

Bench to Bedside



RESEARCH AT THE CHILDREN'S HOSPITAL OF PHILADELPHIA

November 2012

“Simple Reminders” Can Reduce Inappropriate Prescriptions

A new study by The Children's Hospital of Philadelphia researchers has found that reminding clinicians of prescription guidelines, as well as providing them with feedback about their own habits, can significantly improve antibiotic prescribing.

Jeffrey Gerber, M.D., Ph.D., an assistant professor of Pediatrics in the Division of Infectious Diseases, presented his study of antibiotic prescribing practices at the recent **IDWeek** conference, which was held in San Diego, Calif. Dr. Gerber's abstract was named one of the four best presented at IDWeek, a joint meeting of the Infectious Diseases Society of America (IDSA), the Society for Healthcare Epidemiology of America, HIV Medicine Association, and the Pediatric Infectious Diseases Society.

The study — of which Dr. Gerber was co-principal investigator, along with **Theoklis Zaoutis, M.D., M.S.C.E.**, associate director of the Center for Pediatric Clinical Effectiveness Research — examined the prescribing habits of clinicians from across CHOP's network of urban, suburban, and rural primary care practices. In addition to Drs. Gerber and Zaoutis, CHOP investigators **Ron Keren, M.D., M.P.H.**, **Alex Fiks, M.D., M.S.C.E.**, **Louis Bell, M.D.**, and **Robert Grundmeier, M.D.**, contributed to the study.

Roughly half of antibiotics are prescribed unnecessarily, Dr. Gerber noted. Overuse of antibiotics can lead to a number of negative outcomes, including an increase in healthcare costs, adverse events such as diarrhea, and bacterial resistance.

The study was conducted over 32 months, a period comprising approximately 1.4 million visits by more than 185,000 patients. The researchers split the 140 clinicians who took part in the study into two groups, a control arm

and an intervention arm. While the control group was only told of the study's existence, each practice in the intervention group received a one-hour in-office presentation of IDSA and American Academy of Pediatrics prescription guidelines followed by periodic updates on their prescribing practices relative to these guidelines.

Drs. Gerber and Zaoutis found that, before any of the interventions, roughly 28 percent of patients were prescribed off-guideline antibiotics. However, after either informing clinicians that they were being studied or actively intervening, the researchers saw that number decrease. Those clinicians who received the regular updates and the refresher cut their off-guideline prescriptions to 14 percent, while the control group's number went down to 23 percent.

The impact on the intervention group “shows that getting people up to speed and providing simple reminders are helpful,” Dr. Gerber said, adding that the study “also shows that you can leverage electronic health records to put together a relatively low-maintenance system to improve prescribing.”

Going forward, Dr. Gerber and his colleagues plan to continue collecting data to determine whether the reduction in off-label prescriptions is sustainable. The researchers will also gather feedback from physicians “to see what's driving antibiotic prescribing,” Dr. Gerber said.

“We need to know what the important piece of our intervention was, whether the education or the feedback reports,” Gerber said. “What we're ultimately hoping is that by improving adherence to prescribing guidelines, we changed the level of treatment success while reducing unnecessary exposure to broad-spectrum antibiotics.”

ADHD Survey Helps Improve Treatment Outcomes

Researchers at The Children’s Hospital of Philadelphia Research Institute have developed a groundbreaking new tool to help parents and health care providers treat attention deficit-hyperactivity disorder (ADHD). The tool — an in-depth, three-part survey — helps steer families and doctors toward “shared decision-making” (SDM), an approach proven to improve healthcare results in adults, but not yet widely used in pediatric settings.

The study results were recently published in *Academic Pediatrics*.

“Shared decision-making in health care means that doctors and families make decisions together. Doctors contribute their professional knowledge, and families weigh their values and personal experience,” explained lead author **Alexander Fiks, M.D., M.S.C.E.**, an urban primary care pediatrician at CHOP and a **PolicyLab** faculty member.

“We chose to focus on ADHD for this study, because it is a relatively common diagnosis with two recommended treatment options — prescription medication and behavioral therapy — that require the family to make decisions about what will work best for them. Choosing a treatment that doesn’t ‘fit’ can lead to unsuccessful results. We wanted to see if we could create a tool to help guide families and physicians through this process,” Dr. Fiks noted.

According to another **study** published earlier this year, the number of physician outpatient visits in which ADHD was diagnosed in children under age 18 was 10.4 million. Psychostimulants were used in 87 percent of treatments prescribed during those visits.

The CHOP study involved 237 parents of children aged 6-12 who were diagnosed with ADHD within the past 18 months. Using a combination of parent interviews, current research, and input from parent advocates and professional experts, researchers developed a standardized questionnaire to help parents define and prioritize their goals for treatment, attitudes toward medication, and comfort with behavioral therapies. The completed survey serves as a guide to support families and health care providers to reach the most effective and workable treatment for a child’s ADHD.

“It’s important to know whether a parent’s primary goal is to keep a child from getting in trouble at school, improve academic performance, or maintain more peace with family members or peers,” said Dr. Fiks. “We also need to learn about the family’s lifestyle and attitudes toward

behavioral therapy and medication. All of these factor into making the best treatment decision for each individual child and family.”

Pediatric care providers do not usually use SDM to gauge families’ preferences and treatment goals for ADHD. The Institute of Medicine and the American Academy of Pediatrics recommend healthcare providers use SDM to help families select the best treatment option for ADHD, and a well-designed questionnaire may help both patient-families and providers to feel more satisfied with their child’s ADHD treatment. The researchers say this is a promising model for more widespread use to aid with treatment decisions for children with ADHD that in the future could be tailored for use with other medical conditions.

Until the approach is more widely adopted, Fiks and his colleagues recommend parents ask themselves a few questions to help get the most out of their office visit:

- What do you and your child want to achieve as a result of ADHD treatment? (Better behavior or better grades at school? More self-control at home? Less teasing by other kids?)
- Consider your attitudes and your family’s attitudes about medication and behavioral therapy, and why they may or may not be right for you. Write down any questions you have about these treatment options to help remind you during your appointment.

“For the pediatrician’s part, it is our responsibility to fully inform parents about their options for treating ADHD and to seek guidance from families about which options will best meet their treatment goals and be manageable for their lifestyle. Research shows that patients adhere much better to the treatment options that they are comfortable with and that are the most practical for them. We need to make sure we’re asking the right questions,” noted Dr. Fiks.

CHOP is among the first pediatric research institutions to explore how to adapt the philosophy of SDM to a pediatric setting and make it a standard of care. To learn more about PolicyLab’s work in this area, visit <http://policylab.us/index.php/research-and-policy/health-services-research.html>.

Mitochondrial Expert Dr. Douglas Wallace Receives Gruber Genetics Prize



The Children’s Hospital of Philadelphia’s **Douglas Wallace, Ph.D.**, received the **2012 Genetics Prize from the Gruber Foundation** on Nov. 9 at the annual meeting of the **American Society of Human Genetics (ASHG)**.

“The Children’s Hospital of Philadelphia Research Institute is privileged to number Douglas Wallace among our research leaders,” said **Philip R. Johnson, M.D.**, chief scientific officer of the CHOP Research Institute.

The Prize recognized Dr. Wallace’s outstanding career contributions in shaping how mitochondria, the “power plants” inside cells, affect

many different human diseases. As the director of CHOP’s Center for Mitochondrial and Epigenomic Medicine, Dr. Wallace continues to pursue research that shapes new approaches to disease treatments.

“Douglas Wallace’s contributions to our understanding of mitochondrial genetics have changed the way human and medical geneticists think about the role of mitochondria in human health and disease,” said Dr. Elizabeth Blackburn, chair of the Selection Advisory Board to the Prize.

At the award ceremony, Dr. Wallace was flanked by Patricia Gruber, co-founder of the Gruber Foundation, at left, and Dr. Mary-Claire King, president of the ASHG, at right.

To read more about this prize, click here: <http://bit.ly/LTfujy>.

Using CHOP Researcher's Tool, Study Links Genes to Cholesterol Levels

In the largest-ever genetic study of cholesterol and other blood lipids, an international consortium has identified 21 new gene variants associated with risks of heart disease and metabolic disorders. The findings expand the list of potential targets for drugs and other treatments for lipid-related cardiovascular disease, one of the world's leading causes of death and disability.

In its study, the International IBC Lipid Genetics Consortium used the Cardiochip, a gene analysis tool invented by **Brendan J. Keating, Ph.D.**, lead clinical data analyst at the **Center for Applied Genomics**. Since Dr. Keating created the Cardiochip in 2006, researchers have used it to pinpoint gene variants in dozens of studies. The device contains approximately 50,000 DNA markers across 2000 genes implicated in cardiovascular disease.

Alongside Fotios Drenos, Ph.D., of University College London, Dr. Keating was co-senior author of the study, published recently in the *American Journal of Human Genetics*.

Comprising over 180 researchers, the international consortium analyzed genetic data from over 90,000 individuals of European ancestry. First the researchers used the Cardiochip in a discovery dataset of over 65,000 individuals from 32 previous studies. They then sought independent replication in other studies covering over 25,000 individuals, as well as in a previously reported study of 100,000 individuals.

From this meta-analysis, the consortium identified 21 novel genes associated with levels of low-density lipoproteins (LDL, or "bad cholesterol"), high-density lipoproteins ("good cholesterol"), total cholesterol, and triglycerides, as well as verifying 49 known signals. The researchers also found that some of the strongest signals appeared to be gender-specific — some variants were more likely to appear in men, others in women.

"To date, this is the largest number of DNA samples ever used in a study for lipid traits, it clearly shows the value of using broad-ranging global scientific collaborations to yield new gene signals," Dr. Keating said.

"While each of the genetic variants has a small effect on the specific lipid trait, their cumulative effect can significantly add up to put people at risk for disease," Dr. Drenos added. "This study underscores how international sharing of resources and datasets paves the way for robust, continuing discoveries of new and unexpected information from human genetic studies."

Drs. Keating and Drenos coordinated efforts among four main data coordinating sites: the Center for Applied Genomics at The Children's Hospital of Philadelphia; the Institute of Cardiovascular Sciences at University College London; AMC, Amsterdam; and the Department of Cardiology at the University Medical Center, Utrecht.

The consortium plans to follow this published work with a project to identify which of the loci reported directly cause disease, and how this knowledge can help in the development of novel drugs. The consortium will also devote its significant pooled resources to identifying interactions among genetic polymorphisms (single-base variations in DNA) and biological markers of downstream cardiovascular disease.

"Next to already established drug targets such as the LDL receptor and PCSK9, the current study identified 21 potential new targets for drug development that may be beneficial for the treatment of dyslipidaemia in the future," said lead author Folkert Asselbergs, M.D., Ph.D., of University Medical Center, Utrecht. "Our team of researchers are now initiating additional studies to investigate the impact of the found genes on cardiovascular disease."

New Adult BMI Genes Discovered

A large international study has identified three new gene variants associated with body mass index (BMI) levels in adults. A consortium of approximately 200 researchers performed a meta-analysis of 46 studies, covering gene data from nearly 109,000 adults spanning four ethnic groups.

By discovering links to lipid-related diseases, type 2 diabetes, and other disorders, the IBC 50K SNP Array BMI Consortium's study may provide fundamental insights into the biology of adult obesity. Scientists from the Center for Applied Genomics led the study by using the Cardiochip, a gene array containing probes for some 50,000 genetic variants across 2,100 genes relevant to cardiovascular and metabolic functions. The study appeared recently in *Human Molecular Genetics*.

"BMI is a widely used measure of obesity, which affects one third of U.S. adults, and approximately half a billion people worldwide," said Children's Hospital's **Yiran Guo, Ph.D.**, who led the meta-analysis. "Previous studies have shown that genetics plays an important role in obesity, and this study expands our knowledge of BMI genetics."

The researchers first analyzed a dataset of approximately 51,000 individuals of European ancestry (EA) to discover initial gene signals, and then performed replication studies in another 27,000 EA subjects, as well as 14,500 additional EA individuals. Further analyses of data from approximately 12,300 African Americans, 2,600 Hispanics, and 1,100 East Asians strengthened the team's findings.

The consortium uncovered three novel signals, from the genes *TOMM40-APOE-APOC1*, *SREBF2*, and *NTRK2* that were significantly associated with BMI in adults. All three genes had previously been linked to other important disorders. The *APOE* locus is well known to be involved in blood lipid regulation and circulation, and plays an important role in Alzheimer's disease. The *SREBF2* gene is in the same family as *SREBF1*, linked to type 2 diabetes in another CardioChip study. Finally, *NTRK2* codes for a receptor of the BDNF protein, which is known to be related to BMI and is associated with the eating disorder anorexia.

Anorexia is of special interest to Dr. Guo, who holds a Davis Foundation Postdoctoral Fellowship in Eating Disorders. The large dataset from the previous studies allowed the researchers "to enhance our understanding of BMI genetics, as well as the interplay between genetic variants and metabolic disorders such as obesity, type 2 diabetes and lipid-related conditions," he said.

The team was able to test for conditional associations within genes — independent signals from within the same gene locus, Dr. Guo added. In particular, the researchers discovered that two genes, *BDNF* and *MC4R*, each harbor two independent signals for BMI. Both genes were among eight genes previously associated with BMI that the current study was able to replicate, including *FTO*, *SH2B1*, and *COL4A3BP-HMGCR*.

"While the individual effects of each gene may be small, they may provide fundamental clues to the biology of adult obesity," Dr. Guo said, adding that further studies will investigate gene-gene interactions for the same trait.

From Bench to Bedside, Then Back to Bench

Featuring Children’s Hospital investigators as well as researchers from outside the Research Institute, the **Center for Childhood Cancer Research** (CCCR) recently held its inaugural symposium on pediatric cancer research. The daylong meeting was focused on the broad theme of translational research, or “how the work is going to impact patients in real time,” said John Maris, M.D., director of the CCCR.

The day included presentations from a number of pioneering cancer researchers and innovators, including Columbia University’s **Adolfo Ferrando, M.D., Ph.D.**; **Kevin Shannon, M.D.**, from the University of California San Francisco; and the Broad Institute and Harvard Medical School’s **Matthew Meyerson, M.D., Ph.D.** The symposium was made possible with support from **Alex’s Lemonade Stand Foundation** (ALSF).

Originally founded in 2000 by then 4-year-old Alexandra “Alex” Scott (1996-2004) as a lemonade stand to raise money for cancer research, over the years ALSF has evolved into a robust national organization. The foundation’s close relationship with Children’s Hospital dates to 2001, when the Scott family moved to the Philadelphia area so Alex’s neuroblastoma could be treated at CHOP.

“Translational research is so important” because “what we’re really interested in is helping kids with cancer,” noted Alex’s father Jay Scott, co-executive director of ALSF.

In his opening remarks, **Philip Johnson M.D.**, chief scientific officer of the CHOP Research Institute, noted that while he has at times struggled to translate what constitutes translational research into “understandable stories,” the work done by the oncology group always made his job easier. People “get it immediately, they understand that the science impacts the care and the care impacts the science,” Dr. Johnson said.

A number of the day’s presentations focused on using the highly specific targeting offered by genomics to treat cancer. The “challenge of killing these cells becomes less and less as we have more targeted approaches,” said Michael Kastan, M.D., Ph.D. Dr. Kastan, who is currently the executive director of the **Duke Cancer Institute**, gave a talk titled “Therapeutic Targeting of DNA Damage Response Pathways.”

Stephan Grupp, M.D., Ph.D., CCCR director of translational research, discussed his recent work treating acute lymphoblastic leukemia (ALL)

with engineered t-cells. The most common form of childhood leukemia, ALL is largely curable, with an 85 percent cure rate. However, in part because the other 15 percent of ALL patients have limited treatment options, Dr. Grupp has been working on immunotherapeutic treatments for the disease.

Though the mortality rate from childhood cancers was greatly reduced throughout the 1970s, 80s, and 90s, the reduction in mortality has slowed since 1998, Dr. Grupp noted, pointing out that at the current rate of improvement it would take 150 years to get down to zero. Because of this, “we really need to be thinking in a completely new way about how to treat patients with cancer,” he noted.

Later in the day, the CCCR’s **Yael Mossé, M.D.**, gave a talk highlighting her work treating neuroblastoma — the most common solid cancer of early childhood — in patients who express the anaplastic lymphoma kinase (*ALK*) gene. Dr. Mossé’s work with crizotinib, a drug originally developed to treat lung cancer in adult patients who express *ALK*, sparked a frenzy of media attention in the spring after Dr. Mossé and her team found complete responses in a number of patients involved in a phase 1 trial.

Though the “inhibition of mutated *ALK* is complex and remains a therapeutic challenge,” Dr. Mossé’s team has already begun working on *ALK*-targeted immunotherapy and combined treatment strategies. And it is her patients who “really inspire me every day,” Dr. Mossé said.

The symposium’s proceedings were capped off by the presentation of the first Beverly J. Lange CCCR Service Award. Named for longtime CHOP cancer researcher, **Beverly J. Lange, M.D.**, the award honors those “individuals behind the scenes who are the epitome of teamwork and the epitome of getting things done in a collegial and collaborative manner,” said Dr. Maris.

John Simpkins, CCCR administrative director, was awarded this year’s award. “I am truly humbled to be honored as the first to receive the Beverly J. Lange, M.D. Award, Simpkins said. “This recognition has special meaning to me because it is named after Dr. Lange who has not only been a longstanding leader, clinician, researcher and mentor but she has also been a role-model to many because of her dedicated service to CHOP over the last four decades.”



Autism Researcher Receives Grant to Fund Anxiety Investigation

By examining pediatric patients with anxiety and autism, a new study by The Children's Hospital of Philadelphia researchers hopes to better understand how to diagnose, measure, and treat children with autism who have anxiety.

John Herrington, Ph.D., associate director of the Developmental Neuroimaging Laboratory at the **Center for Autism Research**, in July was awarded a grant by the Dublin, Ireland-based pharmaceutical company Shire. The grant will fund Dr. Herrington's investigation of anxiety in pediatric patients with autism spectrum disorders (ASD) through December 2013.

Shire — which has its U.S. headquarters in Wayne, Pa. — is best known for its portfolio of attention deficit hyperactivity disorder drugs, including Adderall (dextroamphetamine and amphetamine), Intuniv (guanfacine), and Vyvanse (lisdexamfetamine).

Since receiving funding, Dr. Herrington has begun recruiting and testing research participants, with a goal of eventually recruiting 150 patients, ages 7 to 18, across four groups. The first group will have ASD but no anxiety, and the second group will have both ASD and anxiety. The third group will consist of children who are developing normally, without a psychiatric diagnosis, while the fourth will be made up of children who have an anxiety disorder but who do not have ASD.

Though the overall purpose of Dr. Herrington's study is to examine anxiety in children with ASD, "the best way to do that is to look at anxiety in typically developing populations as well," he said.

Other CHOP researchers who have contributed to the project include **Hakon Hakonarson, M.D., Ph.D.**, director of the Center for Applied

Genomics, and **Robert Schultz, Ph.D.**, director of the Center for Autism Research. Dr. Herrington has also been collaborating with the University of Pennsylvania's **Martin Franklin, Ph.D.**, of the **Child/Adolescent OCD, Tics, Trichotillomania and Anxiety Group (COTTAGE)**. Because Dr. Franklin and the COTTAGE team routinely treat anxiety, he has been helping Dr. Herrington recruit participants for the anxiety-only arm of the project.

In addition to MRI scans, questionnaires, and computerized tests, the researchers will use eyetracking technology — specifically the **Tobii X120 Eye Tracker** — to determine whether ASD-related anxiety is associated with abnormal eye gaze patterns. Eyetracking technology has the potential to be significantly useful in ASD research, as systems like the one being used by Dr. Herrington's team can track behavior while placing few demands on participants.

"One of the ultimate outcomes of this project ... is to see what the simplest tools possible are to measure anxiety" in ASD, Dr. Herrington said.

Dr. Herrington's study has the potential to benefit a large population, for as many as 40 to 50 percent of children with ASD might also suffer from clinical anxiety, Dr. Herrington said. According to a recent estimate by the Centers for Disease Control and Prevention's Autism and Developmental Disabilities Monitoring Network, roughly 1 in 88 children has ASD.

"It could be that alleviation of anxiety symptoms goes a long way in focusing these kids' attention," Dr. Herrington noted. Overall, he added, the "hope is always that this is going to wind up translating into treatments."

"Miracle Network" Aims to Raise \$7.5 Million for Autism Research

The Children's Hospital of Philadelphia's **Center for Autism Research** has been highlighted as one of The Children's Miracle Network's (CMN) "**Ultimate Gift**" beneficiaries for its social media-based holiday fundraising program, Give Miracles. In addition to this social media presence, ads announcing the campaign will run in the *Wall Street Journal* on November 10th and 24th, and on December 1st and 15th.

Affecting approximately 1 in 88 American children, autism is one of the most common childhood disorders, yet it remains a mystery in many ways, leaving millions of households desperate for answers. Families wonder, what causes autism? What are the best treatments? And when there will be a cure? Donors who support autism programs at CHOP through the Give Miracles campaign will help unlock the mysteries of this perplexing disorder by fueling some of the most needed medical breakthroughs of our generation.

By heading the largest and most innovative studies of autism ever, the Center for Autism Research's (CAR) multidisciplinary teams of psychologists, neuroscientists, and geneticists are revolutionizing our understanding of this disorder. Every day, CAR researchers use state-of-the-art tools to discover autism's causes and to find new treatments, while also providing comprehensive, family-centered care and support to meet each child's specific developmental and educational needs.

CMN's Give Miracles program provides donors with tangible evidence of their gift, from the initial donation to its final use. The program enables donors to choose the hospital they want to support, as well as the amount and type of their gift. Those who donate will also be given ongoing email updates on the gift's impact for children with autism, both at CHOP and far beyond its walls.

"When people donate their hard-earned money, they want to know how it is used," said John Lauck, CEO of Children's Miracle Network Hospitals, adding that the Give Miracles program offers donors "a direct connection to the impact their dollars are making at the local hospitals and on the kids they are supporting."

GiveMiracles.org features a social fundraising platform that allows donors to create a customized fundraising page that calls on their Facebook and Twitter networks for donations. This crowdfunding feature allows multiple contributions which are especially helpful for addressing large fundraising goals like CAR's. These miracle-making gifts can also be purchased by single benefactors, such as corporations and foundations.

CHOP Research Poster Day 2013 Announced

We are pleased to announce the 23rd celebration of CHOP Research Poster Day! All members of the CHOP community (e.g. physician fellows, pre- and postdoctoral researchers, residents, nurse researchers, and respiratory therapists) who are conducting research are welcome to participate.

The event will take place on Wednesday, February 27, 2013 from 9:00 a.m. – 5:00 p.m. in the lobby and first floor of the Colket Translational Research Building. A reception and awards ceremony will be held in Colket following the viewing and judging period. This poster session is sponsored by The CHOP Research Institute and the Department of Pediatrics, and is supported by a generous endowment from the wife of Dr. Klaus Hummeler, the first director of The Joseph Stokes, Jr. Research Institute (now the CHOP Research Institute).

Last year — which marked the 22nd year of this event — we had over 115 poster presentations from numerous hospital departments. Everyone is welcome to join in, and all participants will be eligible for prizes. We specifically encourage all third year fellows and postdocs to participate.

Pre-registration/abstract submission will begin the first week in December and is required for participation in the event. Please note that we will not be able to accommodate presenters who have not pre-registered. Abstracts will be accepted on a first-come, first-serve basis. The online program guide will be available one week prior to the event. Instructions for abstract submission and a complete schedule of the day's events will be provided in the coming weeks.

Presenters should set up their posters by 8:45 a.m., and should be prepared to attend their posters for the judging portion of the event. We emphasize that the posters may be typed, or prepared on computers, for ease of presentation. We invite submissions of work previously presented at national meetings can but cannot accept posters presented previously at CHOP Research Poster Day. The purpose of this event is to promote communication and informal presentation. In fact, case reports can be used as a presentation if they have some degree of analysis or research potential. We are pleased to continue this opportunity and hope this will result in the same degree of enthusiasm as seen in past years!

This year we will continue with a two-track judging system. Participants will be prompted at abstract submission to choose from one of two tracks: Patient-oriented (clinical, human subjects) or Laboratory-based (basic, wet bench). Translational studies could fall into either category at the discretion of the abstract author. Judging and prizes will be uniform for each track and multiple prizes will be awarded. Presenters must attend their posters during the judging session to be considered for prizes.

The CHOP Research Institute Offices of Responsible Research Training and Postdoctoral Affairs are responsible for coordinating this event. General questions may be directed to researchtraining@email.chop.edu. If you have specific questions about the poster tracks, contact William Fox (fox@email.chop.edu) for patient-oriented track questions or Tom Curran (currant@email.chop.edu) for laboratory-based track questions.

HAVE NEWS?

Contact Jennifer Long at ext. 4-2105
or by e-mail at longj@email.chop.edu.

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online at <http://www.research.chop.edu/publications/>.

 The Children's Hospital of Philadelphia®

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