will be taken in the commercialization process to move toward availability of an objective tool that clinicians can purchase and use to inform their judgment.

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Understanding the Prevalence of Systemic Disorders in Patients with Unilateral Congenital Cataracts

By Elias Traboulsi, MD

Congenital cataracts are present in 1.2 to 6 per 10,000 live births in the United States. They can affect one or both eyes and may occur in the setting of a systemic disorder. Because of a lack of data on the prevalence of systemic disorders in patients with unilateral congenital cataracts, the Infant Aphakia Treatment Study (IATS) provided an opportunity to examine this issue in a large number of consecutive cases.¹

This multicenter, randomized clinical trial compared the use of primary intraocular lens (IOL) implantation with spectacle correction of residual hyperopia to the correction of aphakia with a contact lens after cataract surgery in infants with a unilateral congenital cataract between 1 and 6 months of age. Infants considered for the study were scrutinized for the presence of systemic disease, and more than four years of follow-up data were available to ascertain the emergence of systemic diseases not present early in life.

Study design

Cleveland Clinic's team reviewed the records of all patients with unilateral cataracts who were identified for possible inclusion in the IATS and extracted information on associated systemic and ocular abnormalities. Infants < 7 months of age with a unilateral cataract were eligible for IATS screening. Researchers reviewed data pertaining to the exclusion of patients as well as data collected on standardized study forms used at any time for documentation of ocular or systemic disorders.

A total of 227 infants were referred for possible enrollment. Ten had insignificant cataracts, and parents of 32 declined participation. Of those excluded, three were premature, 27 had significant ocular disease [usually persistence of the fetal vasculature (PFV) or corneal diameter < 9mm], and four had systemic disorders. An additional 26 were excluded at first examination under anesthesia, most often because of PFV or variants thereof.

On follow-up, the 114 enrolled patients were diagnosed with Stickler syndrome (1), mitochondrial disease (1), autism (1) and presumed congenital rubella syndrome (1). No patient developed a cataract in the fellow eye.

Key findings

The team noted that while some conditions that can feature unilateral cataracts are diagnosed at birth or very early in life, others may be diagnosed at varying periods thereafter.²

PFV and its variants are the most common associated ocular findings and are present in about a quarter of cases of unilateral congenital cataracts, indicating that while patients with a unilateral cataract may have significant associated abnormalities in the affected eye, the prevalence of associated significant systemic disease is quite low.

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New Postoperative Regimen Improves Patient Experience in Pediatric Orthopaedic Surgery

Indwelling catheters safe and effective for at-home postoperative pediatric care

By Ryan C. Goodwin, MD

Management of postoperative pain has always been a priority in the care of orthopaedic surgical patients, perhaps even more so in the pediatric patient population. Patients' and parents' typical and significant anxiety makes an excellent postoperative pain plan essential.

Oral and intravenous narcotics have been the gold standard for managing postoperative pain, but pediatric dosing can be challenging. Providers tend to undertreat pain in order to prevent side effects and potential complications, including dependency. Side effects such as sedation, nausea and vomiting, and constipation are frequent with a narcotics-only approach.

Reducing side effects and length of stay with a multimodal approach

Cleveland Clinic's Center for Pediatric Orthopaedics and Spine Deformity (the Center) has adopted and is currently fine-tuning a multimodal approach to managing postoperative pain. With colleagues in the Department of Pediatric Anesthesiology, the team has developed pain management strategies that have significantly improved patients' postoperative subjective pain scores, reduced side effects from systemic narcotics and even decreased hospital stays in many cases.

Cleveland Clinic's multimodal and individualized approach has significantly improved patient experience with a reduction in postop pain and narcotics-related side effects without additional morbidity.

Indwelling catheters enhance management

Perhaps the most effective tool in the team's arsenal has been the nerve block with indwelling catheter. An established method in adults, these regional anesthetics are proving tremendously helpful for pediatric patients. They are administered either in the preop area or under anesthesia with ultrasound guidance, based on the comfort level of the patient. Either a single shot is given or an indwelling catheter placed, which the patient can use for up to five days in the outpatient setting. The group contacts the family daily to assess the patient's pain and answer questions if an indwelling catheter is in place. Patients discontinue the catheter on day five, or sooner if it is no longer needed.

The Center for Pediatric Orthopedics is actively studying the effectiveness of indwelling catheters in the control of postoperative pain and results are encouraging. Preliminary results are exceptionally promising, suggesting no deep infections or nerve injuries in the catheter group. Patients undergoing foot/ankle reconstruction are home the day of surgery in over 95 percent of cases. Patients undergoing femoral procedures such as osteotomies routinely leave the hospital after a 23-hour stay with a femoral nerve catheter (Figure), a significant improvement over the traditional hospitalization of two to three days.

Open knee procedures are now routinely outpatient with either type of nerve block, a single shot or femoral nerve catheter. Preliminary results suggest pain scores and narcotics consumption also decrease in both groups of patients. Patients typically embrace the concept of the catheter, and few have difficulty managing it at home, as it requires essentially no direct attention from the patient or family members.

Liposomal bupivacaine under study

The Center has also embraced and is currently studying weight-based use of liposomal bupivacaine. Early results within the team's scoliosis protocol suggest a benefit without additional



Figure. Femoral nerve catheter in pediatric patient.

side effects. The current scoliosis pain management protocol continues to work well, with average length of stay slightly over three days, largely attributable to the aggressive pain management protocol.

Overall, management of postoperative pain remains critically important in all orthopaedic surgery, especially in the care of children. Cleveland Clinic's multimodal and individualized approach has significantly improved patient experience with a reduction in postop pain and narcotics-related side effects without additional morbidity. Ongoing studies are quantifying the benefits of these invaluable techniques in the postoperative management of pediatric orthopaedic patients.

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Antibiotic-Induced Clostridium Difficile Infection: Combating Bacteria with Bacteria

By Gail Cresci, PhD, RD

Over half of hospitalized patients receive an antibiotic for at least one day. While lifesaving, antibiotics can also put patients at risk for further infections, such as Clostridium difficile infection (CDI). The overall incidence of CDI is rising in hospitals, long-term care facilities and the community, with cases increasing in complication severity, deaths and higher healthcare-associated costs. Amongst the pediatric population, the rate of asymptomatic CD colonization is increasing. CDI is both costly and debilitating, and risk factors include exposure to antibiotic therapy, hospitalization, gastrointestinal procedures and surgery.

While antibiotic treatment is the major risk factor for CD colonization, treatment of CDI also involves antibiotic therapy. Although most patients respond to treatment, CDI recurrence rates are 15 to 30 percent, with patients highly likely to have second and third recurrences. In children, reported CD recurrence rates are 20 to 24 percent and more commonly classified as community-associated,¹ with patients being younger (ages 3 to 10 years). To date, the best preventive measure for CDI is restricting inappropriate antibiotic usage.

In Cleveland Clinic's Pediatric Research Center, ongoing research focuses on the gut microbiota, centering on clinical situations in which gut dysbiosis occurs, with investigations targeting alterations in metabolic byproducts of the gut microbiota. The

A “healthy” gut microbiota supports epithelial cell health and nutrient metabolism and breakdown, and provides an indirect mucosal defense against pathogenic bacteria.

long-term goal is to develop therapies for optimizing the gut microbiota and its metabolic byproducts to prevent or treat disease.

Gut microbiota, butyrate and intestinal health

The human intestine houses trillions of commensal bacteria (gut microbiota) dominated by nearly 800 different species. According to 16S rRNA gene analysis, Bacteroidetes and Firmicutes are the two most abundant bacterial phyla in humans after about 3 years of age; the Firmicutes contain lactic acid and butyrate-producing bacteria. A “healthy” gut microbiota supports epithelial cell health and nutrient metabolism and breakdown, and provides an indirect mucosal defense against pathogenic bacteria.² The gut microbiota ferments nondigestible polysaccharides to yield short-chain fatty acids (SCFA); acetate, propionate and butyrate. Butyrate is the most dynamic SCFA and important for intestinal health. In addition to serving as the primary fuel source for colonocytes, butyrate maintains gut integrity and modulates inflammation and immune function. Without butyrate, intestinal tissue is vulnerable to apoptosis, inflammation, mucosal atrophy and colonic pathology.³

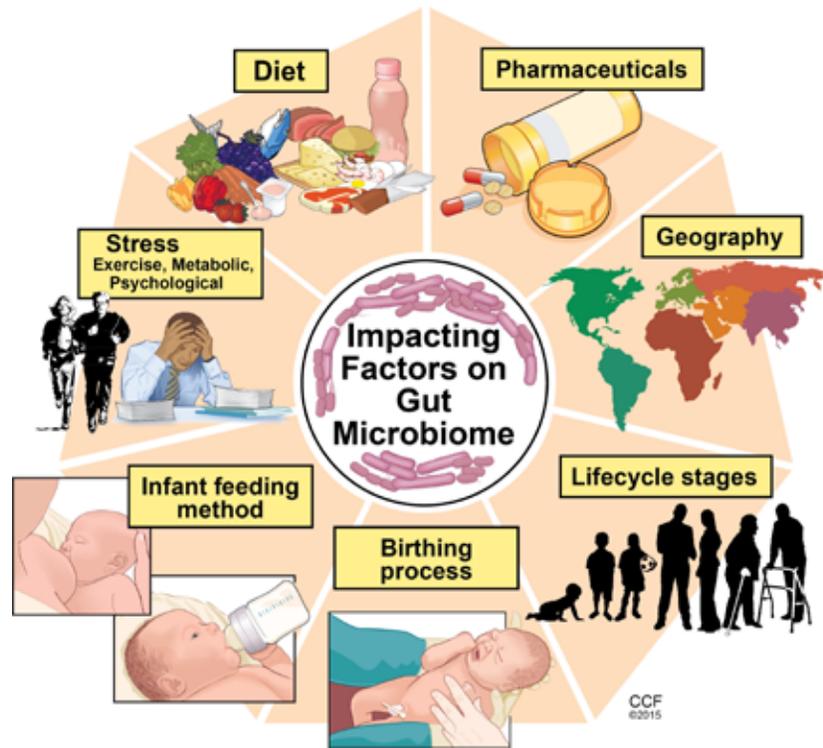
Pediatrics and gut microbiota

Initial intestinal colonization is influenced by various factors including infant mode of delivery and feeding method.² Both formula-feeding and cesarean delivery are risk factors for carriage of CD,² with the rate of CD colonization lower among breast-fed infants at six weeks (21 percent vs. 47 percent) and six months (19 percent vs. 39 percent).^{1,6} Infants born by C-section compared with those vaginally delivered are twice as likely at the age of 4 weeks to be colonized with CD.⁴

Antibiotics, butyrate and intestinal protection

Antibiotic therapy is one of many causes of gut dysbiosis (Figure 1), depleting commensal butyrate-producing bacteria, resulting in reduced luminal butyrate levels. Data from mouse models of broad-spectrum antibiotic therapy reveal butyrate delivery, in

Figure 1. Factors impacting the gut microbiome



the form of the structured lipid tributyrin, provides intestinal protection of tight junction proteins and an anion exchanger (NEH3) (Figure 2).⁵

Antibiotic-induced gut dysbiosis creates an environment supporting CD germination and growth. Commensal Clostridia play an important role in the metabolic welfare of colonocytes by releasing butyrate as a fermentation end-product. A recent study analyzed the gut microbiome of patients with CDI, categorizing the patients as responders or nonresponders to initial therapy.⁶ Butyrate-producing bacteria were identified in responders and absent from nonresponders.

Counteracting pathogenic bacteria with probiotics, not antibiotics

Multiple probiotics have been tested as a possible means to prevent and/or treat CDI, with limited effectiveness likely due to an untargeted approach. A synbiotic is a physical combination of a probiotic and a prebiotic. A designer synbiotic aims to target a specific bacteria species and/or its metabolic byproducts. The

group has investigated the role of a butyrate-yielding synbiotic in protecting mice during CDI. Preliminary in vivo data reveal that compared with saline, a butyrate-yielding synbiotic provided during three days of clindamycin exposure followed by a single CD spore challenge allows for early immune responses that are rapidly resolved (Figure 3A) as well as protection of gut integrity (Figure 3B).

Future directions

Pediatric patients with recurrence tend to receive additional antibiotics for non-CDI indications during their course for the initial episode of CDI. Research findings collectively show the SCFA butyrate is important for maintaining intestinal health during a single exposure to antibiotics. As a large number of patients receive multiple antibiotics, often requiring several antibiotic courses, finding a preventive treatment for recurrent CDI during antibiotic therapy would eliminate much of the health and economic burden and improve patient quality of life. Future research will be focused on developing a pediatric recurrent mouse model that can be tested for future therapies against CDI.

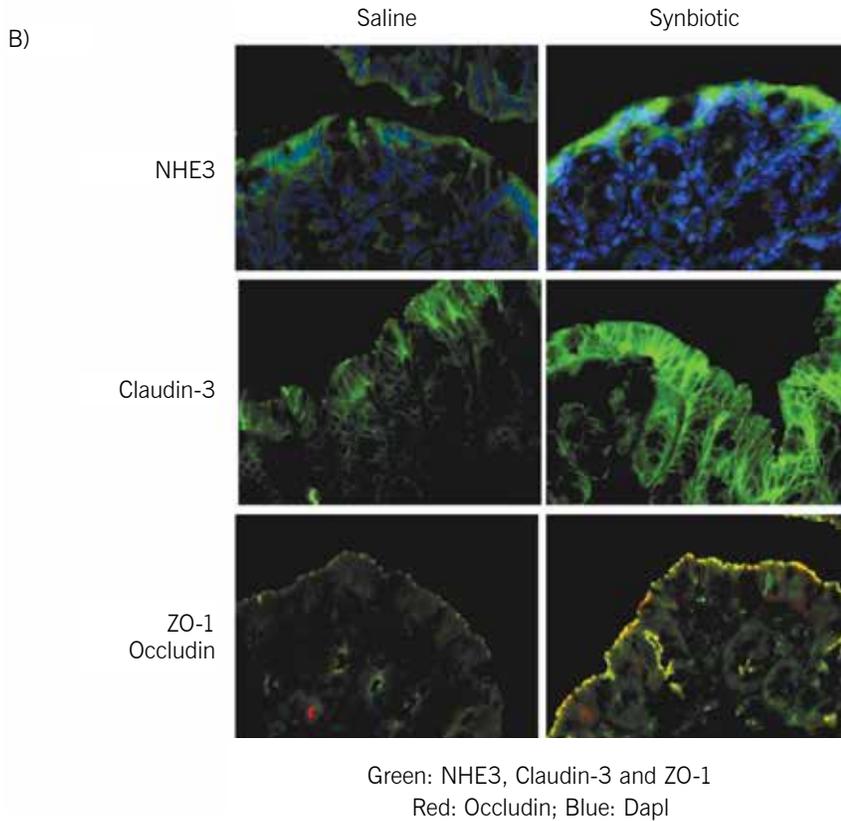
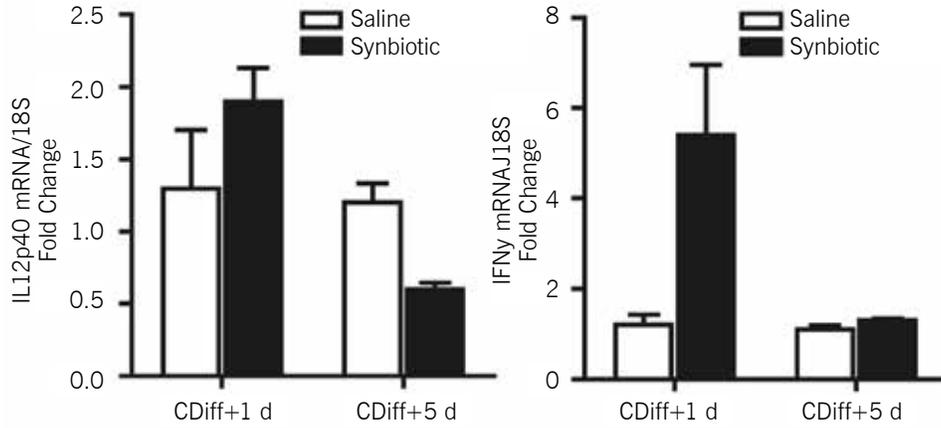


Figure 3. Butyrate-yielding synbiotic optimizes immune responses and gut integrity following antibiotic and *C. difficile* challenge. NSA mice exposed to clindamycin (IP, 15 mg/mL) for three days then oral spores of VA17 (104 CFU) four days later were cotreated with saline or synbiotic orally. Mice were allowed free access to water and chow food. Mice were euthanized one or five days after CD challenge. Proximal colon was dissected for histology. (A) mRNA expression of 1L12p40 and IFN γ ; (B) NHE3, claudin-3, ZO-1, occludin localization in proximal colon by IHC. Image representative of three to five mice per group.

Preventing Suicide in Youths

By Tatiana Falcone, MD; Migle Staniskyte, BA; and Jane Timmons-Mitchell, PhD

Suicidal ideation (SI) and suicide attempts (SAs) are frequent in adolescents. Among American teens, 22 percent had seriously considered suicide in the past year, 15 percent had made a plan and 8 percent reported that they had attempted suicide. Suicide remains the most serious complication of any psychiatric disorder and is the second leading cause of death in youths.

Lifetime prevalence of SA peaks between 16 and 18 years of age. Every year, approximately 157,000 youths receive medical care for suicide-related injuries at emergency departments (EDs) throughout the U.S. According to the Healthcare Cost and Utilization Project, a study surveying data from 1,045 hospitals in 46 states (97 percent of the U.S. population), there was a substantial increase in inpatient visits for SA and SI in children from 2006 to 2011, accounting for 104 percent and 151 percent increases, respectively, for children aged 1 to 17 and 10 to 14. In 2006, 12,184 children were admitted for SI, and that number increased to 59,000 in 2011 — a 252 percent increase in the national average.

Prevention research

The objective of the team's ongoing research is to identify the risk factors for suicide in adolescents consulting to the ED or an inpatient psychiatric unit to assess: (a) what differentiates those who return within a year for another suicide complaint; and (b) describe differences among those with repeated ED admissions between youth with SI and SA.

Of 1,200 adolescent patients who came to any of Cleveland Clinic Health System's 13 EDs with suicide-related complaints in 2013, 320 patients returned in the next three months for SI or related behavior. Researchers reviewed the electronic health records of 176 of those patients, who ultimately constituted our sample. Among these, 97 youths did not return for a suicide complaint during the year (nonrepeaters), and 79 did return for a suicide complaint (repeaters).

Patients were predominantly male (69 percent) and Caucasian (57 percent). Ages ranged from 6 to 17 years, with an overall mean of 14.21 years (SD = 1.99). Groups were equivalent on gender, race/ethnicity and age, with no significant differences between repeaters and nonrepeaters or between those with SAs and those

with SIs. For ED encounters and inpatient admissions, repeaters had a significantly higher number than nonrepeaters; SAs and SIs did not differ across these variables. Patients with SAs were significantly more likely to be repeaters than those with SIs using a one-sided Fisher's exact test ($P = .042$). Among repeaters, patients with SAs reported a greater degree of emotional and sexual abuse than those with SIs.

Repeaters were significantly more likely to present with an SA complaint while nonrepeaters were more likely to present with an SI complaint (Table 1). Among repeaters, patients with SAs were significantly more likely to report both sexual and emotional abuse than those with SIs (Table 2).

Promoting access to stop suicide (Project PASS)

There is an important gap in services for SA survivors after discharge. Mental health services are often not securely in place, and a first appointment can take several weeks to arrange. Caregivers frequently express their frustration regarding their inability to access mental health services sooner; many suicidal youths do not receive outpatient mental healthcare because of limited access. With the hope of improving the care that is provided to this high-risk youth population, the team has designed Project PASS.

After an SA, enhancing effective access to mental health services in the first week after discharge may decrease the risk of a second attempt.

The aims of this project include: (1) to decrease the number of repeat suicide attempts in adolescents; (2) to decrease the number of readmissions after a suicide attempt in adolescents; (3) to implement a new care model and compare the effectiveness of three services.

Participants will be randomly assigned to one of the three treatment arms: (1) enhanced treatment as usual*; (2) enhanced treatment as usual plus crisis intervention; (3) enhanced treatment as usual plus crisis intervention as well as wraparound services (intensive individualized care).

Table 1. Difference Between Repeaters and Nonrepeaters

| | Suicide Attempt | Suicide Ideation |
|-------------|-----------------|------------------|
| | (N = 52) | (N = 110) |
| Repeater | 59.6 | 43.6* |
| Nonrepeater | 40.4 | 56.4 |

* P < .05; Significance based on Fishers Exact one-sided.

Table 2. Influence of Abuse on Repeaters

| | Repeaters (N = 79) | |
|-----------------|--------------------|--------------------|
| | Suicide Attempt | Suicide Ideation |
| | (N = 31) | (N = 48) |
| Emotional Abuse | 79.2 ^a | 47.6 ^{b*} |
| Sexual Abuse | 50.0 ^c | 20.5 ^{d*} |

Note. ^a based on 24 cases. ^b based on 42 cases. ^c based on 22 cases. ^d based on 39 cases. * P < .05; Significance based on chi-square comparisons.

Figure 1.



Project PASS will be providing services to high-risk youths in Ohio. Moreover, the project is conducting a study that can measure improvement in young people at high risk for suicide. The randomized controlled trial, for youths discharged from an inpatient psychiatric hospital, will be able to determine what combination of services is most likely to prevent subsequent SAs and rehospitalization. In the four-year duration of this study, recruiting at least 135 participants is expected.

Advancing Strategies for Youth Suicide Prevention is a collaborative research study between Case Western Reserve University, Ohio Suicide Prevention Foundation and Cleveland Clinic. The Substance Abuse and Mental Health Services Administration is funding this collaboration (SM62894-01).

*Enhanced treatment as usual refers to 10 positive personalized postcards (Figure) the participants will receive throughout the 12-month study, beginning after their recruitment to the study.

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Nutrition in Pregnancy Affects Metabolic and Respiratory Outcomes in Offspring

By Giovanni Piedimonte, MD

The prevalence of both obesity (17 percent) and asthma (9.6 percent) in children continues to rise in the United States.¹ While pathophysiologic links between obesity and asthma have been proposed, such linkage remains controversial.²

Nutrition's role in the asthma-obesity link

Cleveland Clinic Children's investigators previously demonstrated in a study of 18,000 school-age children that those with asthma tend to have higher serum triglyceride levels and higher rates of insulin resistance, regardless of body mass.³ This finding brought forth a potentially game-changing idea: Early abnormalities of lipid and glucose metabolism may be associated with the development of asthma, confounding asthma's epidemiologic link to obesity.

Building on this population-based correlation, the research team subsequently undertook an animal study to determine whether maternal nutrition in pregnancy affects postnatal metabolic and respiratory outcomes in offspring. The study, recently published in *Pediatric Research*⁴ and funded in part by a grant from the National Institutes of Health, was fueled by the likelihood that both obesity and asthma begin in utero and in early childhood. Therefore, nutritional factors — especially prenatal and early infant diet — may play a role in the pathogenesis of both conditions.

Enormous resources are currently spent on treating the manifestation of diseases, yet the only way to stop them efficiently is to deal with them at the source.

In this follow-on study, the team sought to determine whether fetal exposure to a maternal high-fat hypercaloric diet (HFD) — even in the absence of maternal obesity prior to pregnancy — could result in a predisposition to pathological airway responses to environmental challenges.

Study highlights

Using a rat strain without a genetic predisposition to obesity, researchers fed dams an HFD or a control diet (CD) during pregnancy and lactation. We compared the offspring in terms of:

- Metabolic profiles
- Inflammatory status
- Neurotrophic pathways
- Lung function in early versus adult life

The offspring of the HFD and CD dams also were exposed to the most common respiratory pathogen in infancy, respiratory syncytial virus (RSV), to evaluate the interactions between maternal and environmental factors on postnatal lung function.

Findings included the following:

- Pups born from HFD dams developed metabolic abnormalities that persisted throughout development.
- Cytokine expression analysis of lung tissues from newborns born to HFD dams revealed a strong proinflammatory pattern.
- Gene expression of neurotrophic factors and receptors was upregulated in lungs of weanlings born to HFD dams.
- HFD dams delivered pups that were prone to develop more severe RSV following infection.

Based on these findings, the team concluded that maternal nutrition in pregnancy is a critical determinant of airway inflammation and hyperreactivity in offspring.

Take-home points

This study demonstrated that changing to an HFD in a normal-weight dam during gestation leads to offspring with abnormal

metabolic profiles, chronic airway inflammation and increased susceptibility to RSV infection. Pups born to mothers fed an HFD during pregnancy had hypertriglyceridemia and increased body fat without a corresponding change in body weight.

One of the most important findings of this study is that increased availability of nutrients to the placenta was associated with airway inflammation and hyperreactivity during development.

Because this was an animal study, researchers were able to analyze the lung mechanics without obesity as a mechanical confounder, which confirmed the previously described population-based association of abnormal pulmonary function with elevated triglycerides.³

This study did have limitations, including the fact that the team did not investigate variables related to maternal metabolism, such as gestational weight gain. In addition, since the dams were on the HFD prior to delivery for only about three weeks, a diet that would be considered extreme for humans had to be used.

Clinical implications: Early interventions look more compelling

In this study, the team developed a new model of airway inflammation and hyperreactivity induced by prenatal dietary imbalance. While this same model cannot be ethically achieved in clinical research, the clinical implications are clear, especially in light of the previous population-based study.³ A greater focus on the diet and metabolic health of pregnant women could have a significant impact on the global epidemics of childhood obesity and asthma — more so than other, more expensive postnatal prevention strategies or therapies.

When considered with the team's earlier population-based study in school-age children,³ the results of this animal study clearly suggest that public health interventions must occur as early in life as possible — especially in pregnant women and young children. Enormous resources are currently spent on treating the manifestation of diseases, yet the only way to stop them efficiently is to deal with them at the source. The consequences of a mother's health — including nutrition — during pregnancy are not only

important, but long-lasting.

At Cleveland Clinic, two programs focus on early nutritional and other health interventions that could serve as models for other centers. The Healthy Expectations program gives women the support and information they need to optimize their weight and health before and during pregnancy, as well as after delivery. And Cleveland Clinic Children's Be Well Kids Clinic brings together a comprehensive team of clinicians and researchers with expertise in childhood weight management to help children and families develop strategies and create plans for healthy lifestyle changes.

Our continuing research will focus on maternal and early-life nutrition as well as additional studies predicated on the notion that indoor and outdoor pollution (e.g., tobacco smoke, fine particles), bacterial or viral infections, psychological or physical traumas, or anything else a mother encounters in the environment during gestation can affect the well-being of a fetus or child and also have long-term health consequences in adulthood.

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The Evolution of Radiology into a Remote Practice: Why Do Some Referring Providers Continue to Value Interaction?

By Brooke Lampl, DO, and Elaine Schulte, MD, MPH

Radiology has increasingly become an electronic and remote practice, with radiologists reviewing images from patients located hours or even states away. Although this remote practice allows for subspecialization and increased coverage, it can erode the traditional interaction between radiologists and referring providers and consequently decrease the perceived value of radiologists in terms of patient care.

Some referring providers continue to make every effort to maintain contact, either by electronic means, phone calls or visits to the reading room. In addition, pediatric radiologists, in particular, value the physician-physician interaction that is often noted as a key factor for selecting the pediatric subspecialty over other areas of radiologic subspecialization.¹

A survey of pediatric practitioners was conducted to determine what inspires them to seek out interactions with pediatric radiologists even when they have remote access to images, and published the results in the *Journal of the American College of Radiology*.²

Survey of pediatric faculty

An anonymous, voluntary, nine-question multiple-choice survey was created and sent to pediatric practitioners within Cleveland

The most frequent reasons respondents gave for choosing not to visit the reading room included distance (40 percent) and insufficient time (27 percent).

Clinic Children's. The survey asked respondents for information about their demographics, number of visits to the reading room, reasons and preferences regarding visits, and comfort level with independent review of images.

Of the 320 pediatric general practitioners and specialists surveyed, 93 (29 percent) responded. Specialists were the most frequent visitors to the reading room (47 percent). Among the respondents, 24 percent were most likely to consult the radiologist for a complex case, 18 percent were inclined to visit because of a positive previous experience and 16 percent went to the reading room to clarify an ambiguous statement in a report. The most frequent reasons given by responders for why they chose not to visit the reading room included distance (40 percent) and insufficient time (27 percent). Forty percent said that they would visit the reading room more frequently if the radiologist was in their clinical workspace.

Radiologist-referring provider interactions

The evolution of radiology into an increasingly electronic field allows for improved subspecialty coverage and patient convenience, with radiologists reading films from varied locales. This change, however, greatly affects the referring provider-radiologist relationship and the perceived value of radiologists. When films were read as hard copy on an alternator with a typewritten dictation in a paper chart, the referring provider often came to the reading room to discuss the case and see the image, which fostered good relations and added to patient care. With the loss of this required interaction, physicians often only enter the reading room on an as-needed basis, either to discuss a challenging case or to ask a specific question. In a survey of radiologists choosing to subspecialize in pediatric radiology, a key reason included physician-physician interaction.

Pediatric radiologists are part of a team of providers and have been trained to participate in not only the diagnosis of pediatric



disease but also the treatment. With increased communication, pediatric radiologists can add value and substance to the referring providers' care. It is imperative that these interactions are developed and nurtured, not only to ensure the well-being of the patient, but also to maintain radiologists' role in patient care.

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Associations Between Short-Term Pollution Exposures and Childhood Autoimmune Diseases

By Andrew S. Zeff, MD, MPH

Autoimmune diseases are an understudied area in the field of pollution-related health effects research. By examining representative childhood autoimmune diseases, Cleveland Clinic Children's pediatric rheumatologists hope to further understand the effects of acute, short-term pollution exposures on the clinical presentation of autoimmune diseases.

What triggers the clinical onset and exacerbation of autoimmune diseases? The trigger may be driven by certain environmental exposures that precipitate immune activation in genetically susceptible individuals. In fact, twin studies indicate that environmental factors play a significant role in disease development.

Testing short-term ambient fine particulate matter exposures

One hypothesis is that short-term pollution exposures that stimulate pulmonary-mediated, systemic inflammation trigger the clinical presentation of pro-inflammatory autoimmune diseases. This idea is testable, since the Environmental Protection Agency coordinates pollution-monitoring sites in and around urban areas throughout the United States.

Particulate matter concentration measurements from the monitors can be spatially modeled (correlated), and when climatic data from the National Weather Service are factored in, day-to-day particulate matter can be used as an exposure measurement for environmental epidemiology study. Fine particulate matter (diameter ≤ 2.5 μm , PM_{2.5}) is a measurable component of ambient pollution.

With a three-year grant from the EPA, the research team examined whether short-term ambient fine particulate matter exposures are associated with the clinical presentation of two childhood autoimmune diseases; systemic-onset juvenile idiopathic arthritis (SJIA) and Kawasaki disease (KD).

These diseases typically have an acute presentation, so they are ideal for a time-series (temporally dependent) case-crossover epidemiologic study design. Cases have been identified in different metropolitan regions of North America where ambient particulate matter is a significant public health concern.

The team previously examined the effect of short-term ambient fine particulate matter on the clinical presentation of JIA in a regional cohort with Brigham Young University research collaborator, C. Arden Pope III, PhD.¹ Researchers demonstrated that short-term ambient fine particulate matter may influence the presentation of JIA in young children, particularly those having the systemic-onset subtype.

A look at study findings for SJIA

In this current study, a case-crossover study design was used to analyze associations of short-term PM_{2.5} exposures with the clinical event of SJIA symptom onset in children residing in five metropolitan regions.

Time trends, seasonality, month and weekday were controlled for by matching. Selected exposure windows (to 14 days) of PM_{2.5} were examined. Positive, statistically significant associations between PM_{2.5} concentrations and elevated risk of SJIA were not observed. The most positive associations between short-term PM_{2.5} exposure and SJIA were in children < 5.5 years (RR 1.75, 95% CI, 0.85-3.62). However, an ad hoc extended pooled analysis including previously reported cases from Utah's metropolitan areas identified an increased risk of SJIA for children < 5.5 years (RR = 1.76, 95% CI, 1.07-2.89 per 10 $\mu\text{g}/\text{m}^3$ increase in 3-day lagged moving average PM_{2.5}). Small, statistically insignificant PM_{2.5}-SJIA associations were observed in this multicity, multiperiod study. However, as found in a prior study, the PM_{2.5}-SJIA association is most suggestive in preschool-aged children. Larger numbers of SJIA cases spatially located in geographic areas that experience a greater day-to-day ambient particulate burden may be required by the analysis to demonstrate effects.

Conclusions further understanding of KD

The study's second objective was to analyze associations between short-term fine particulate matter exposures (PM_{2.5}) and the event date of fever onset in KD cases in seven metropolitan regions. A case-crossover study design was used. Time trends, seasonality, month and weekday were controlled for by matching. Researchers assembled PM_{2.5} exposure measurements from urban monitors

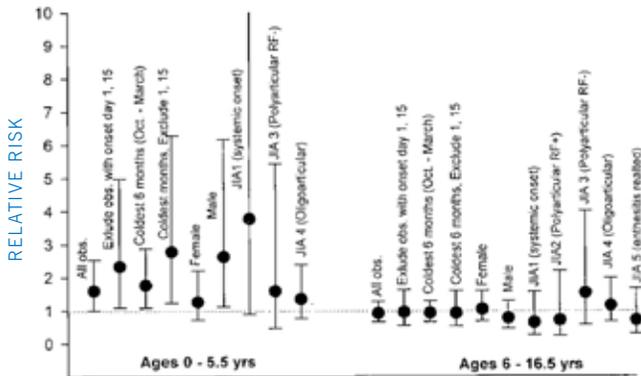


Figure 1. Relative risks (and 95% CIs) of an onset event of JIA associated with a 10µg/m3 of PM2.5 for ages 0–5.5 and 6–16.5 and for selected subgroups.

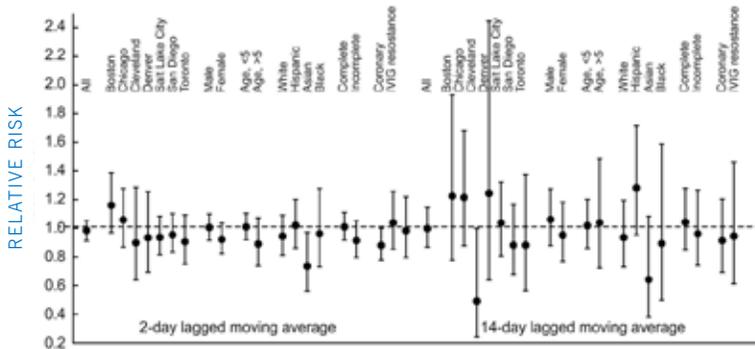


Figure 2. ORs (and 95% CIs) of onset event of KD associated with 10 mg/m3 PM2.5 stratified by city, sex, age, race, and disease attributes with central monitor data plus imputed data from nearby sites. Coronary, presence of coronary aneurysm ≥8 mm; IVIG resistance, received repeat IVIG dose.

and imputed PM2.5 to provide day-to-day temporal variability and resolution for a time-series index of exposures. Selected exposure windows (to 14 days) of PM2.5 were examined. The data included 3,009 KD events in which the subjects resided in a study metropolitan area and the event date occurred during years with available PM2.5. The estimated odds ratios (95% CIs) of an event of KD associated with a 10 µg/m³ PM2.5 lagged moving average concentration of lagged exposure period [concurrent, preceding day(s)] revealed no evidence of a consistent, statistically significant, positive association between elevated PM2.5 exposure and elevated risk of KD.

Extended analysis with stratification by city, sex, age, ethnic origin, incomplete or complete clinical manifestations, the presence of coronary aneurysms and IVIG resistance did not provide evidence of a consistent, statistically significant, positive association between elevated exposure to PM2.5 and elevated risk of KD for any of the strata.

The results of this relatively large, multicity study failed to

establish a risk of the event of KD with short-term fine particulate exposure. The negative findings add to the growing field of environmental epidemiology research of KD.

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Renal Transplantation Occurring Later Among Patients with Congenital Urinary Tract Disorders

By Hadley Wood, MD; David Goldfarb, MD; Herman S. Bagga, MD; Songhua Lin; Alun Williams; and Jesse Schold, PhD

Kidney transplantation remains the gold standard for treating children with end-stage renal disease (ESRD), providing a known survival advantage compared with dialysis management.

Congenital disorders, such as anomalies of the upper and lower urinary tract and hereditary nephropathies, are disproportionately responsible for the development of chronic kidney disease (CKD) in children. In the United States, approximately 60 percent of pediatric CKD is attributed to such congenital disorders.¹

The team hypothesized that advancements in the management of patients with congenital urinary tract disorders may slow renal demise and result in delayed renal transplant among these patients. Furthermore, such advances could translate into improved renal transplant graft and patient survival.

Evaluating transplant recipient data

The hypothesis was tested using the Scientific Registry of Transplant Recipients (SRTR) database of transplant statistics collected by the Organ Procurement and Transplantation Network, which is a collection of hospitals and organ procurement organizations across the United States. Since 1987, the SRTR has maintained comprehensive information on all solid organ transplants in the country, and includes current and past information on the full spectrum of transplant activity. Data include information on organ donors, candidates and recipients, as well as organ-specific and patient outcomes.

The SRTR was queried to identify first renal transplant and graft and patient survival data within congenital uropathy (CU) and patients with congenital pediatric kidney disease (CPKD) between 1996 and 2012.²

Those in the CPKD group were substantially older at age of first transplant than were those with CU, resulting in differences between the two groups in renal transplant donor and recipient variables. On age-matched comparison, most variables were not significantly different between the two groups, including cognitive ability, body mass index and rates of diabetes across all age groups. A notable exception was hypertension. Among those 35 to 49 years old, individuals with CPKD had higher rates

of hypertension compared with CU patients (72 percent vs. 81 percent, $P < 0.0001$). Among those 12 to 17 years old, those with CU had higher rates of hypertension compared with CPKD patients (46 percent vs. 40 percent, $P = 0.018$).

Trend toward later age at first transplant

The average age of first transplant did not significantly change during the study interval (Figure 1). However, analysis of individual age groups reveals several significant trends (Figures 2 and 3).

When considering graft survival (Figure 4) at 5 years, both groups demonstrated approximately 90 percent survival; however, at 10-year follow-up, CU patients had better graft survival than did CPKD patients (80.7 percent vs. 75.9 percent, $P < 0.001$). When considering patient survival after renal transplant, the groups again had similar survival at 5 years (93.2 percent for CU patients vs. 95 percent for CPKD patients, $P > 0.05$). Correspondingly, at 10 years, CU patients had significantly better patient survival than did CPKD patients (82.3 percent vs. 77 percent, $P < 0.001$). When comparing CU and CPKD patients within age groups, however, graft and patient survival differences were not significant.

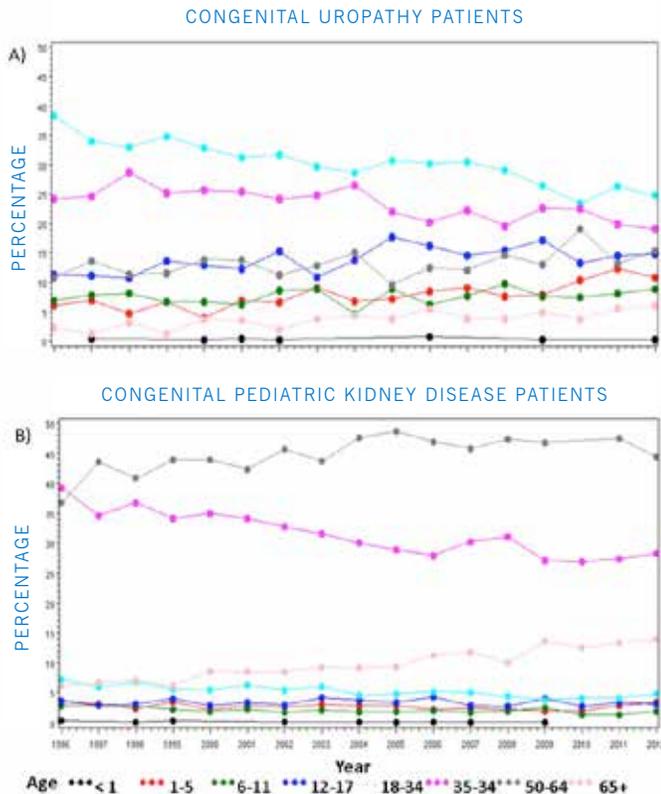
This study demonstrates that patients with congenital uropathies and nephropathies indeed trended toward later age at first transplant during the 14-year period that was examined in the SRTR database. Furthermore, after matching CU and CPKD patients for age, the team demonstrated equivalent 10-year graft survival between the two groups.

What's behind the improved outcomes?

Researchers postulate that these findings can be explained by one or more of the following changes during the study period:

- Improved prenatal screening and care
- Improved early nephrological intervention and care for afflicted patients
- Improved donor and recipient selection
- Improved post-transplant medical care and surveillance

Figure 1. Age at first renal transplant as a percentage of all renal transplants over time among (A) congenital uropathy and (B) congenital pediatric kidney disease patients.

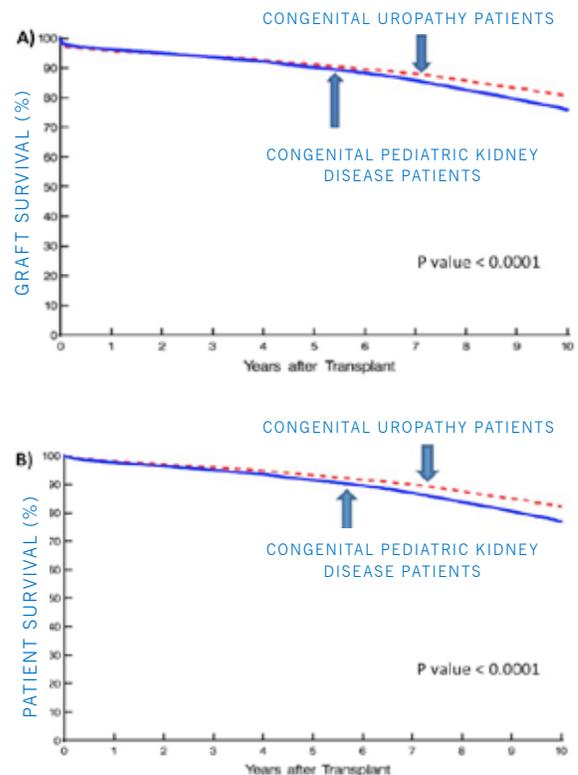


Among patients with CPKD, subsequent management strategies include appropriate hypertension management, hormone supplementation, protein replacement, nutritional supplementation and, when appropriate, medical therapies such as steroid or immunosuppressive agents. Care for patients with CU such as those with posterior urethral valves, prune belly syndrome, congenital neuropathic bladders, obstructive megaureters and significant ureteral reflux includes appropriate use of anticholinergics, intermittent catheterization, antibiotics and appropriate surgical intervention.

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Figure 2. (A) Graft and (B) Patient survival after renal transplant by group over time.



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300+
pediatricians,
practitioners
& specialists

- 2
adolescent
medicine

- 8
allergy and
immunology

- 15
anesthesiology

- 3
autism

- 22
behavioral health

- 1
brain tumor and
neuro-oncology

- 16
cardiology

- 3
cardiothoracic
surgery

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critical care medicine

- 4
dermatology

- 5
developmental
pediatrics/physical
medicine and
rehabilitation

- 6
endocrinology

- 10
epilepsy

- 13
gastroenterology

- 6
genetics

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gynecology
(pediatric and
adolescent, 14+)

- 16
hematology, oncology
and blood & marrow
transplantation

- 36
hospital medicine

- 4
infectious disease

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integrative medicine

- 14
neonatology

- 5
nephrology

- 8
neurology

- 2
neuropsychology

- 5
neurosurgery

- 9
ophthalmology

- 6
orthopaedic surgery

- 4
otolaryngology

- 7
palliative medicine

- 4
plastic surgery

- 100
primary care pediatrics

- 12
psychiatry/psychology

- 8
pulmonary medicine

- 3
radiation oncology

- 9
radiology and
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- 4
rheumatology

- 3
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- 22
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- 6
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beds

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