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FRONTIER PROGRAMS CREATE NEW PATHS FOR RESEARCH DISCOVERY AND CLINICAL CARE

Frontiersmen historically are a rare breed of adventurers willing to brave the unknown in order to discover new paths. The physician-researchers who are leading new Frontier Programs at Children's Hospital of Philadelphia embody this pioneering spirit as they forge ahead to help children achieve optimal health and better lives.

The Frontier Programs initiative at CHOP designates funding to large internal programs that connect translational research and clinical care in extraordinary ways. This spring, 19 programs applied, and after a rigorous review process, the oversight panel selected two outstanding programs: the Thoracic Insufficiency Syndrome (TIS) Program and the Inflammatory Bowel Disease (IBD) Program.

BREATHING EASIER: THORACIC INSUFFICIENCY SYNDROME PROGRAM

TIS encompasses a group of at least 28 rare and potentially fatal disorders in which spinal and chest wall deformities early in life compromise children's lung growth and ability to breathe. Robert Campbell, MD, director of the Center for Thoracic Insufficiency Syndrome (CTIS) at CHOP and an attending surgeon, invented the first FDA-approved Vertical Expandable Prosthetic Titanium Rib (VEPTR device) that enables surgical reconstructive procedures to enlarge these children's rib cages and help to correct scoliosis to increase their chances of lung growth.

As VEPTR has become the standard of care for treating TIS, CTIS has treated more patients and more acute cases from all over the world and increased surgical volume for patients with TIS by an average of 15 percent every year since 2012 at CHOP. The need for more TIS research has grown along with the Center.

Being named a Frontier Program will allow Dr. Campbell and a multidisciplinary team of specialists to perform sophisticated imaging, construct new metrics for clinical outcomes, better understand the biomechanics of TIS, and establish reliable evidence to support new surgical strategies and develop new medical devices.

"The Frontier funding supports programs that are clinically robust and have the potential for rapid advancement," Dr. Campbell said. "It's like getting a turbo charger. It's hard to win the race if you don't have one."

CTIS hit the starting line with about 20 research projects that are underway. For four years, Dr. Campbell and his colleagues have collaborated with Jayaram Udupa, PhD, a professor of Radiologic Science from the University of Pennsylvania Department of Radiology Medical Image Processing Group, to develop dynamic lung magnetic resonance imaging (dMRI) image analysis as a way to measure thoracic performance — which is how well the thorax, spine, and rib cage work in combination — before and after surgical intervention for TIS. The research team will refine and scientifically validate this new assessment technique in correlation with pulmonary function.

In order to get a complete view of the anatomy in these unusual diseases that the CTIS treats, the research team also collaborates with Sriram Balasubramanian, PhD, an associate professor in the School of Biomedical Engineering, Science and Health Systems at Drexel University, to perform detailed software analysis of computed tomography (CT) scans of patients, which shows bone better than MRIs.

Together, these approaches will be the basis for the CTIS' advanced imaging research program. One of the investigators' first projects is called the Virtual Growing Child, which will help to establish normative data for comparative analysis. Quantifying the degree of dysfunction in the rib cage and diaphragm will provide a new metric to define thoracic performance in TIS.

CTIS also is launching a basic science lab that will establish an animal model of TIS. Casey Olson, PhD, a medical bioengineer who recently joined the CTIS team, will be leading this research to better understand at an anatomic level how expanding these children's chests promotes lung growth. This biological platform will help them to develop new devices and surgical methods that closely mimic thoracic function to treat TIS.

As this body of research forms the scientific basis for TIS surgical interventions, Dr. Campbell also is excited to pursue studies that focus on patients' and families' quality of life outcomes. Measuring these surgeries' success goes beyond if the MRI and CT images look better, he pointed out. Many children who receive VEPTR devices are no longer dependent on oxygen support or mechanical ventilators. When these children can breathe easier, so can their parents, in many ways.

Dr. Campbell shared the example of a mother who had been sleeping every night at her son's bedside so that she could suction him if he became congested or had mucus plugs in his lungs. As the surgery slowly allowed her son's lungs to expand and move, he became more comfortable and could sleep through the night — and so could mom in her own bed.

"After treatment, these children feel better, are happier," Dr. Campbell said. "They gain weight. They don't go to the emergency room or intensive care unit as much, and they recover faster from illnesses. We don't measure those type of things yet, but the Frontier funding will make it possible. We're very appreciative of this. There are so many innovations at CHOP just waiting to happen."

MAKING IT PERSONAL: INFLAMMATORY BOWEL DISEASE PROGRAM

Frontier funding will expand pediatric IBD care and research at CHOP, as an inventive multidisciplinary team takes a new approach that combines genomics and microbiome analysis to fulfill an unmet need for improved diagnostic modalities and therapeutics. IBD is a chronic autoimmune disease that includes Crohn disease and ulcerative colitis, and it has been rapidly increasing in incidence — especially among young children — mostly likely due to a complex combination of genetic and environmental factors.

The Center for Pediatric Inflammatory Bowel Disease at CHOP is the largest of its kind in the country, providing care for more than 1,400 children and adolescents. Under the combined leadership of Robert Baldassano, MD, and Andrew Grossman, MD, co-directors of the Center for Pediatric IBD; and Judith Kelsen, MD, a pediatric gastroenterologist and researcher; the Frontier program will increase the Center's size and scope to provide the most advanced comprehensive care to pediatric patients with IBD from the U.S. and internationally. At the same time, their scientific observations will generate novel insights into pediatric IBD, which often is harder to treat than older-onset IBD, and can have dramatic consequences including poor growth, malnutrition, and the need for intravenous feeding and surgeries.

"The bottom line is we're trying to improve the care of children who are suffering with this disease all over the world," Dr. Baldassano said. "We believe that the model we are creating will be used at other institutions five or 10 years from now." At the heart of this model is CHOP's ability to provide personalized medicine for children with IBD. Patients treated by the Center for Pediatric IBD undergo next-generation sequencing to identify the genetic defects that may underlie their disease. This not only aids diagnosis, but it also suggests which medications have the best chance of being effective. Another benefit is that it provides CHOP the opportunity to develop new gene-based therapies.

For example, previous research by Dr. Baldassano and his colleagues at the Center for Applied Genomics at CHOP discovered that many children with pediatric IBD and other autoimmune diseases have loss of function mutations in a specific immune regulatory protein that dampens inflammation caused by a pro-inflammatory protein called LIGHT. As part of a CHOP collaboration with industry partners that was announced in June, Dr. Baldassano will help to test a potential therapy that would be a first-in-class anti-LIGHT monoclonal antibody that binds excessive LIGHT to help control inflammation in pediatric patients with IBD.

The Center for Pediatric IBD also aims to move science forward by analyzing patients' microbiome, which is the community of microbes that live on and within your body (the bulk of these organisms live in the gut) and contribute to

numerous biological functions. Growing evidence supports the idea that the microbiome helps drive inflammatory bowel disease in people who are genetically predisposed.

In order to better understand the intestinal environment associated with IBD and characterize the disease more comprehensively, the Center for Pediatric IBD collects stool samples from IBD patients and uses next generation sequencing techniques available through the PennCHOP Microbiome Program, which Dr. Baldassano also codirects, to sequence hundreds of microorganisms' genomes. The researchers will establish microbiota signatures of subsets of pediatric IBD, and then they will correlate these key communities of bacteria with patients' genetic variants to help select the most appropriate therapeutic options.

"We believe the future of treating IBD will require us to combine the microbial information with the genetic information to figure out how the immune system is being manipulated by both," Dr. Kelsen said. "Ultimately, we want to really understand the individual person's disease to provide optimal therapy."

The Center for Pediatric IBD team's national leadership in clinical, translational, and basic research in IBD is exemplified by its expertise in treating very-early onset IBD (VEO-IBD), which is IBD that presents before age 5. Children with VEO-IBD are a unique part of the IBD patient population because they frequently present with more severe symptoms and greater extent of GI tract involvement than older children and adults with IBD. In addition, these patients tend to respond poorly to conventional IBD therapies used for older patients.

Research led by Dr. Kelsen identified some of the underlying genetic causes of VEO-IBD that may allow for targeted therapy in these children. These gene variants appear to influence the immune system and may result in defective or inappropriate immune responses that contribute to the development of VEO-IBD. For many of the patients who Dr. Kelsen sees in the VEO-IBD clinic that she runs with Kathleen Sullivan, MD, PhD, chief of the division of Allergy and Immunology, they are now using therapies that are directed to diseases of the immune system, instead of prescribing traditional IBD drugs.

Dr. Kelsen shared the inspiring story of a young infant with a form of IBD who spent four months in CHOP's ICU being cared for by specialists from gastroenterology, immunology, and rheumatology who were committed to figuring out why she was so gravely ill. They discovered that she had a gene defect that caused an overwhelming inflammatory response. The team received compassionate use permission from the U.S. Food and Drug Administration to try an investigational drug that blocked that inflammatory process from happening. They recently described the patient's case in the *Journal of Allergy and Clinical Immunology*.

"She went from an infant who was incredibly sick and couldn't tolerate even an ounce of formula by mouth to a little girl who is now eating pizza and growing," Dr. Kelsen said.

Dr. Kelsen and her colleagues expect to have many more success stories to tell, as the Center for Pediatric IBD at CHOP utilizes this multidisciplinary translational research approach to provide personalized therapy to more children worldwide. Already, they receive biospecimens from IBD patients nationally and internationally to perform sophisticated sequencing, analysis, and interpretation.

"We are incredibly excited," Dr. Kelsen said. "This is an opportunity to provide better care and better science so that hopefully we can change the natural history of the disease."

VALUABLE LESSONS LEARNED FROM RESEARCH IN SCHOOLS

Why are top-notch scientists at Children's Hospital of Philadelphia going back to school? They are conducting enlightening research projects — from implementing behavioral health interventions to analyzing what's on school cafeterias' menus — to ensure that students are prepared to learn and excel. Let's take a look at some of the research in education that rose to the head of the class this year. (Now pay attention ... there may be a quiz later!)

EMPOWERING "MEAN" GIRLS TO USE POSITIVE SOCIAL INFLUENCE

One of these thought-provoking projects is a small-group in-school educational program that teaches positive social skills, called Friend to Friend (F2F). F2F has been in development and testing for more than 15 years by Stephen Leff, PhD, co-director of the Violence Prevention Initiative (VPI) at CHOP and professor of Clinical Psychology in Pediatrics and Psychiatry in the Perelman School of Medicine at the University of Pennsylvania, in collaboration with CHOP experts, students, parents, teachers, and other school stakeholders.

The program's curricula and innovative teaching methods include videos, cartoons, and role-plays targeted to urban, ethnic minority girls. These educational tools are designed to help girls in third to fifth grade find friendlier alternatives to relational aggression, the set of behaviors colloquially known as "mean girl" behaviors that are often a component of bullying.

One year after a randomized controlled trial of F2F, participating relationally aggressive girls had sustained improvements in social behaviors, Dr. Leff and colleagues reported in the journal *Psychology of Violence*. Another CHOP study reported in the journal *Behavior Modification* showed benefits for the entire classroom environment. The program's inclusion of a co-teaching role for girls to share their new friendship-focused skills with their classmates may have turned the greater social influence that many such "mean girls" often hold into a force for good. Through VPI, future directions for the program are focused on scaling F2F to reach more classrooms in more schools.

PROGRAM HELPS PARENTS FIND THE GOOD IN BAD CHILD BEHAVIOR

Joanne Wood, MD, MSHP, is an attending physician and faculty member in PolicyLab at CHOP, and she also is a mom who knows how stressful parenting can be when children are misbehaving. Dr. Wood and colleagues Philip Scribano, DO, MSCE and Steven Berkowitz, MD, in PolicyLab realized that, in some cases, negative and reactive parenting can lead to increased child behavior problems and downstream undesired effects on school readiness, academic outcomes, and behavioral health disorders.

"And really we want to keep kids from getting there," said Dr. Wood, who is also an assistant professor of Pediatrics at Penn.

She found a promising tool to do so in a small-group parenting intervention called CARE, which she helped implement and evaluate during PolicyLab's work with the city of Philadelphia helping caregivers in the foster care system. Through a combination of lectures with discussions, role plays, and other interactive elements, caregivers became familiar with positive parenting and stress-management skills for themselves and for their children.

Providing a six-week version of this program, called PriCARE, to parents of preschool-age children at CHOP's primary care facility in South Philadelphia was effective at improving ratings of child behavior and improving parent attitudes. Dr. Wood and her colleagues reported these results in the journal *Academic Pediatrics*. They hope that with further study the program will prove to prevent children's later problems in school or with mental health.

NEW PROJECT AIMS TO REDUCE INNER CITY STUDENTS' ANXIETY

When children from low-income, urban backgrounds start their school days, often their minds are already filled with weighty issues that can lead to anxiety disorders and aggressive and antisocial behavior. Unfortunately, counselors in inner city schools usually are scarce, overextended, and lack adequate training to provide effective behavioral health services.

Bringing mental health services to underserved schools and students has been the research focus of Ricardo Eiraldi, PhD, a psychologist in the department of Child and Adolescent Psychiatry and Behavioral Sciences and program director of the Behavioral Health in Urban Schools program at CHOP, for two decades. His latest project is to use a "train the trainer" approach to train mental health agency supervisors and therapists to provide cognitive-based therapy in schools and reduce behavior problems.

Dr. Eiraldi and his study team received a new grant this year from the National Institute of Mental Health to find effective approaches to build internal capacity within under-resourced schools in order to provide mental health services to children who present excessive anxiety. Thirty-six schools in Philadelphia will participate, and the researchers expect to enroll 90 therapists, a minimum of 18 clinical supervisors, and 360 students in grades four through eight. By the conclusion of the five-year grant, the study team aims to report on the children's outcomes, implementation outcomes, and cost-effectiveness. The study protocol was published in the journal *Implementation Science*.

"Low income, ethnic, minority children are much less likely to receive high quality mental health services compared to those in the middle class who are not ethnic minorities, so schools can play a very major role in addressing mental health issues in children," said Dr. Eiraldi, who also is an associate professor of Clinical Psychology in Pediatrics and Psychiatry at Penn.

In another study currently in its fourth year in six schools in Philadelphia, Dr. Eiraldi and colleagues are testing two levels of support provided to school personnel for the implementation of School-Wide Positive Behavioral Interventions and Supports (SWPBIS), a service delivery framework used to improve school climate and children's mental health. This project is described in detail in Implementation Science. In an article published in *Behavior Modification*, Dr. Eiraldi and his study team reported that a pilot study of SWPBIS showed children with a diagnosis of depression, anxiety, or behavior problems who received the small group–based services over 14 once-a-week sessions had a decrease in their diagnostic severity level.

CAFETERIA LUNCHES COME WITH A SIDE OF STATE LAWS, BUT ARE THEY EFFECTIVE?

State and local lawmakers over the last few years have introduced healthy changes in the places where kids spend most of their day, most of the year: schools. Such laws take a range of approaches, such as requiring in-school nutrition education, restricting the sale of junk food in cafeterias and school vending machines, or requiring specific credentials for school food service directors. But there is limited data about the effectiveness of these policies.

A CHOP study published in *Preventive Medicine* examined nine types of such laws and identified two that were associated with decreased obesity, although the data couldn't determine cause and effect. Deepak Palakshappa, MD, MSHP, an attending physician at CHOP, instructor in General Pediatrics at Penn, and faculty member in PolicyLab and the Center for Pediatric Clinical Effectiveness, and his colleagues' main analysis looked at possible associations between the strength of state nutrition laws in 2010 and the weight of children age 10 to 17 in those states in 2011, controlling for state-level differences in children's weight in prior years and for reported differences between children's nutrition and physical activity that could affect their weight status outside of school.

Strong laws limiting the sales of unhealthy or junk foods in cafeterias, vending machines, and school stores (known as competitive food and beverage laws) had a significant association with lower obesity in the 10-year-old, elementary-aged children. And strong laws limiting food and beverage advertising in schools were associated with lower obesity in all ages of youth studied. The other seven categories of laws showed no significant associations.

MAKING A BETTER CONNECTION FOR CHILDREN WITH ATTENTION-DEFICIT HYPERACTIVITY DISORDER

Remember that experiment when you and your best friend made a telephone using just cups and some string? But when the string went slack, your conversation was lost. In much the same way, a poor connection exists between the two separate systems — healthcare and schools — that are involved with the treatment of children who have attention-deficit hyperactivity disorder (ADHD). Alexander G. Fiks, MD, MSCE; Thomas J. Power, PhD; Robert W. Grundmeier, MD; Jeremy Michel, MD; and colleagues at the Center for Pediatric Clinical Effectiveness, PolicyLab, and the Department of Biomedical and Health Informatics at CHOP have developed an electronic portal called ADHD Care Assistant to help better coordinate communication between pediatricians and teachers, bringing their treatment plans into alignment with families' goals.

"ADHD Care Assistant closes this barrier where there might be intermittent doctor-family communication sometimes, and it brings the teacher centrally into the conversation," Dr. Fiks said.

The electronic portal helps to gather information from parents and teachers of children with ADHD on their symptoms, treatment, and medication side effects. They complete online check-in surveys using ADHD rating scales, and the results are shared with the children's primary care physicians via the hospital's electronic health record (EHR).

Findings from a feasibility study conducted across 19 primary care providers in CHOP's network showed that 67 percent of providers activated the ADHD Care Assistant system for at least one patient, and 32 percent activated it for five or more cases. The results appeared in *Advances in School Mental Health Promotion*. In that article, the authors also discussed the challenges of developing the portal, such as meeting the needs of multiple school districts with different resources and policies about electronic information sharing.

"Our ongoing work is related to building relationships between the health system and the schools that enable there to be trust and understanding of what's going to be accomplished on both ends so that information can move to the benefit of kids without encountering substantial barriers," Dr. Fiks said.

A new clinical trial called Communication to Improve Shared-Decision Making in ADHD (ADHD-Link) led by James Guevara, MD, MPH, an attending physician at CHOP, an associate professor of Pediatrics and Epidemiology at Penn, and a founding member of PolicyLab, will explore whether using the online portal plus a care manager can help to improve care coordination. The care manager will contact families every three months during the study to discuss their child's ADHD care and help to communicate their goals and preferences to the child's physicians and teachers, identify new concerns, and problem-solve. Approximately 300 participants will be enrolled, and they will be randomly assigned to use either the EHR portal alone or the portal plus a care manager. The Patient-Centered Outcomes Research Institute is providing funds for the study.

"Good health isn't housed only in the health system," said Dr. Fiks, who also is an ADHD-Link co-investigator. "It requires collaboration across school systems and engagement of a community."

SEEING THE UNSEEN TO CHANGE THE PICTURE FOR LYMPHATIC DISORDERS

A baby born with fluid-filled body cavities and unusual swelling is a rare sight in neonatology, but experienced neonatologists know these chylous disorders can be dire. With few medical interventions available for these largely mysterious and often devastating conditions of the lymphatic system, these infants face a poor prognosis if the symptoms do not resolve on their own.

"Caring for neonates with lymphatic disorders can be very challenging given the limited understanding we have on these diseases," said Dalal Taha, DO, an attending neonatologist at Children's Hospital of Philadelphia and assistant professor of Clinical Pediatrics at the Perelman School of Medicine at the University of Pennsylvania. "We are beginning to see that change, now that we have the capability to perform advanced imaging."

Interventional radiologist Maxim Itkin, MD, and pediatric cardiologist Yoav Dori, MD, PhD, are the pioneers behind new imaging techniques and minimally invasive interventions for lymphatic disorders. Their efforts have kick-started the rapid emergence of lymphatics as a new specialty in medicine and led to the establishment of the Center for Lymphatic Imaging and Interventions Program at CHOP and the Hospital of the University of Pennsylvania (HUP), directed by Dr. Itkin. They are showing that the lymphatic system plays an understudied role in many diseases, providing new ideas for minimally invasive treatments, and offering insights into fields from pulmonology to immunology. Neonatology is only one of these many specialties where the pair is beginning to make inroads with help from so-called "lymphomaniacs," like Dr. Taha, who see the potential in their new approaches.

"Max and I have gone from department to department giving lectures and showing images, and we're still doing this constantly," said Dr. Dori, director of Pediatric Lymphatic Imaging and Interventions and Lymphatic Research at CHOP and assistant professor of Pediatrics at the Perelman School of Medicine. "We're trying to educate and get everybody up to speed about what we're dealing with, what are these disease processes, and how to treat them."

IMAGING DRIVES EVERYTHING

The lymphatic system is a set of vessels throughout the body that collects fluids from soft tissues and organs, especially the liver and intestine. It carries those fluids to the thoracic duct, the largest lymphatic vessel, from which the fluid is transported back into the veins. But due to the vessels' small size and unpredictable anatomy, older standard lymphatic imaging methods, which involve injecting imaging dye through a patient's foot, are both difficult and time-consuming, while producing low-resolution and incomplete imaging of the flow of lymph through the body.

Drs. Itkin and Dori's new methods to image the lymphatic system have revolutionized the potential for treatments in the way imaging innovations transformed treatments in many of the body's other systems 50 years ago. The advent of magnetic resonance imaging (MRI), arteriography, CAT scans, and other imaging technologies in the 1960s and 1970s suddenly made physical abnormalities of many of the body's systems visible to physicians. Many of those abnormalities could then be treated with easy-to-explain interventions — embolizing to close off passages that should not be open, inserting stents to open those that should not be closed. But the lymphatic system was notoriously hard to image, so it was left out of that medical revolution of a generation ago.

"Imaging drives many fields," said Dr. Itkin, who is also an associate professor of Radiology at the Perelman School of Medicine. "The more you can see, the better you can treat."

The drive for better imaging in lymphatics belatedly emerged from the first treatments for the lymphatic system, which were themselves relatively recent. Twenty years ago, one of the fathers of interventional radiology, Constantin Cope, MD, conceptualized the idea of accessing the lymphatic system through the abdomen to treat traumatic cases of a condition involving leakage of lymph into the chest, called chylothorax. This idea initially sounded like science fiction to other experts in the field, but, slowly, the concept emerged as the main treatment approach. As Dr. Cope neared retirement, Dr. Itkin came to Penn to learn these techniques. He ultimately continued the tradition and refined the eight-hour surgical procedure into a 40-minute one.

In 2012, Dr. Itkin also began to make progress on a new imaging method, the intranodal lymphangiogram. In this method, he injected dye into the lymph node in a patient's groin, making it possible to see the lymphatic anatomy almost immediately. This technically simple replacement of a traditional lymphangiogram technique made lymphatic interventions easier to perform and more widely accepted by other physicians. But this method still lacked the level of detail of cross sectional imaging methods such as MRI and computerized tomography.

The next step forward for lymphatic imaging was the lucky outcome of a conversation after a recreational basketball game between Dr. Itkin and Dr. Dori. Until that day, the pair had never worked together, and Dr. Dori had never given much thought to the lymphatic system. But Dr. Itkin had given a lot of thought to pediatric cardiology, trying for some time to find collaborators at CHOP to explore the possible role of lymphatic flows in complications of congenital heart disease. Together, Dr. Dori and Dr. Itkin conceptualized the idea of MRI lymphangiography. This technique utilizes the same approach as the intranodal lymphangiogram but delivers a magnetic resonance contrast agent.

"Suddenly we discover the whole world of lymphatic abnormalities," Dr. Itkin said. "Nobody had ever done that before. We can actually light up almost the whole lymphatic system and see abnormalities there."

SHOWING SUCCESS WITH PLASTIC BRONCHITIS

Before long, they tried their new imaging technique on a patient with the devastating condition plastic bronchitis, in which the lungs suffuse with fluid that hardens into rubbery casts. With that first patient, it was immediately clear to Drs. Itkin and Dori that some lymph from the thoracic duct was leaking into the lungs — and they have since found a similar flow pattern in patients with other conditions. Dr. Itkin hypothesizes that such lymphatic leaks into the lungs are a normal variant that some people are born with, and that typically does not cause major medical problems.

But it predisposes some people to plastic bronchitis. Although this condition can occur at any age and without any specific triggering event, doctors see it most commonly in children who have undergone a Fontan operation for congenital heart disease. The researchers suggest that this occurs because, in children who have congenital heart failure on the right side, soft tissues are congested, and the amount of fluid that the lymphatic system would normally absorb and carry away exceeds the system's capacity. Far too much excess lymph flow can then accumulate in the lungs in patients prone to these flow leakages.

Now that they can see the abnormal flows in plastic bronchitis, Drs. Dori and Itkin are treating them with a minimally invasive procedure that is as simple to explain as the revolutionary, imaging-driven treatment changes in many other fields a generation ago: While imaging the abnormal flows in a patient, they selectively embolize lymphatic passageways to stop the fluid from leaking into the lungs.

"Predictability is almost 100 percent," Dr. Itkin said. "It's a simple plumbing problem."

In 2016, the team caught the world's attention with the publication of their results treating 18 patients with plastic bronchitis. Fifteen of the 17 patients who underwent their new intervention procedure had a significant improvement in symptoms nearly a year later, they reported in the journal *Circulation*. Previously, the only intervention that offered some patients long-term relief from plastic bronchitis was a heart transplant. This effort confirmed the role of the lymphatic system in the mechanism of the disease. And their success is likely just the first of many to emerge from the team's lymphatics discoveries.

FLOWING TOWARD THE FRONTIERS IN RESEARCH

"We have opened a small door to enormous opportunities to discover new diseases and explanations for known diseases," Dr. Itkin said. "And we're already working on that."

The team's efforts have been designated as a CHOP Frontier Program, a type of program awarded priority funding to combine cutting-edge clinical discovery with fundamental research in critical areas of medicine where CHOP has unique strengths. Frontier funding gives the team the opportunity to further refine their imaging techniques, including the development of different dye agents to better show lymph in different areas of the body. For example, the liver and intestinal lymphatic systems generate a high volume of lymph, but the exact role of the lymphatic system in liver and intestinal disease is still poorly understood. The team is investigating the role of the lymphatic system in the liver disease ascites, as well as in a group of rare diseases, lymphangiomatosis.

A large part of the Frontier Program funding from CHOP is further helping to establish a comprehensive research program focused on lymphatics. The center has hired research assistants to gather data and create a database to track patients seen for suspected lymphatic disorders in a prospective study, and they are establishing a basic science research lab to better understand the lymphatic system in model organisms.

The lymph itself is opening up new possibilities for study in immunology as well.

"We now have the first-time opportunity to sample the lymphatic system from live human beings and analyze it," Dr. Itkin said. "We are working closely with the Penn Institute for Immunology, of which CHOP is a member, with multiple studies planned and already going on to understand the immune function of the lymphatic system better than ever before. This has enormous implications in areas such as HIV and cancer immune therapy."

For now, this intensive study and treatment innovation in lymphatics is unique to CHOP and Penn, found nowhere else in the world.

"This is kind of a new organ system," Dr. Dori said. "It's extraordinarily rare in medicine to fall on something like this, an organ system that has been ignored because people couldn't see it."

NEW GENETICS COLLABORATIVE FOLLOWS UNIQUE BLUEPRINT TO INDIVIDUALIZE MEDICINE

It was only 15 years ago that the first human genome sequence was revealed, the result of a huge National Institutes of Health project that spanned over a decade and cost $2.7 billion. This spurred a period of genomic discovery that has changed exponentially how we understand human health, with the field of pediatric medicine at the forefront. Today, mostly due to advances in technology that have dramatically reduced the cost and turnaround time of genomic sequencing, the newly established Roberts Individualized Medical Genetics Center (Roberts IMGC) at Children's Hospital of Philadelphia can coordinate a genetic testing plan that provides patients and families accurate and comprehensive results within a few weeks.

"It is revolutionizing what we do in medicine," said Ian Krantz, MD, an attending physician in the division of Human Genetics at CHOP, who also codirects the Roberts IMGC along with Livija Medne, MS, LCGC, a senior genetic counselor. "We now have this power to do next-generation sequencing, and as tests have become more and more complex, and we're able to understand more and more of the genome, testing in genetics has broader applications across all fields of pediatric medicine."

This unprecedented growth of genomics was the impetus for creation of the $50 million Roberts Collaborative for Genetics and Individualized Medicine that launched in September at CHOP. It is the first program in the nation that will apply genetic testing technology to individualize diagnostics in pediatrics and then translate patients' unique genetic blueprints to inform clinical management, family education and counseling, innovative research, and eventually new therapeutics.

A $25 million gift by the Roberts family made the Collaborative possible. CHOP is matching the gift with $25 million in internal funding, and together they will support multidisciplinary efforts that harness the energy and enthusiasm of genomics experts across the institution, including the Roberts IMGC, the division of Human Genetics, the division of Genomic Diagnostics, the Center for Applied Genomics, the department of Biomedical and Health Informatics, The Raymond G. Perelman Center for Cellular and Molecular Therapeutics, and others.

"We are extremely grateful to the Roberts family for this remarkable gift, which will help the Children's Hospital of Philadelphia usher in a new era of genetics and broaden the scope of genetic medicine across all clinical areas of the hospital," said Madeline Bell, president and CEO of CHOP. "Research is core to CHOP's mission, and growing CHOP's Research Institute is fundamental to our strategy and commitment to breakthroughs."

CHOP's new integrated approach that capitalizes on understanding the genetic underpinnings of childhood diseases already is making a difference in young lives. Dr. Krantz shared the story of 9-year-old Emily, who came to the Roberts IMGC after experiencing two years of progressive hearing loss. She had genetic testing for a panel of about 75 genes that are known causes of hearing loss, but the tests came back normal. Two years later, Emily returned after developing some visual loss. Dr. Krantz and his genetics team dug deeper for answers and analyzed Emily's entire genome — all 20,000 genes in a single test.

"The results showed that she had a rare, one-in-a-million diagnosis for a progressive neurological disorder that would lead to death in early adulthood," Dr. Krantz said. "Her genetic changes caused a problem in the way she metabolized a vitamin called riboflavin. This was very important for the family to know because both parents carried the same genetic mutation. We could counsel them about recurrence risk and prognosis. And even more exciting is that there was a treatment."

Emily went on high dose therapy for the missing vitamin, and although her symptoms may not be reversible, her condition has stabilized. The genetics team also tested her asymptomatic 5-year-old brother and found that he also has the gene mutation. He is receiving treatment as a preventive strategy, and hopefully he will not develop any symptoms.

This family's experience is a good example of where Dr. Krantz sees genomic medicine heading in the next decade — toward the screening of all newborns and individuals with genetic testing technology to give clinicians the opportunities to intervene early, such as by recommending lifestyle changes or prescribing pharmacologic therapies. Genetic testing may help to identify risk factors for many of the common diagnoses that adults face, such as diabetes, hypertension, and Alzheimers, that may be able to be managed and treated during childhood in order to improve outcomes throughout lifetimes, Dr. Krantz suggested.

The biggest stumbling block currently for genomic medicine is uncertainty. Scientists do not yet understand everything that they see in the genome, and that can sometimes be anxiety-provoking for families and clinicians. It also could lead to unnecessary tests that could increase healthcare costs. For instance, genetic testing may reveal that a child has a potential risk for a heart problem, but it may be unclear if the identified mutation will actually result in a damaging physical change. As a precaution, the child might need to visit a cardiologist once a year for an echocardiogram.

"Until we find a balance, or study and understand that the benefits outweigh those costs, people are a little hesitant to make genetic screening universal," Dr. Krantz said.

In the meantime, the Roberts IMGC has three pediatric geneticists, Cara Skraban, MD; Kosuke Izumi, MD, PhD; and Matthew Deardorff, MD, PhD; and two genetic counselors, Emma Bedoukian, MS, LSCG, and Jennifer Tarpinian, LSGC, who ensure that families receive thorough clinical evaluations, education, and counseling before and after genetic testing on its usefulness and limitations. They also discuss families' choices about the type of results that they want back. In some cases, families may only want answers to the possible genetic problems that their child is experiencing, while others may also want to know about secondary findings that could be medically important. The counselors meet with families about the results to explain their potential significance and put them in touch with specialists if needed.

So far, the Roberts IMGC has worked with about 2,000 patient referrals, and they continue to see about 100 patients a month, a number that Dr. Krantz expects will expand along with the availability of affordable genetic testing. As more medical insurance companies begin to acknowledge the utility of genetic testing, Roberts IMGC clinical coordinator Jasmine Montgomery navigates the nuances of pre-authorization and billing so that families do not end up with big balances to pay.

In many ways, genetic testing could be seen as a long-time investment in children's healthy futures because it provides insights into their genetic predispositions that are never static. A central mission of the Roberts Collaborative is to integrate patients' genetic makeup into their electronic health records so that this valuable information is always accessible and portable.

"We can test a 6-month-old's genome today and not find an answer, but two years from now, we may go back and re-analyze that information and find one," Dr. Krantz said.

Genomic medicine straddles both the clinical and research sides of CHOP. It may guide physicians in patient management, but it also generates a huge amount of data that, with appropriate consent from families, researchers can leverage to make discoveries to improve care. They can search for new genes or associations, figure out how changes in suspected disease genes are functioning, and translate that knowledge into developing therapies. Part of the Roberts IMGC's goal is to invite every patient that they see to participate in a protocol approved by the Institutional Review Board to have their samples put in a biorepository to drive research. Already, the Roberts IMGC has found six brand-new genes that they are evaluating.

“I think the world is going to change dramatically,” Dr. Krantz said. “And it’s happening really, really fast, as far as medicine goes. It challenges all of us in genomics to constantly be at the cutting edge and stay on top of these breakthroughs so that we can translate them directly back to our patients, which is our mission here at CHOP.”

RESEARCH AFFINITY GROUPS CREATING STRONG TIES, PATTERNS FOR SUCCESS

Affectionately known by their acronym, RAGS, Research Affinity Groups at Children's Hospital of Philadelphia's Research Institute are like the bits of cloth that a resourceful crafter weaves together to create a colorful tapestry. In the same way, two new RAGS launched this year — the Global Health RAG and the mHealth RAG — assemble investigators from varied disciplines with common research interests to form strong ties and intertwine novel ideas and approaches that are the fabric of pediatric research.

Investigators who join the Global Health RAG, led by Elizabeth Lowenthal, MD, MSCE, research director for CHOP's Global Health Center, can learn from their own backyard about the challenges unique to international pediatric research. They also can find out about existing resources and infrastructure available within CHOP, the Penn Center for Global Health, and other affiliated groups such as the Penn Center for AIDS Research (CFAR) that currently support research projects in 14 countries, including regions in sub-Saharan Africa, Latin America, and Asia. Many of these low-income communities have huge populations of children who are suffering from treatable, preventable illnesses.

One researcher's journey to advance international pediatric research took him back to his homeland. Osayame Ekhaguere, MBBS, a CHOP neonatology fellow from Nigeria, is leading a randomized trial that seeks to improve infant immunization rates there. He will test an intervention that involves sending reminder text messages, calls, and emails to parents before their scheduled immunization visits are due.

In the Dominican Republic, where rates of anemia are high, a recent Global Health Center resident, Ryan Close, MD, is studying if giving families an iron ingot shaped like a fish and instructions on how to cook with it could be a successful long-term dietary supplementation strategy to support children's growth and development.

With funding from a pilot grant through CHOP's Global Health Center, orthopedic surgeon David Spiegel, MD, is assessing the long-term outcomes of a procedure to repair clubfoot in children living in Nepal.

While their results could catalyze improvements in pediatric health worldwide, these projects still have a long road ahead. Global Health RAG members will help them navigate some of the practical and ethical considerations that often come up when working in resource-limited settings, such as financial management, data security in settings with limited internet access, onboarding foreign research staff, and reporting results to appropriate international stakeholders.

"I hope the Global Health RAG will bring us all together and give us some inspiration on how we can expand and strengthen our programs and systems within the institution to allow us to have strong collaborations on the other end," Dr. Lowenthal said. "I'd like to hear from CHOP researchers about the amazing global health research they're doing and what their dreams are so that we can help them to find potential collaborators and move their ideas forward."

Another brave new world for pediatric researchers is the uncharted territory of mHealth, or mobile health, which incorporates an array of communication technologies — from basic text messages, apps and social media; to more complex wearable devices that link to electronic health records; to futuristic ideas such as implantable and ingestible devices — to connect with young patients and families.

"mHealth is a new paradigm of research in a lot of ways," said Nadia Dowshen, MD, an adolescent medicine specialist at CHOP and an assistant professor of Pediatrics at the Perelman School of Medicine at the University of Pennsylvania.

Dr. Dowshen is a co-chair of the mHealth RAG along with co-chairs Lisa Schwartz, PhD, a CHOP psychologist and assistant professor of Pediatrics at Penn, and Linda Fleisher, PhD, MPH, a senior scientist in CHOP's Center for Injury Research and Prevention, and a senior fellow in Penn's Leonard Davis Institute of Health Economics.

An important aspect of mHealth, the three co-chairs pointed out, is that mobile technology is constantly changing. The mHealth RAG members will help each other keep pace with this fast-moving field to ensure that their research activities remain relevant and are aligned with the latest mHealth trends. Also, mHealth gives researchers opportunities to understand human health and behavior in more detailed ways, but the amount and type of data that it generates will require bioinformatics specialists who can relate their knowledge of mHealth data management and analysis.

For example, Dr. Dowshen conducted a mHealth trial to improve adolescents' adherence to antiretroviral medication using two-way text messaging and an app with interactive features. She kept track of every text sent and received by the 25 participants during the six-month study. Previous research relied on electronic signals from pill boxes or bottles to record adherence, but Dr. Dowshen found that her patients with HIV did not routinely use them to store their medication in order to protect their confidentiality. Collecting mHealth data through text messaging was feasible and acceptable for youth and allowed Dr. Dowshen to look at patterns of adolescents' adherence to antiretroviral therapy in a way that previously would not have been possible.

mHealth certainly has the potential to encourage patients to take more responsibility for their health and improve their quality of care; however, more evidence is needed to determine the best approaches for mHealth, from policy to implementation. Researchers will need to act quickly, as consumers' expectations for mobile patient engagement continue to rise.

"Patients and families certainly want to use these new ways of communicating, but there is a lot of research to be done to understand how best to do that, who uses it, who doesn't use it, and in what situations," Dr. Fleisher said. "Although mHealth seems ubiquitous already, there is much we don't know."

An internal survey conducted by the mHealth Working Group revealed that almost 50 percent of the 173 CHOP researchers who responded were interested in learning more about mHealth, and almost 35 percent were currently conducting mHealth research or quality improvement projects. Those already involved in mHealth research said they would welcome support in the areas of in-house development, information systems, and vetting commercial and academic partners. As more research funding opportunities for mHealth begin to emerge, it is likely the mHealth RAG will attract even more investigators who want to interlace mHealth research methods into their projects.

"The mHealth Research Affinity Group will get the key players and stakeholders together to compare notes, experiences, and expertise to determine how we can best move mHealth research forward at CHOP," Dr. Schwartz said.

CHILDHOOD CANCER RESEARCH EFFORT SHOOTS FOR THE MOON

A parent experiencing a cancer diagnosis in his child knows a unique pain. Often, that pain transforms to passion directed against the disease. Rarely, that passion ignites a rocket powering massive change. This was clearly the case for former U.S. Vice President Joe Biden. In the wake of the loss of his adult son Beau to brain cancer in 2015, Biden took the helm of an ambitious national effort to dramatically accelerate progress against cancer in all its forms.

"The goal of this initiative is simple — to double the rate of progress. To make a decade's worth of advances in five years," Biden said upon the February 2016 launch of the initiative, dubbed the Cancer Moonshot. The effort is designed to increase public and private resources to fight cancer while breaking down silos to bring cancer fighters together. It is built on the premise that together, a coordinated strategy and well thought-out flight plan can reach a lofty shared goal like NASA's effort to reach the moon.

Fortunately for the many advocates and scientists focused on childhood cancer, a prominent leader in pediatrics was among those helping to plot the scientific course for this initiative in its planning stages. As a member of the Blue Ribbon Panel for the Cancer Moonshot initiative, Peter Adamson, MD, a pediatric oncologist at Children's Hospital of Philadelphia and professor of Pediatrics at the Perelman School of Medicine at the University of Pennsylvania, was one of a select group of experts from academia, industry, and advocacy, who guided the National Cancer Institute (NCI) on how to achieve this goal.

"It was very important that the NCI recognized that out of all the potential areas for accelerating research, childhood cancer must be a priority," said Dr. Adamson, who also chairs the Children's Oncology Group (COG). "Cancers in children are often fundamentally different from cancers that occur in adults. The approaches to treatment may differ, and the scientific opportunities may prove unique."

Childhood cancer has also historically been underrepresented in research and research funding, and the need for progress on more effective and targeted treatments remains urgent. Childhood cancer is the leading cause of death from disease in children, and even those cancers that have high survival rates leave many children with lifelong health difficulties related to their treatments.

As co-chair of the Blue Ribbon Panel's working group focused on pediatric cancer, one of seven such groups addressing major topic areas, Dr. Adamson convened leaders from across the country to identify innovative areas of science that were poised to make transformative advancements with the appropriate investments. Two of Dr. Adamson's colleagues from CHOP, Stephen Hunger, MD, director of the Center for Childhood Cancer Research, and John Maris, MD, a pediatric oncologist and co-head of the Pediatric Cancer Dream Team, served as members of the working group, which took a broad view of the state of the science and considered recommendations solicited from the public. The chairs of multiple working groups met as the ideas began to take shape, in order to identify cross-cutting themes and develop shared recommendations.

The Moonshot effort comes at a key junction in pediatric cancer research and cancer research in general. Technologies for sequencing the human genome, once seen as the great frontier in developing more precise treatments, have yielded a number of findings of genetic mutations that drive various types of cancer. As this technology has become inexpensive, fast, and ubiquitous, however, scientists are beginning to reach its limits.

One limitation: Pediatric cancers turn out to have fewer mutations than adult cancers, leaving a need for further explanation through epigenetic or other mechanisms. Another limit: Sequencing studies reveal that many cancers that appear to be a single type under a microscope in reality comprise distinct molecular subtypes that may respond to distinct treatment approaches. As a consequence of making already-rare cancers even rarer, these findings make it all the more necessary for national and international collaborations to make new discoveries and test new therapies. Such collaborations and sharing infrastructure that have already been part of efforts through the NCI, COG, and other groups, are poised to reach new levels as the Cancer Moonshot plan gets off the ground.

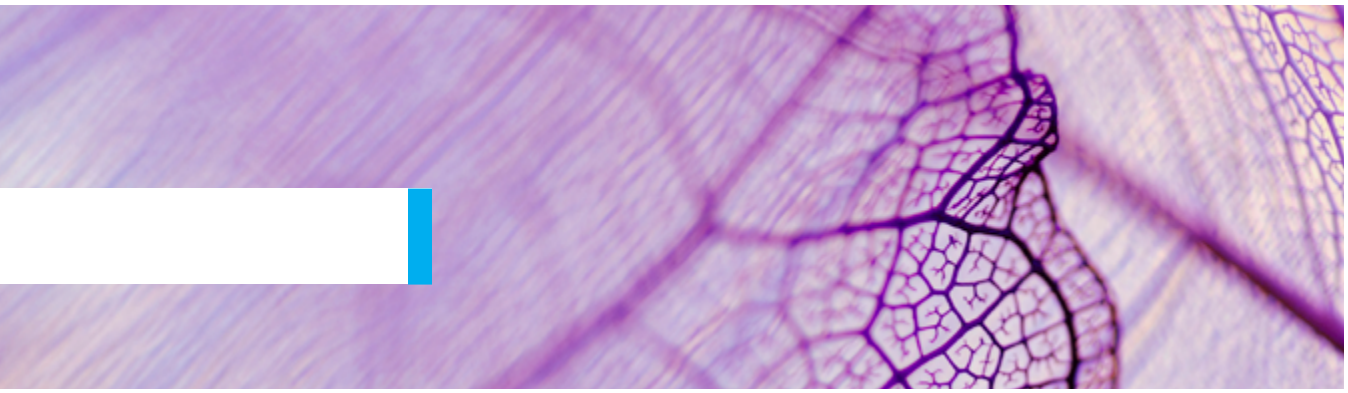
The Blue Ribbon Panel's scientific roadmap, adopted in September 2016 by the NCI's National Cancer Advisory Board (on which Dr. Adamson is also a member), encompassed 13 transformative research recommendations. Many of them span multiple types of cancer and address the most critical needs for large-scale infrastructure and collaboration. Three recommendations in particular have direct relevance to the greatest challenges facing pediatric cancer today.

One of the key recommendations for pediatric cancer research focuses on cancer therapy resistance — as experts recognize that if cancer returns after treatment, it often is far deadlier than a newly diagnosed cancer.

A second area of pediatric cancer research that the Blue Ribbon Panel chose to highlight is fusion oncoproteins. These proteins arise as a result of two genes becoming inappropriately fused together, like two stuck pages in a cookbook. The protein those fused genes then produce is akin to preparing a mixed-up recipe, such as a dish that is half creamy English trifle, half meaty shepherd's pie. Serving those unpleasant entrees in specific cell types turns out to be essential in driving many childhood cancers, including certain leukemias, brain tumors, and many types of sarcomas. Better organized and better funded efforts can fill the large knowledge gaps about how these fusion proteins drive cancer and lead to new therapies that target these proteins.

Likewise, more work remains to be done to advance therapies that harness the body's immune system to attack cancer. At CHOP, research on Dr. Maris' Dream Team and in the T-cell therapy research of Stephan Grupp, MD, PhD, and colleagues, are prime examples of immunotherapies' emergence as some of the most promising approaches to cancer. Yet research thus far suggests that molecular targets that the immune system will need to attack in pediatric cancers are likely to be distinct from those in adult cancers. The Blue Ribbon Panel therefore recommended creating cancer immunotherapy clinical trials networks for both pediatric and adult cancers. The networks would coordinate efforts nationwide both for developing new therapies and testing them effectively.

"I see a way forward to develop specific treatments for cancers that have defied targeted treatment for many years," Dr. Adamson said. "Knowing the drivers of the cancers, but not understanding how those drivers work, and not knowing how to develop a therapy for them, is perhaps one of the more frustrating situations not only for clinicians and scientists, but most importantly for patients and families. We still use drugs developed in the 50s, 60s, and 70s to treat these cancers. If we can change the paradigm and understand how these fundamental genetic changes in the tumor lead to cancer and how we can develop a therapy towards that, then we will begin in earnest to enter an era of precision medicine that is both more effective and less toxic."



COLLABORATION ›

CHOP EXPERT ADVISES BLUE RIBBON PANEL FOR NATIONAL CANCER MOONSHOT INITIATIVE

Peter Adamson, MD, a pediatric oncologist at Children's Hospital of Philadelphia and chair of the Children's Oncology Group, joined the Blue Ribbon Panel for the National Cancer Institute (NCI), as a part of former U.S. Vice President Joe Biden's national Cancer Moonshot initiative.

The panel served as a working group of the presidentially appointed National Cancer Advisory Board, which Dr. Adamson was named to in June 2015 by President Obama. Panel members considered how to advance new approaches in cancer research, and in September, they issued issue 13 recommendations for the Cancer Moonshot, three of which focused on childhood cancer.

"For the Panel's pediatric working group, we assembled leaders from around the country in a very short timeframe to identify innovative areas of science today that could accelerate progress in pediatric cancer," Dr. Adamson said. "And we're fortunate that many of the leaders in childhood cancer research are right here at CHOP, including Stephen Hunger, MD, chief of the division of Oncology and director of the Center for Childhood Cancer Research at CHOP, and John Maris, MD, a pediatric oncologist at CHOP and co-head of the Pediatric Cancer Dream Team, who are pursuing new treatments for the most challenging childhood cancers. As part of the working group, they helped us focus the discussion and think about transformative research ideas."

Read more about the pediatric research in the Moonshot era.

RESEARCH INSTITUTE'S LEADER ADVANCES LIFE SCIENCES INDUSTRY

Bryan Wolf, MD, PhD, Chief Scientific Officer of CHOP's Research Institute, will contribute valuable insight from 25 years of working with pediatric health researchers and scientists in his new role as a member of Life Sciences Pennsylvania's (LSPA) Board of Directors.

LSPA, formerly Pennsylvania Bio, is a statewide trade association representing 700 members that aims to ensure the economic vitality of the life sciences industry by promoting collaboration and public policies that support innovation in the pursuit of improving human health. As a board director, Dr. Wolf will foster supportive relationships within this vibrant community of scientists, biotechnology companies, drug manufacturers, and entrepreneurs.

"A key role of the Research Institute is to take the discoveries and breakthroughs from the research labs into everyday clinical practice, in order to have the greatest impact on the care of our children," Dr. Wolf said.

As one of Pennsylvania's top industries, the life sciences sector employs about 78,000 people directly and is known for its highly skilled workforce. LSPA has honored several leading visionaries in this scientific arena for their groundbreaking research and medical engineering performed at the Research Institute and at the Perelman School of Medicine at the University of Pennsylvania.

Read more in Cornerstone.

MITOCHONDRIAL EXPERT SHARES INSIGHTS ON ETHICS OF EMERGING GENETIC TOOLS

Marni Falk, MD, an attending physician in the division of Human Genetics who directs the Mitochondrial Disease Clinical Center at Children's Hospital of Philadelphia, participated in an expert committee convened by the Health and Medicine Division (formerly Institute of Medicine) of the National Academies of Science, Engineering, and Medicine to evaluate the ethical, social, and policy considerations of emerging techniques that could provide a new reproductive option for mothers who face the risk of passing mitochondrial disease on to their child.

Mitochondria have their own genetic material called mitochondrial DNA (mtDNA) that babies inherit only from their mother and can cause various medical disorders if mutations occur. Through the modification of an egg or fertilized egg, mitochondrial replacement techniques (MRTs), could help prevent mtDNA disease by replacing the intended mother's mitochondria that contains a pathogenic mtDNA mutation with mitochondria containing healthy mtDNA from a female donor.

Dr. Falk and committee members issued a report in February 2016 that recommended clinical research into MRTs proceed with careful oversight, and they contributed to a *New England Journal of Medicine* perspective article on MRTs' implications for clinicians.

"It was a great experience because of the unique opportunity to get to interact with such thoughtful people having deep expertise in policy and ethics and have them learn and carefully consider the broader implications of quite intricate aspects of science and medicine," said Dr. Falk, who is also an associate professor of Pediatrics at the Perelman School of Medicine at the University of Pennsylvania.

Read more in Bench to Bedside.

NEW DIRECTOR BROADENS SCOPE OF PEDIATRIC RESEARCH IN OFFICE SETTINGS NETWORK

Alexander Fiks, MD, MSCE, FAAP, a primary care pediatrician at Children's Hospital of Philadelphia, became director of the Pediatric Research in Office Settings (PROS) network in January 2016. The American Academy of Pediatrics developed PROS to help foster research through partnership between practicing pediatricians and researchers. Once developed, questions could be researched throughout this national network of primary care practices.

In his new leadership role, Dr. Fiks aims to broaden the range of PROS studies to include large clinical trials, secondary analyses of electronic health record data from practices, and longitudinal surveys of practitioners.

"The key to achieving these goals will be making sure that researchers and practitioners around the country know that PROS is interested in learning about their research and ideas," Dr. Fiks said. "In this way, PROS can best serve as a resource to improve the effectiveness of primary care."

Dr. Fiks is associate medical director for CHOP's Pediatric Research Consortium; associate director of the Center for Pediatric Clinical Effectiveness; a founding member of the Department of Biomedical and Health Informatics; and a PolicyLab faculty member. He also mentors multiple faculty and academic fellows, and he is an associate professor of Pediatrics at the Perelman School of Medicine at the University of Pennsylvania.

Read more in Cornerstone.

RESEARCH CHAIR OF PCORNET HELPS TRANSFORM CLINICAL STUDIES

Christopher Forrest, MD, PhD, a professor of Pediatrics at Children's Hospital of Philadelphia and the Perelman School of Medicine at the University of Pennsylvania, wants to generate faster, cheaper, and better clinical research. As newly appointed chair of the research committee for the national patient-centered clinical research network called PCORnet, he is helping research studies take shape to include a participant population of up to 80 million Americans who are part of 33 large research networks.

"PCORnet's sweet spot is taking existing treatments and understanding how well they work in the real-world population," Dr. Forrest said. "A lot of times decisions are made based on gut feelings or based on physicians' practices that were handed down to them from their teachers, and there may not be good research that underpins them. Clinical trials that show a medication actually does work, don't take account of all the diversity we have in patient populations. PCORnet, with 80 million people, is able to address that diversity."

Dr. Forrest was already principal investigator of one of PCORnet's component networks, PEDSnet, which brings together data from eight children's hospitals including CHOP to accelerate discovery in pediatric clinical research.

Read more about Dr. Forrest's work with PCORnet and PEDSnet in the Collaboration section.

CHOP RESEARCHER APPOINTED TO MILITARY FAMILY READINESS COUNCIL

Children of military families face special circumstances as a result of their parents' deployments and frequent relocations. David Rubin, MD, MSCE, director of PolicyLab at Children's Hospital of Philadelphia, is using his expertise in a new role to ensure that they have timely and efficient access to pediatric healthcare services.

The United States Department of Defense (DoD) appointed Dr. Rubin to its Military Family Readiness Council, which makes recommendations to the Secretary of Defense about policies and programs for servicemen and servicewomen so that they are well-supported while focusing on their mission.

Dr. Rubin's team at PolicyLab has been conducting research for the DoD's Defense Health Program (DHP) since 2011, specifically examining the stress families experience when soldiers return home from deployment. Their findings published January 2016 in the *American Journal of Public Health* illustrate the need to support families throughout the deployment cycle.

"As a pediatrician at CHOP, I care for children from all different kinds of families, including those in the military," Dr. Rubin said. "And as a researcher, I know that these children face unique challenges and are greatly affected by the deployment of their parent. I look forward to serving military families as a member of the Military Family Readiness Council."

Read more in a CHOP press release.

POOLING CLINICAL DATA AIDS PATIENT-REPORTED OUTCOMES

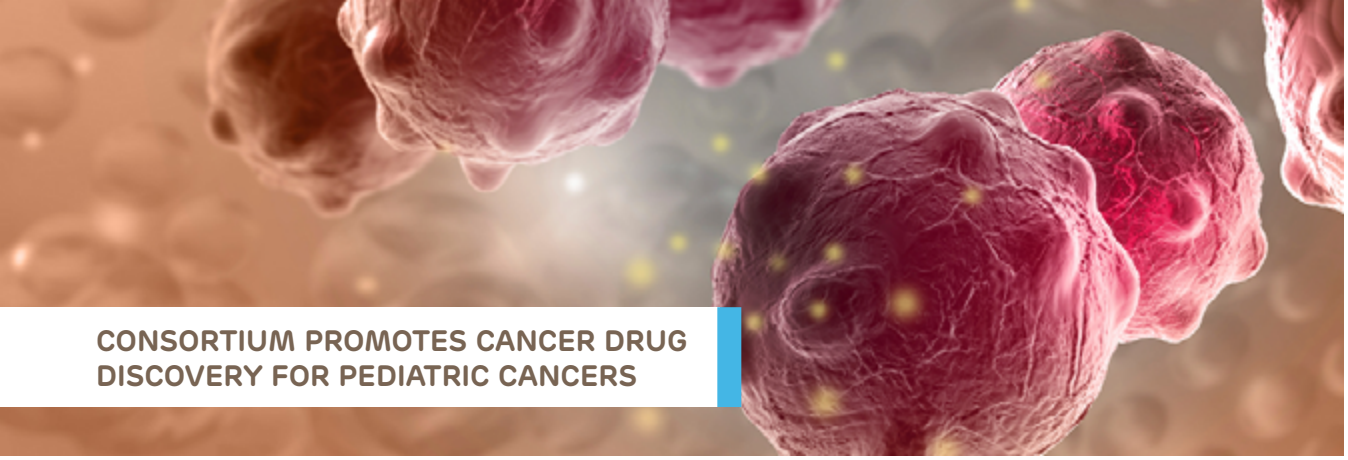
Going it alone is a no-go when it comes to making discoveries about rare diseases, a category that includes most serious pediatric diseases. No single pediatric institution usually has enough patients to generate large numbers of study participants, so research networks that provide access to diverse, nationally representative health information from millions of children are key to accelerating scientific discovery by facilitating a range of study designs and efficient study processes. A leader in many such networks, Children's Hospital of Philadelphia has received several new opportunities just in the last year to advance collective efforts against rare and chronic pediatric diseases.

PEDSnet, a clinical data research network that combines clinical data from eight children's hospitals, including CHOP, plus several specialty disease networks, received $8.6 million in funding to continue its discovery and implementation of new ways to provide the best care and outcomes for children. PEDSnet is one of 13 clinical data research networks under the umbrella of PCORnet: the National Patient-Centered National Clinical Research Network. The three-year grant from the Patient-Centered Outcomes Research Institute (PCORI), an independent nonprofit organization based in Washington, D.C. which also oversees PCORnet, allowed PEDSnet to enter its second phase in its second year, integrating data from each of its members.

"With our first phase of funding, PEDSnet developed infrastructure for rapid learning with observational studies and clinical trials," said CHOP's Christopher Forrest, MD, PhD, who is the principal investigator of PEDSnet and a professor of Pediatrics at the Perelman School of Medicine at the University of Pennsylvania and was also named chair of the research committee for PCORnet in 2016. "This second phase of funding will enable PEDSnet to reach a high level of operational excellence, ultimately moving into a sustainable research network that advances children's health through faster and cheaper clinical research."

Dr. Forrest's work as principal investigator of PEDSnet will benefit another major initiative he leads as Steering Committee Chair, the Validation of Pediatric Patient-Reported Outcomes in Chronic Diseases (PEPR) Consortium. The PEPR consortium was launched with grants from the National Institutes of Health in September 2015 to advance the science of patient-reported outcome measures. The effort aims to validate standardized patient survey tools so that patients' own reports of outcomes such as fatigue, stress, and positive affect can be quantified and compared over time and across study populations in the same way that blood pressure, cholesterol, and other lab test results can be compared today. CHOP is a leader of one of four centers receiving NIH PEPR awards and serves as the consortium's administrative leader, supporting resources and technical expertise for projects undertaken by PEPR investigators at the other three centers. The infrastructure developed under PEDSnet offers a data management platform and standardized data formats and sharing for PEPR research data.

Read more about the PEDSnet Phase 2 award and the PEPR Consortium on Cornerstone.



CONSORTIUM PROMOTES CANCER DRUG DISCOVERY FOR PEDIATRIC CANCERS

Accelerating drug discovery for pediatric cancers through robust preclinical testing is essential to translate genomic discoveries into targeted therapies. Preclinical testing provides reliable data for scientists to decide which agents to test in human clinical trials. Children's Hospital of Philadelphia's involvement as one of four centers in the new Pediatric Preclinical Testing Consortium (PPTC) launched by the National Cancer Institute aims to help researchers identify more effective treatments for children with cancer.

Pediatric oncologist John M. Maris, MD, who leads CHOP's research program within the PPTC, focuses on forms of neuroblastoma that are at high risk of treatment failure despite chemotherapy, radiation therapy, and immunotherapy. Neuroblastoma is a tumor of nerve tissue that develops in infants and children. Dr. Maris' laboratory has created preclinical models of neuroblastoma that incorporate genetic material from patient tumor cells. Because neuroblastoma is particularly complex and variable, this approach allows scientists to understand the unique genetics of a patient's tumor and develop patient-specific therapies that target a cancer's vulnerabilities while sparing healthy cells.

"Before testing a drug in children, we need a scientific basis for using it, based on deep understanding of the biology involved, and supported by promising results in cell and animal models," Dr. Maris added. "These preclinical findings will provide stronger evidence for us to engage proactively with drug companies who could partner in developing these drugs."

Dr. Maris also envisions that preclinical research will lead to rational drug combination strategies for more effective treatments, rather than a reliance on single agents. Dr. Maris is collaborating on this project with CHOP co-investigators Yael P. Mossé, MD, Kateryna Krytska, and Matthew Tsang. The other centers in the PPTC, selected like CHOP after a highly competitive process, focus on leukemia (Lowy Cancer Research Center, Australia), brain tumors (Texas Children's Hospital), osteosarcoma (tumors in bone; The Children's Hospital at Montefiore, New York), and other sarcomas and kidney tumors (Greehey Children's Cancer Research Institute, San Antonio, Texas).

TEAM SCIENCE ESSENTIAL KEY TO ACCELERATING AUTISM RESEARCH

Big problems require big thinkers. That is why the Center for Autism Research (CAR) at Children's Hospital of Philadelphia teamed up with 20 other medical institutions in a new online initiative dubbed SPARK, designed to become the largest autism study ever undertaken in the U.S.

Sponsored by the Simons Foundation Autism Research Initiative, SPARK (stands for Simons Foundation Powering Autism Research for Knowledge) will collect information and DNA for genetic analysis from 50,000 individuals with autism and their families. Autism spectrum disorder has a strong genetic component, researchers say, but while 65 genes that definitely play a role in autism have already been identified, scientists estimate about 300 or more are involved.

"Identifying genes is critically important for developing new therapies for autism; however, one of the greatest challenges for researchers is the sheer number of gene variants associated with autism, combined with the tremendous variability in the symptoms and manifestations of autism," said Robert T. Schultz, PhD, director of CAR and professor of Pediatrics at the Perelman School of Medicine at the University of Pennsylvania, who is leading CHOP's research site in the study along with clinical neuropsychologist Juhi Pandey, PhD, a senior scientist at CAR and clinical assistant professor of Psychiatry at the Perelman School of Medicine. "In order to begin to see a pattern of genetic causes, extremely large samples of patients are needed for research. Team science and collaboration is the only viable path forward for rapidly making progress, and SPARK provides us with just such an opportunity."

Within less than a year from its kickoff in February 2016, the SPARK network collected samples from more than 10,000 people, with approximately 2,500 of those coming from the CHOP site.

For more information, visit www.SPARKforAutism.org/CHOP. To learn about other areas of CAR research, visit www.centerforautismresearch.org.

STAY OR GO HOME? STUDY LOOKS AT DISCHARGE STRATEGIES FOR AML PATIENTS

Children's Hospital of Philadelphia is leading a $1.8 million multicenter study to shed light on how physicians could safely approach patient discharge scenarios after children with acute myeloid leukemia (AML) receive a course of chemotherapy at a hospital, while also considering family preferences.

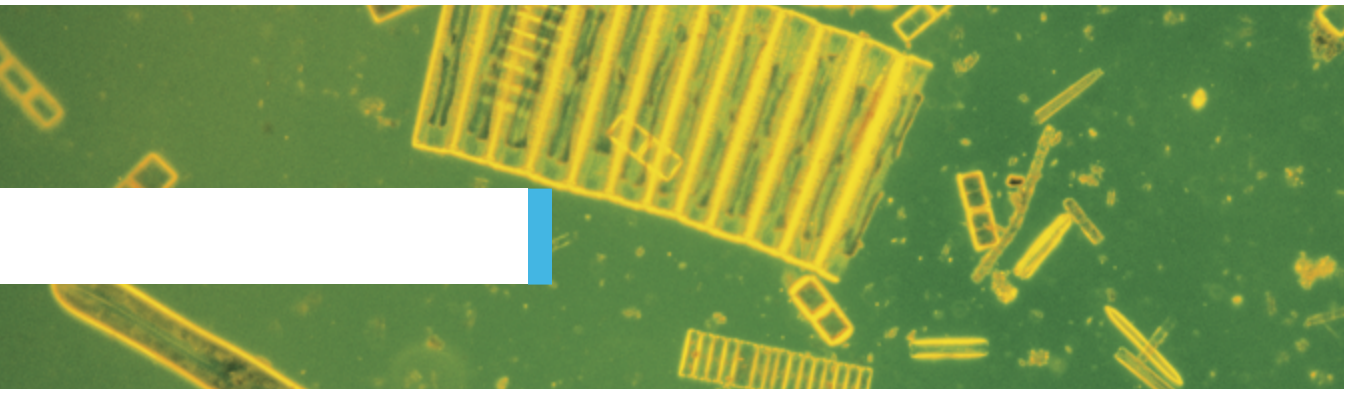
During the periods following treatment, pediatric cancer patients can have a difficult time fighting off bloodstream infections and related complications. Because of this risk, some physicians prefer that children with AML stay in the hospital for close monitoring after treatment. Other doctors allow patients to go home and return to the hospital if a fever occurs. However, physician-researchers do not have enough evidence to know with certainty if patients are better off remaining in the hospital or going home with their families.

The study, entitled "Home or Away From Home," will compare 490 patients' medical records to determine the risks/benefits of outpatient vs. inpatient management of neutropenia in children with AML. Fifteen pediatric hospitals from across the U.S. will participate. In addition to collecting data so that the study team can compare each discharge strategy's medical outcomes including bloodstream infection and delays in subsequent courses of chemotherapy, several sites also will assess patient outcomes by surveying patients and families about their quality of life.

"We are very excited about this highly collaborative study that we hope will help us improver our care for children with acute myeloid leukemia," said Richard Aplenc, MD, PhD, a CHOP pediatric oncologist and AML researcher and professor of Pediatrics at the Perelman School of Medicine at the University of Pennsylvania who is the principal investigator of the three-year study funded by the Patient-Centered Outcomes Research Institute.

Dr. Aplenc also was recognized in March by Hyundai Hope on Wheels with a $1 million Hyundai Quantum Award to advance his work on innovative immunotherapy approaches. The new grant will enable his team to identify specific proteins on the outside surface of AML cells that could be the most appropriate targets for immune cells programmed to attack cancers.

"This award will help CHOP physicians and their collaborators develop new therapies for children with AML that has not responded to current therapies, or has relapsed despite those therapies," said Stephen Hunger, MD, chief of the division of Oncology and director of the Center for Childhood Cancer Research at CHOP and professor of Pediatrics at the Perelman School of Medicine.



HONORS ›

LEADING THE WAY BY HARNESSING 'BIG DATA' TO HELP LITTLE PATIENTS

Childhood cancers, infectious diseases, genetic diseases, and many other contemporary biomedical and health problems are full of challenges. But an astounding glut of data created in the course of trying to solve those problems may itself be one of the most dominant challenges in 21st century.

Analyzing patients' biological samples with newer sequencing tools results in huge amounts of data about genes and genomes, RNAs, and proteins — and making sense of that sequencing data requires a huge amount of computational power. At the same time, organizational structures divide how clinical and research data can be shared and used to gain collaborative insights. Fortunately, innovators at Children's Hospital of Philadelphia are deftly navigating these emerging roadblocks to success with the next phase of pediatric discoveries. CHOP experts are pursuing multiple leading-edge ways of harnessing and sharing big data to improve children's health and lives in the realms of bioinformatics and clinical informatics.

A population health project spearheaded by two CHOP clinical informatics fellows is one such example. The Population Health Risk Assessment Support Engine (PHRASE Health) is an electronic portal built to integrate into any electronic health record (EHR) system that allows for a two-way flow of data between clinicians and public health agencies. Such a flow could be especially useful in the event of evolving public health situations, such as the outbreak of Zika virus. Public health officials can provide timely updates about evolving disease and patient risk factors through the system, while clinicians consume these recommendations in the EHR and utilize one-click reporting of disease cases back to the public health department.

In December 2015, PHRASE creators Marc Tobias, MD, and Naveen Muthu, MD, of CHOP's Department of Biomedical and Health Informatics (DBHi), received first prize in the "Closing the Data Divide" Virtual Challenge, jointly sponsored by the de Beaumont Foundation and the Practical Playbook. In July 2016, PHRASE was named a Phase 1 winner of the Provider User Experience Challenge by the U.S. Department of Health and Human Services' Office of the National Coordinator for Health Information Technology.

While PHRASE represents an approach to harness and empower medical data for population health (and vice-versa), another CHOP-led effort launched this year shows how collaborative approaches to data can strengthen and speed discovery of new biomedical approaches to pediatric disease. The Center for Data-Driven Discovery in Biomedicine (D3b) was established in December 2015 as a way to break down silos that keep data separate and limit its usefulness for discoveries in pediatric cancer and other pediatric diseases. By building platforms that empower patient participation in research, make data more open, and encourage sharing and collaboration, D3b aims to accelerate discoveries that would not be possible when individual researchers and institutions keep data to themselves. Led by CHOP's Research Institute and DBHi, D3b builds on related, successful examples of CHOP-led multi-institutional research and clinical trial consortia, including the Children's Brain Tumor Tissue Consortium (CBTTC) and the Pacific Pediatric Neuro-Oncology Consortium (PNOC).

One of D3b's first major initiatives is the launch of its open-access pediatric genomic data cloud, CAVATICA, announced in October 2016 as a private commitment in conjunction with the national Cancer Moonshot. CAVATICA gives clinicians and scientists access to big data about diverse pediatric diseases that is empowered for secure, collaborative analysis

through scalable cloud computing — meaning that the users of the service do not need to bring their own high-powered computers in order to perform complex analyses of vast quantities of data. Researchers worldwide will be able to access this information and work together to fully empower and share novel ideas and approaches for new biological targets for precise, less toxic clinical treatments on behalf of children.

"Data and patients are the organizing principle of how we do what we do," said Adam Resnick, PhD, scientific chair of the CBTTC and PNOC and co-director of D3b with Neurosurgery Division Chief Phillip "Jay" Storm, MD. "Data can be immortalized forever, and that's a legacy that patients and families leave behind when they choose to contribute to and participate in research in the face of serious and sometimes lethal diseases. It is our responsibility as partners in research to honor that legacy to support rapid discovery of new treatments and new cures for childhood diseases through partnership and collaboration."

Read more about PHRASE Health and about the launch of D3b in Bench to Bedside.

MAKING HEADWAY IN UNDERSTANDING AUTISM IN THE BRAIN

A chair equipped with a high-tech helmet is a new hot seat of innovation in research on autism spectrum disorder (ASD). Studies at Children's Hospital of Philadelphia that use noninvasive magnetoencephalography (MEG) brain imaging are allowing researchers to understand more about ASD and other neurological conditions. Compared to other types of brain-imaging methods, MEG enables researchers to look deeper inside the brain, to better visualize brain functions in conjunction with structural brain images to gain new insights, and to engage high-need patient populations who have been underserved in research.

"When neural activity is happening, it produces electrical and magnetic fields," said J. Christopher Edgar, PhD, a clinical neuropsychologist and brain imaging researcher in the department of Radiology at CHOP and associate professor of Radiology at the Perelman School of Medicine at the University of Pennsylvania. "We use this machine to measure the magnetic field. We do that to look at brain function."

In recent years, Dr. Edgar and Timothy Roberts, PhD, vice chair of research and director of the Lurie Family Foundation's MEG Imaging Center in Radiology at CHOP and professor of Radiology at Penn, and their colleagues in Radiology and CHOP's Center for Autism Research (CAR), have used MEG to identify neural differences that correlate with the level of clinical impairment of individuals on the autism spectrum, particularly in the realm of language ability. Those subtle functional neural differences can now be used as biomarkers to detect whether an interventional approach has a measurable impact on the brain in some individuals, even if a behavioral impact is difficult to measure — and several ongoing studies are headed in that direction. And MEG is also allowing the team to ask more basic questions about the physiology of ASD.

One such question, according to Dr. Roberts: "Is the autism spectrum continuous or discrete in terms of these brain markers?" In a study he co-leads with Dr. Edgar and CAR clinical psychologist Emily Kuschner, PhD, he is able to address that question by enrolling nonverbal and minimally verbal individuals on the autism spectrum who are otherwise rarely included in brain-imaging research, and who therefore cannot be assumed to benefit from most such studies' findings.

This is made possible by an innovative study design that takes advantage of some of MEG's distinct benefits compared to other brain-imaging techniques: It measures brain responses that automatically occur without intentional action by the participant, such as auditory nerve signaling when hearing sounds or resting-state brain rhythms that occur without any action. And MEG scanning does not require participants to stay completely motionless for extended periods of time. This approach, called MEG-PLAN (MEG Protocol for Limited Ability Neuroimaging), also incorporates unique behavioral design elements to tailor the experience for this population, taking the standard effort at autism-friendliness in research to a new, more personalized level.

The study is funded by the Eunice Kennedy Shriver National Institute of Child Health and Human Development of the National Institutes of Health (NIH) and part of CHOP's Intellectual and Developmental Disabilities Research Center.

With other MEG studies, researchers at CHOP are taking a deeper look at structural and functional aspects of brain differences in ASD which may be the critical missing step in developing new and better therapies. For example, in MEG studies funded by the National Institute of Neurological Disorders and Stroke and National Institute of Mental Health of

the NIH, Dr. Edgar is using MEG to obtain measures of activity throughout the entire brain, rather than just on the surface of the head — starting with the thalamus, a deep brain structure that may be the source of a fundamental brain rhythm that coordinates brain activity more broadly.

In children and teens with and without ASD, he aims to examine the association between the structure of the thalamus, pathways from the thalamus to the brain surface, and brain activity. He will also measure changes in these brain structural and activity measures in participants over time to see if differences in brain development can distinguish youth on the autism spectrum from their typically developing peers. If Dr. Edgar's findings bear out the hypothesis that the thalamus is associated with these fundamental brain-rhythm abnormalities in ASD, they could indicate a need for new treatment strategies that target related pathways.

Read more about MEG-PLAN and MEG studies of thalamus-related brain rhythms in Bench to Bedside.

DYNAMIC CANCER TRIAL CLOSES THE LOOP BETWEEN LAB AND CLINIC

Precision medicine is the gleaming new hope for defeating disease. These newer treatments targeted to the underlying molecular causes of cancer, in particular, have shown exciting promise. But the ways new drugs are tested are perhaps still too blunt.

"We're setting ourselves up for failure," said Yael Mossé, MD, a pediatric oncologist at Children's Hospital of Philadelphia and associate professor at the Perelman School of Medicine at the University of Pennsylvania, describing traditional clinical trials for pediatric cancer. Most trials of new drugs enroll patients with relapsed or refractory disease for whom no curative options remain — regardless of whether there is any reason to think that the investigational drug will act on the molecular cause of the patient's cancer. And they test just one drug at a time.

Dr. Mossé is leading an innovative new trial for neuroblastoma that dynamically and quickly translates findings from the lab into new, personalized treatments for children with relapsed or refractory neuroblastoma. Usually appearing as a solid tumor in the chest or abdomen, neuroblastoma accounts for a disproportionate share of cancer deaths in children, despite many recent improvements in therapy.

Neuroblastoma is "a microcosm of the childhood cancer problem," Dr. Mossé said.

This group of tumors of the peripheral nervous system has one name and generally looks similar under the microscope. Yet, by working with patients, researchers have learned time and again that the disease is extremely heterogeneous, due in large part to the many different underlying genetic and molecular causes of disease, which can both interact to affect treatment responsiveness and change over time in cases where the cancer relapses after treatment.

Dr. Mossé's new study is the first prospective clinical trial in children with cancer that, by design, addresses the cancer's hidden biological diversity — one disease by name, many diseases at the molecular level. Known as the **NE**xt-generation **P**ersonalized **NE**uroblastoma **THE**rapy (NEPENTHE) trial, it is moving forward with a new $1.5 million grant from Alex's Lemonade Stand Foundation (ALSF), announced in December 2015. Earlier support for this trial was provided by the Band of Parents and Arms Wide Open, Solving Kids' Cancer Foundation, and the Open Hands Overflowing Hearts Foundation. The NEPENTHE trial, which opened to patient accrual in August 2016, is a collaborative effort, enlisting the expertise of co-investigator and internationally prominent CHOP neuroblastoma researcher John Maris, MD, and numerous other specialists throughout CHOP and other institutions.

"The novelty of this trial could be viewed on numerous levels," Dr. Mossé said. "It's based on rigorous preclinical data, understanding the molecular drivers that are important in this disease. It's combining multiple novel drugs, not just one at a time. And it's bringing that to the clinic and assigning patients to therapy based on what their tumor genetics are teaching us at the time that they meet us with relapsed or refractory cancer."

Dr. Mossé hopes that ultimately investigators can use NEPENTHE as a model for future precision medicine clinical trials — dynamically linking clinical needs to preclinical insights — that could apply more broadly to other childhood cancers.

Read more in Bench to Bedside.

ENTREPRENEURIAL SPIRIT REVVING UP PEDIATRIC RESEARCH AT CHOP

Sometimes the most innovative thing a scientist can do is to venture outside of research. For a rapidly growing cohort of investigators and clinicians at Children's Hospital of Philadelphia, doors are opening to new entrepreneurial ventures that take their ideas from the lab and clinic and disseminate them to save and improve lives in the wider world through commercialization.

"The big issue for me is that this is actually going to have a life beyond scientific papers and impact lives," said Flaura Winston, MD, PhD, founder and scientific director of the Center for Injury Research and Prevention (CIRP) at CHOP and professor of Pediatrics at the Perelman School of Medicine at the University of Pennsylvania.

Dr. Winston anticipates having this impact through Diagnostic Driving Inc., a spinoff company of which she is co-founder and chief scientific advisor. It is one of three companies to accelerate into business based on ideas developed at CHOP in the last year with help from the Office of Entrepreneurship & Innovation (OEI), which was established in May 2015.

Diagnostic Driving is built on more than two decades of foundational research on motor vehicle crashes, a leading cause of death and disability in the U.S. This research, conducted by Dr. Winston and her colleagues, was funded by the National Science Foundation, the National Institutes of Health, the Commonwealth of Pennsylvania, and other sources, and culminated in a five-year process of creating and validating a Simulated Driving Assessment software package. The software reliably identifies dangerous drivers and leverages these data to mitigate risk and coach drivers to be safer on the road.

"For driving assessment software, there just so happened to be an initial market in corporate fleets," said Venk Kandadai, MPH, co-founder and CEO of Diagnostic Driving, who initially worked with Dr. Winston as a project manager and a data scientist at CIRP.

The pair gained this insight through participation in the business accelerator Dreamit Health in 2015. They conducted market research, finding that the corporate fleet market is worth $4 billion, of an estimated $60 billion per year that these companies spend on automotive crashes; they built a mobile prototype of their software; and they piloted the software with a Fortune 100 corporation. The team sees other markets emerging, including with U.S. states around driver licensing procedures.

"By commercializing this software we can intervene to prevent disability, lost work, and cost for employers and society," said Dr. Winston, who also chairs the Scientific Advisory Committee for OEI. "Through hard and diligent work, Venk is transforming what is strong science but not really practical into something that is very practical and can have utility far and wide. That is incredibly gratifying."

OEI and other CHOP offices continuously offered logistical support to the fledgling company prior to its launch, in the form of protected time for Kandadai to focus on the entrepreneurial venture while he was still a CHOP employee, support with IRB and conflict-management processes to ensure ethical and transparent approaches to business activities, and more. After the startup's official launch as an independently owned and operated company, CHOP owns equity in the company. These are among the many ways OEI works to create an entrepreneurial spirit throughout CHOP, both in

the Research Institute and in clinical and administrative domains. It identifies and supports promising ideas that can be nurtured and developed into licensable assets, new clinical services, and spinouts; develops strategic partnerships; and helps people at CHOP to develop early stage ideas including innovative devices, therapies, mobile applications, and software tools.

OEI's SPRINT program, begun in late 2015, provides in-house business incubation for a wide variety of entrepreneurial ideas generated within the CHOP community. A few examples emerging from CHOP research include the PHRASE Health software to connect public health data and patients' electronic health records in clinical settings and a beverage to reduce the risk of diabetes.

"CHOP has always been a leader in research, a place full of people generating ideas that improve health," said Patrick FitzGerald, vice president for entrepreneurship & innovation. "Now what we're trying to do is build on that strength with the entrepreneurial skill set to bring those ideas to market in a faster and more commercially focused way."

Read more about Diagnostic Driving in Bench to Bedside.

COMMITMENT ›

PATIENT IMPACT AWARD GOES TO FETAL SURGERY INNOVATOR, N. SCOTT ADZICK, MD

N. Scott Adzick, MD, Surgeon-in-Chief and the founder and director of the Center for Fetal Diagnosis and Treatment at Children's Hospital of Philadelphia, has dedicated his career to pursuing groundbreaking prenatal treatments to correct debilitating and life-threatening birth defects.

In recognition of his innovative accomplishments, Dr. Adzick received the Patient Impact Award at Life Sciences Pennsylvania's, formerly Pennsylvania Bio's, annual dinner in March.

"Congratulations to Dr. Adzick for this well-deserved award," said Bryan Wolf, MD, PhD, Chief Scientific Officer and director of the CHOP Research Institute and a Life Sciences Pennsylvania board member. "He is relentless in his pursuit of perfection, passionate about treating our most fragile patients, visionary and innovative in the OR, a leader and builder of an exceptional multidisciplinary team, and a great colleague."

Dr. Adzick led a research team funded by the National Institutes of Health that demonstrated surgically repairing spina bifida before birth resulted in significantly better outcomes for children than repairing it after birth.

"It is so rewarding to see patients, who before even being born received grave diagnoses, growing up healthy and strong," said Dr. Adzick, reflecting on the impact of 20 years of caring for patients at the Center for Fetal Diagnosis and Treatment, some of the earliest of whom have thrived and are reaching young adulthood.

In November, Dr. Adzick was also honored by Congenital Hyperinsulinism International with its "Be My Sugar" Award for Surgical Excellence. In 1999, Dr. Adzick helped world renowned HI pioneer, Dr. Charles Stanley, create the Congenital Hyperinsulinism Center at CHOP. The Center offers evaluation, diagnosis, treatment and follow-up care for children with HI, and is the largest and most active HI Center in the world.

To learn more about Dr. Adzick and the courageous families who come to the Center for Fetal Diagnosis and Treatment, see the PBS documentary series "Twice Born — Stories From the Special Delivery Unit," that received an Emmy award in September from the National Academy of Television Arts & Sciences.

VACCINE HERO PAUL OFFIT, MD, RECOGNIZED ON MANY FRONTS

Paul Offit, MD, director of the Vaccine Education Center at Children's Hospital of Philadelphia, celebrated in October the 10th anniversary of the rotavirus vaccine's approval by the U.S. Food and Drug Administration. Dr. Offit co-invented the vaccine, which has dramatically reduced the incidence of the disease in the U.S. upon its inclusion in the recommended vaccine schedule for babies in 2006.

"Before rotavirus vaccination, roughly half a million children would go to U.S. emergency rooms every year from this infection," Dr. Offit said. "Of that number, 75,000 children would be hospitalized with severe dehydration, and 20 to 60 would die. Today, child hospitalizations from rotavirus have dropped by 85 percent in this country."

In October 2015, Dr. Offit, who is also is the Maurice R. Hilleman Professor of Vaccinology and professor of Pediatrics at the Perelman School of Medicine at the University of Pennsylvania, was inducted into the American Academy for Arts and Sciences along with the likes of journalist and novelist Tom Wolfe and singer-songwriter Judy Collins. The recognition for his accomplishments continued as he joined the class of 2015 Fellows elected by the American Association for the Advancement of Science (AAAS), and was recognized at the 2016 AAAS Annual Meeting in Washington, D.C. Dr. Offit also received the 2016 Porter Prize from the University of Pittsburgh, which honors an individual's exceptional performance in health promotion and disease prevention.

In 2016, Dr. Offit also won the Franklin Founder Award from the city of Philadelphia, the Lifetime Achievement Award from the Philadelphia Business Journal, and the Jonathan E. Rhoads Medal for Distinguished Service to Medicine from the American Philosophical Society. To top off all those awards, Dr. Offit became a Vax Pack Hero, one of about 50 central figures who played roles in the history of vaccines and are featured in a new educational program launched in 2016 by the Vaccine Education Center.

Dr. Offit is an author and vocal advocate for vaccine safety, childhood immunization, and stricter vaccine waiver requirements, publishing more than 150 papers in medical and scientific journals and six award-winning medical narratives.

Learn more about Dr. Offit in a Q&A that appeared in Bench to Bedside.

KWAKU OHENE-FREMPONG, MD, RECEIVES GHANA MILLENNIUM EXCELLENCE AWARD

Kwaku Ohene-Frempong, MD, has a personal connection to sickle cell disease that has driven his research efforts to make a worldwide impact.

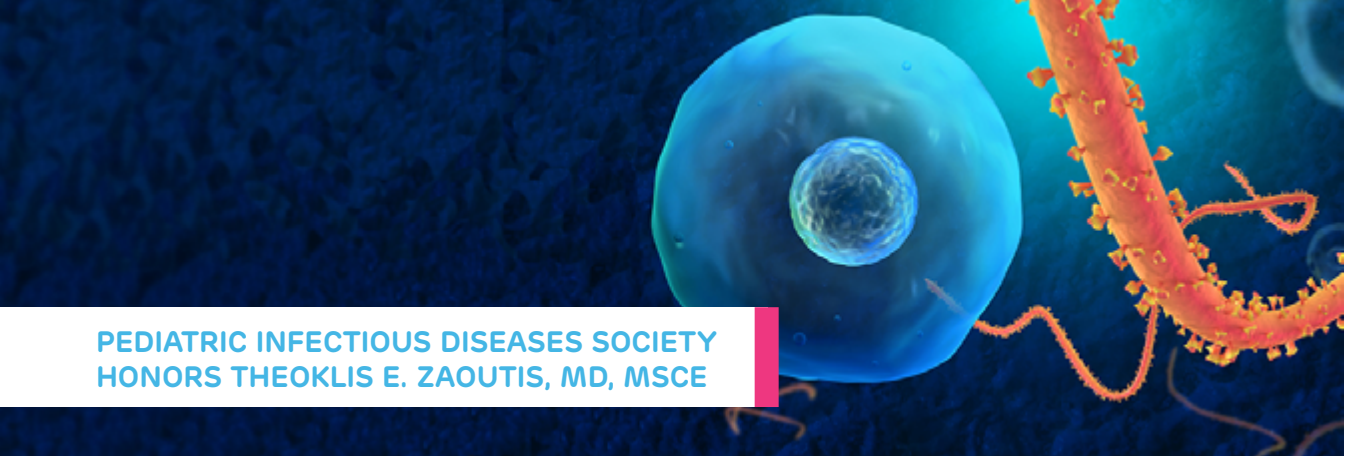
Director Emeritus of the Comprehensive Sickle Cell Center at Children's Hospital of Philadelphia, President of the Sickle Cell Foundation of Ghana, and a world-renowned authority on sickle cell disease, Dr. Ohene-Frempong received a Millennium Excellence Award from the Millennium Excellence Foundation of Ghana in December 2015.

Dr. Ohene-Frempong, who is himself a carrier of the sickle cell trait, was recognized for his ongoing research on the disease and his efforts that established the first newborn screening program for the disease in Africa, a program which he is helping to expand nationwide. In addition, he has helped establish several sickle cell clinics in Ghana, the largest of which now has more than 10,000 patients.

"I was completely surprised, and it was a pleasant recognition not only of my work in sickle cell disease, but for the work my colleagues in Ghana have been able to accomplish," Dr. Ohene-Frempong said. "I am only a catalyst for much of that activity, since I'm a visitor from time to time, but there are many others who continue to work hard."

In addition to his research focus on clinical complications from sickle cell disease at CHOP, Dr. Ohene-Frempong treats children with thalassemia, hemophilia, anemias, and other blood disorders.

Learn more about Dr. Ohene-Frempong in Bench to Bedside.



PEDIATRIC INFECTIOUS DISEASES SOCIETY HONORS THEOKLIS E. ZAOUTIS, MD, MSCE

The World Health Organization lists antibiotic resistance as one of the three greatest threats to human health. Theoklis E. Zaoutis, MD, MSCE, chief of the division of Infectious Diseases at Children's Hospital of Philadelphia, was recognized in October 2015 by the Pediatric Infectious Diseases Society (PIDS) with a Distinguished Service Award for his superb leadership and research contributions that are on the frontline of this public health issue.

The award recognizes an outstanding society member who is dedicated to the specialty of pediatric infectious diseases. Dr. Zaoutis is involved in several national studies funded by the National Institutes of Health to determine what is the least amount of antibiotics physicians can use to effectively treat infections.

"The less antibiotics you use, the less likely you are to develop a resistant bug or bacteria," Dr. Zaoutis said. "A lot of my research is focused on using antibiotics more appropriately so that we do not develop antibiotic resistance."

The award also recognized Dr. Zaoutis' strong track record in publishing. When PIDS launched the *Journal of the Pediatric Infectious Disease Society* in 2011, Dr. Zaoutis was named the inaugural editor-in-chief.

"He has been an extremely effective editor of the journal, as he is thoughtful, efficient, well-organized, fair-minded, well-informed, outspoken in the right way, and passionately committed to the causes he champions," according to a PIDS announcement of the award given during IDWeek 2015, a combined annual scientific meeting of PIDS and several other professional organizations focused on infectious diseases.

Dr. Zaoutis is also director of the Center for Pediatric Clinical Effectiveness at CHOP and Werner and Gertrude Henle Professor of Pediatrics and professor of Epidemiology at the Perelman School of Medicine at the University of Pennsylvania.

Learn more about Dr. Zaoutis in a Q&A that appeared on Cornerstone.

DOUGLAS WALLACE, PHD, EARNS ELITE RECOGNITION FOR MITOCHONDRIA RESEARCH

Douglas Wallace, PhD, director of the Center for Mitochondrial and Epigenomic Medicine at Children's Hospital of Philadelphia, was selected for two distinguished honors in the past year in recognition of his scientific contributions as the founder of the field of mitochondrial medicine. In October, the Franklin Institute announced Dr. Wallace as the recipient of the 2017 Benjamin Franklin Medal in Life Science, just a few months after he was inducted as a foreign member of the Italian Academy of Sciences during its 234th Annual meeting May 5 in Rome.

The Franklin Medal, a highly esteemed international award established in 1824, has been awarded to scientific superstars including Albert Einstein, Thomas Edison, Stephen Hawking, Marie Curie, Nikola Tesla, Niels Bohr, Bill Gates, and Max Planck. More than 100 Franklin Medal laureates have also received Nobel Prizes.

Founded in 1782 as the Italian Society, the Italian Academy of Sciences has a mission of encouraging scientific research and disseminating the progress of science to schools and the general public. Its membership is limited to 40 Italian scientists and 25 foreign members. Its exclusive membership rolls have listed such luminary names as the Italian scientists Alessandro Volta, Camillo Golgi, and Amedeo Avogadro, and non-Italians Louis Pasteur, Benjamin Franklin, and Albert Einstein.

"We are deeply honored that this very elite international scientific organization has recognized Dr. Wallace's accomplishments," said Bryan Wolf, MD, PhD, Chief Scientific Officer and director of the Research Institute, on the occasion of Dr. Wallace's induction to the Italian Academy.

Analysis of the mitochondrial DNAs of a diverse array of patients led Dr. Wallace to discover mitochondrial DNA diseases and that mitochondrial DNA variation contributes to a wide range of rare and common metabolic and degenerative diseases as well as cancer and aging. His research program is an important part of our newly launched Roberts Collaborative for Genetics and Individualized Medicine.

Dr. Wallace joined CHOP in 2010 as the founding director of the CMEM, and is a professor of Pathology and Laboratory Medicine at CHOP and the Perelman School of Medicine at the University of Pennsylvania. He is also a member of the U.S. National Academies of Sciences and Medicine and the American Academy of Arts and Sciences.

Learn more about Dr. Wallace in a Q&A that appeared in Bench to Bedside.

MENTORSHIP ACHIEVEMENTS OF ELAINE ZACKAI, MD, STAND OUT

The American Society of Human Genetics (ASHG) named Elaine H. Zackai, MD, director of clinical genetics at Children's Hospital of Philadelphia and professor of Pediatrics and Obstetrics and Gynecology at the Perelman School of Medicine at the University of Pennsylvania as the first-ever recipient of its Mentorship Award. A presentation at the ASHG Annual Meeting in October honored Dr. Zackai as the winner.

The Society, founded in 1948, is the primary professional membership organization for human genetics specialists worldwide with the mission to advance human genetics in science, health, and society, through excellence in research, education, and advocacy.

"Dr. Zackai's nomination included testimonials from 38 former trainees who now occupy research and clinical positions at institutions around the world," said Raju Kucherlapati, PhD, chair of the ASHG Awards committee. "Their comments credited her dedication to her students, leadership by example, compassion for patients, and rigorous approach to diagnosis with inspiring them to successful careers in human genetics."

Dr. Zackai is a long-time member of ASHG and served on its Awards and Abstract Review Committees in 1998. She has held faculty and hospital appointments at CHOP and the University of Pennsylvania, where she has focused on diagnosis, dysmorphology, and applied clinical research responding to real-world situations.

Learn more about Dr. Zackai in a Q&A that appeared on Cornerstone.

NEONATOLOGIST BARBARA SCHMIDT, MD, FRCP(C), MSC, GIVEN PRESTIGIOUS AWARD

A neonatologist at Children's Hospital of Philadelphia received an honor comparable to the Presidential Medal of Freedom, the highest civil award in the U.S. Barbara Schmidt, MD, FRCP(C), MSc, who works in the division of Neonatology at CHOP and the Hospital of the University of Pennsylvania, was made a Member of the Order of Canada for her contributions to advancing the standard of care for critically ill newborns in Canada and abroad.

The Canadian Governor General presents honors and awards on behalf of all Canadians to recognize those people who have demonstrated excellence, courage, or exceptional dedication to service in ways that bring special credit to Canada.

Dr. Schmidt, who is a Canadian citizen, has been the lead investigator of three major clinical trials that have changed how care is provided in neonatal intensive care units across North America. Additionally, her novel approach to long-term patient follow-up has influenced the design of all studies involving newborns.

"I am honored and humbled by this award and delighted that rigorous clinical research in neonatal medicine has received this recognition from the Canadian government," said Dr. Schmidt, who is also a professor of Pediatrics and the Kristine Sandberg Knisely Chair in Neonatology at the Perelman School of Medicine at the University of Pennsylvania.

THREE TALENTED RESEARCHERS WIN YOUNG PHYSICIAN-SCIENTIST AWARDS

Good things always come in threes, so the saying goes, and the rule certainly held true for three outstanding physician-researchers at CHOP who received 2016 Young Physician-Scientist Awards. As part of this special recognition, they shared their novel insights at a joint meeting of the Association of American Physicians, the American Society for Clinical Investigation, and the American Physician Scientists Association in April.

GREGORY E. TASIAN, MD, MSC, MSCE

Although kidney stones are more common in adults, the diagnosis of this painful condition in children has risen dramatically over the past 25 years. Despite that fact, little is known about the best treatment course and prevention strategies for children with kidney stones. Gregory E. Tasian, MD, MSc, MSCE, witnessing this trend firsthand as a pediatric urologist and epidemiologist, has developed a research program that seeks to identify determinants of kidney stone disease and effective interventions to reduce the risk of kidney stone recurrence among children.

His findings gained attention for identifying the effect of daily temperatures on kidney stone presentation. In his study, published in *Environmental Health Perspectives*, Dr. Tasian reported that extremes of hot and cold temperatures were associated with an increased risk of presenting with kidney stones. These results suggest that current and future climate change may contribute to increased morbidity from kidney stones, which currently affects approximately 9 percent of the U.S. population. Specifically, he found that the delay between high daily temperatures and kidney stone presentation was short, peaking within three days of exposure to hot days. Sizzling temps increase evaporative water loss, which leads to a higher concentration of calcium and other minerals in the urine that promote the formation of kidney stones.

“The goal of my research is ultimately to lead to personalized, targeted interventions to increase fluid intake and decrease the risk of recurrence,” said Dr. Tasian, who also is an assistant professor of Surgery and Epidemiology at the Perelman School of Medicine at the University of Pennsylvania. “If we can identify those periods of risk, then we also can identify interventions to offset that risk.”

Read more about Dr. Tasian’s kidney stones research in our blog.

MICHELLE DENBURG, MD, MSCE

Michelle Denburg, MD, MSCE, is an attending physician in the division of Nephrology at CHOP and an assistant professor of Pediatrics and Epidemiology at the Perelman School of Medicine. In addition to both earning Young Physician-Scientist Awards, Dr. Tasian and Dr. Denburg have something else in common: Their research interests overlap in fascinating ways.

Kidney stones are increasingly being recognized as a chronic disorder of mineral metabolism, which is a focus of Dr. Denburg’s research on bone health in childhood chronic kidney disease. Dr. Denburg and Dr. Tasian worked together on a research paper published in the *Clinical Journal of the American Society of Nephrology* that showed people with kidney stones — especially male teens and young women — are at a higher risk for bone fractures than the general population.

"Recognizing that these children are at high risk for compromised bone health, the next step is identifying factors that we can modify to optimize their bone accrual as much as we can and set them up for entering adulthood in a better state," Dr. Denburg said.

At the joint meeting of the young investigators in Chicago, Dr. Denburg presented a related study published in *Kidney International* that evaluated the impact of interventions for kidney stones on the development of hypertension and chronic kidney disease. This study confirmed that patients with kidney stones are at higher risk for developing hypertension and chronic kidney disease, and found that shock wave lithotripsy to the kidney is independently associated with a significantly higher risk of hypertension, while ureteroscopy is not. Therefore, this study has important implications for the management and long-term follow-up of these patients.

Dr. Denburg's research program is also focused on bone and mineral metabolism in patients with another form of kidney disease, nephrotic syndrome. A new project that Dr. Denburg is excited to launch is her collaboration with PEDSnet and the NephCure Kidney Network to create a Pediatric Glomerular Disease Learning Network (GLEAN) along with pediatric nephrologists from eight participating institutions, including CHOP. Patients with glomerular diseases lose protein in their urine. When these protein losses are very high, called nephrotic syndrome, patients experience swelling, low blood protein, and potentially deterioration of kidney function and other complications.

GLEAN investigators are using data captured in the electronic health record to identify patients with glomerular disease across the eight pediatric centers and create a large cohort of participants to enable outcomes and comparative effectiveness research, quality improvement studies, and eventually pragmatic clinical trials. One of the initial goals Dr. Denburg aims to accomplish through GLEAN is to perform the first study of musculoskeletal outcomes in children and adolescents with glomerular diseases.

"Since PedsNet has more than 5 million children represented, GLEAN is an opportunity to study patients with these rare diseases on a much larger scale than in the past and to address many of the challenges to implementing high quality trials," Dr. Denburg said.

SHANA MCCORMACK, MD, MTR

Shana McCormack, MD, MTR, an attending physician in the division of Endocrinology and Diabetes at CHOP who studies neuroendocrine regulation of energy balance, was proud to be in the company of her fellow colleagues who were honored with Young-Physician Scientist Awards. Dr. McCormack is especially interested in finding potential common pathways of mitochondrial dysfunction in patients with diabetes and patients with genetic mitochondrial disorders.

Dr. McCormack received great feedback at the joint meeting that gathered all the young investigators when she presented her project that uses novel magnetic resonance imaging (MRI) studies of muscle mitochondrial function. The new noninvasive technique, developed by her colleagues at the University of Pennsylvania's Center for Magnetic Resonance and Optical Imaging, estimates mitochondrial energy production.

More precisely, this technique can detect changes in muscle creatine content before and after exercise that allow estimation of mitochondrial oxidative phosphorylation (OXPHOS) capacity, an important indicator of energy production. Some of the advantages of this new approach, called creatine chemical exchange saturation transfer (CrCEST), are that it is noninvasive, avoiding the need for a muscle biopsy, and that it provides excellent anatomic resolution, allowing researchers to assess mitochondrial function in different muscle groups simultaneously.

"The mitochondria are the energy-producing factories of the cell, and there are a number of endocrine conditions that are characterized by decreased oxidative phosphorylation capacity, where the mitochondria are not producing energy properly," Dr. McCormack said. "This problem has all sorts of downstream effects, and different muscle types can be affected differently in response to metabolic diseases. In order to study the phenomenon better, we need to have a good, noninvasive way of measuring mitochondrial oxidative phosphorylation capacity, especially if we wish to study children longitudinally to assess the impact of a metabolic disease."

In a paper published in the November issue of *JCI Insight*, Dr. McCormack and her colleagues demonstrated that CrCREST is a viable technique to measure OXPHOS capacity in individuals with genetic mitochondrial diseases. This new tool will help researchers to gain insights into mitochondrial bioenergetics and provide an objective biomarker for clinical treatment trials so that they can determine if an intervention is helping a patient's mitochondria to function better.

Dr. McCormack is also an assistant professor of Pediatrics at Penn. Read more about her research on disorders of energy balance in our blog.

VISIONARIES ›

A STRATEGY TO REDEFINE PEDIATRIC RESEARCH EXCELLENCE

For over nearly a century, Children's Hospital of Philadelphia has been home to one of the most vibrant and robust pediatric research institutions in the world. Our position as a leader in pediatric research underscores that innovation is both a differentiator for CHOP and critical to the Research Institute's mission.

We've made myriad contributions to understanding the causes of pediatric diseases and conditions and developing new ways to treat patients and improve care every day. Whether in the laboratory or the clinic, the commitment, compassion, and vision of our investigators and their teams has unquestionably broadened the world of possibility for more children.

Amid our accomplishments, it's good policy to periodically pause and assess where the organization has been and its future directions. During FY16 we engaged in an in-depth and extensive strategic planning process aimed at gaining a fresh perspective – one based on honest assessment, benchmarking, and insight from key stakeholders – to create a roadmap for the next stage in the evolution of the Research Institute.

The strategic planning initiative was, in essence, an opportunity to not only promote our tradition of excellence but to redefine what excellence means as we strive to create healthier futures for each generation.

Underlying this nearly yearlong initiative is the unwavering support of our preeminent community of researchers who together have the breadth and depth of scientific expertise to continue leading the world in basic scientific discovery and creating breakthroughs in care for all children. At the conclusion of the strategic planning process, we are devoted to cultivating an even higher-performing environment that mobilizes the right experts to solve the most challenging problems in child health.

The culture of the Research Institute will evolve into one that fosters "faculty-first" collaboration. This means we will fortify our infrastructure and channel our unique resources to build upon our research teams' previous successes at CHOP and accelerate our progress to achieve greater pediatric research excellence from bench to bedside and beyond. We will accomplish this by implementing the following specific tactics:

- Strengthen our expertise in **fundamental basic sciences** to fuel scientific breakthroughs, leading to treatments/cures for rare diseases
- Develop pediatric-focused interventions and treatments to **prevent onset of adult disease**
- Understand how diseases progress into adulthood and **optimize treatments to enhance function and improve lives** as children become adults
- Develop **novel therapies, medical devices, and treatment techniques** that cure disease and reward innovation
- Lead the world in **first-in-pediatrics clinical trials** for new drugs and devices
- Create scientific capacity to **address critical public/population health challenges and engage with the Philadelphia community** and beyond
- Develop a first-of-its-kind **multi-dimensional data collection, integration, storage, and analytic capability**

As we reach our ambitious goals, the Research Institute's efforts will truly redefine pediatric research excellence to advance scientific discovery at CHOP and improve the lives of children everywhere.

CENTER FOR APPLIED GENOMICS MARKS DECADE OF DISCOVERIES

When Children's Hospital of Philadelphia established the Center for Applied Genomics (CAG) in 2006 with a $40 million commitment, it was one of the largest single investments in a research program in the hospital's history. The ambitious idea spearheaded by CAG's founder and director, Hakon Hakonarson, MD, PhD, was to establish the world's largest pediatric genomics biobank and to use that vast quantity of genetic data to discover the causes of disease and disability hidden within a population's genes. A decade later, that ambition has translated to spectacular, world-leading successes thanks to hundreds of scientists' intelligence and hard work and hundreds of thousands of families' help.

The enormous collection of DNA samples, powered by family participation, is the lynchpin of that effort. From the earliest days after CAG was established, well over 100 CHOP investigators were eager to build this biobank. Together with members of the CAG staff, many of whom have been with the program since its inception, they have contributed to patient recruitment, phenotyping, and sample collections from families who volunteered to participate.

"This is by far the biggest pediatric biobank in the world," said Dr. Hakonarson, who is also a professor of Pediatrics at the Perelman School of Medicine at the University of Pennsylvania. "No one has anything remotely close to what we have built here at CHOP."

Today, the CHOP biobank includes samples from more than 400,000 people, including about 100,000 CHOP patients and their family members. With such a large number of samples, CHOP investigators have great statistical power to detect genetic variations underlying diseases in the population and to discover links between genetic underpinnings and disease phenotypes among patients. The biobank has contributed to discoveries that have been published in more than 500 scientific papers, many of them appearing in top-tier journals such as *Nature* and *Cell*. These encompass findings about the gene variations and genetic pathways involved in a wide range of conditions, including asthma, autism spectrum disorder, attention deficit hyperactivity disorder, cancers, schizophrenia, and Type 1 diabetes. In addition, CAG investigators and their collaborators have helped hundreds of families to resolve the underlying genetic causes of their extremely rare diseases.

More recently, CHOP researchers have begun to translate the collaborative genomic discoveries made with the CAG into novel therapies. For example, Yael Mossé, MD, a pediatric oncologist at CHOP and associate professor of Pediatrics at Penn, led a team that in 2008 discovered that a mutation in the gene ALK was a driver of most cases of rare, inherited neuroblastoma, a pediatric nervous system cancer. Within months after this discovery, neuroblastoma patients were able to receive an ALK-inhibitor drug, crizotinib, which had been approved for adults with lung cancer. Dr. Mossé and colleagues have continued to build on this work, identifying more effective ALK inhibitors to help patients whose tumors were less responsive to crizotinib. She is working to launch a clinical trial for a new drug.

A decade ago, success was by no means assured. But today, CAG's influence is evident across the research landscape and is poised to grow as more of the center's genomic discoveries lead to improved therapies and possibly cures for some of the most complex and devastating conditions affecting children.

Read more in a Bench to Bedside article.

TEAM SPREADS SUCCESS OF SMARTER CPR FOR CHILDREN

Heart-stopping. Critical moment. Life-or-death. The catchphrases that define powerful dramatic scenes have real-life antecedents in pediatric intensive care units (PICUs), where sick children are at the highest risk of cardiac arrest in the hospital. After an arrest, more than half of children do not survive to hospital discharge, adding up to more than 3,000 deaths each year.

But a decades-long effort at Children's Hospital of Philadelphia to make cardiopulmonary resuscitation (CPR) smarter has begun to tip that balance in favor of survival, locally, nationally, and internationally.

In recent years, a CHOP team has demonstrated an approach producing significant improvements in both CPR quality and patients' survival — and patient survival with favorable neurological outcomes has doubled. CHOP is developing the nation's first specialized pediatric cardiac arrest center, combining extraordinary clinical care, pioneering translational research, and global education and outreach.

"CHOP has led the field in discovering what is important for the quality of CPR for children, in the knowledge exchange and implementation science of how to perform and disseminate high quality CPR, and in modeling how CPR affects outcomes and quality of life for critically ill and injured children," said Vinay Nadkarni, MD, MS, a critical care physician at CHOP and professor at the Perelman School of Medicine at the University of Pennsylvania. "Kids are not just little adults. We are getting closer to solving the challenges of figuring out the impact of age, size, and developmental life cycle on performance and outcomes of CPR."

With a new grant from the National Institutes of Health awarded this spring, CHOP research scientists led by Robert Sutton, MD, MSCE, an attending critical care physician and assistant professor at the Perelman School of Medicine at the University of Pennsylvania, aim to disseminate CHOP's success across eight hospitals in a national clinical trial. They are helping hospitals across the globe to replicate their bundled approach of bedside refresher training, resuscitation to physiologic blood pressure targets, and post-arrest debriefing using quantitative data (almost like instant replay in sports) for the entire unit to learn from and improve the process of care after each cardiac arrest.

This bundle's effectiveness is the result of a combination of basic and translational investigation with bedside implementation of clinical therapies at CHOP over the past five years. The new emphasis on physiologic targets for CPR outcomes, for example, contrasts with older methods that focus only on the rate and depth of chest compressions. This innovation began with CHOP's large animal studies in the lab of Critical Care Medicine Division Chief Robert Berg, MD, that led to providing this more personalized CPR approach to patients. This approach also included the development of specialized training manikins on rolling carts so that clinicians could practice the newer methods at the bedside on a frequent basis.

With the new NIH grant, they will test whether this successful bundled approach leads to similar improvements in outcomes at other children's hospitals throughout the Collaborative Pediatric Critical Care Research Network (CPCCRN), a core group of eight top-tier medical centers with an intense focus on studying resuscitation improvement in pediatric ICUs. CPCCRN and other larger clinical research networks for resuscitation, such as the pediatric Resuscitation Collaborative (pedi-RES-Q) led by CHOP and supported by an unrestricted educational grant from the Zoll Corporation,

extend the work CHOP does as the nation's first specialized pediatric cardiac arrest center across the nation and the globe. The evidence-based methods that demonstrate success in these expanding concentric circles of research and quality improvement networks, in turn, shape the evidence and future guidelines for organizations such as the American Heart Association, which set the standard for how all hospitals respond to and treat cardiac arrest nationwide.

Read more in a Bench to Bedside article.

RESEARCH TO OUTSMART SUPERBUGS GETS RENEWED COMMITMENT

While many emerging diseases are scary, for many infectious disease specialists, antibiotic-resistant superbugs remain enemy number one. That is because these are the bugs that have learned how to evade our best defenses. Two million people in the U.S. become infected each year with organisms that are resistant to antibiotics, and those infections are the direct cause of at least 23,000 deaths annually, according to the Centers for Disease Control and Prevention (CDC). And, as more bugs are exposed to more drugs and evolve new tricks to elude them, the threat continues to grow.

Research on the best ways to keep antimicrobial medicines working as well as possible, for as long as possible, got a shot in the arm in June 2016 when the CDC announced $26 million in renewed funding for five of its Prevention Epicenters, more than doubling its previous awards and extending the program to 2020. The program brings together a small number of elite academic research centers, now 11 in total, to address problems in healthcare-associated infections.

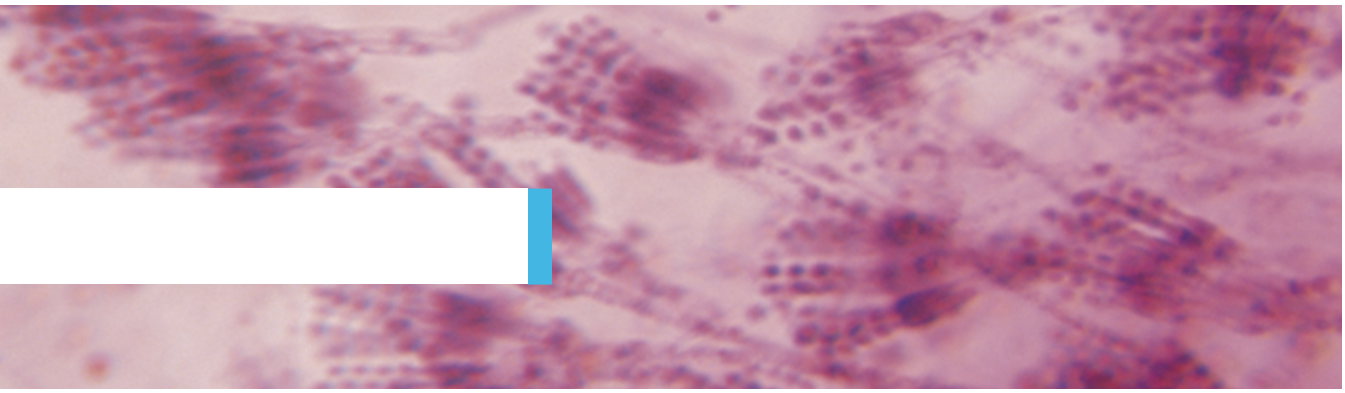
The Children's Hospital of Philadelphia and Perelman School of Medicine at the University of Pennsylvania Epicenter site received more than $5 million to continue its work, now with an increased emphasis on pediatrics, in addition to adult patients. With the renewal, Jeffrey Gerber, MD, PhD, medical director of the antimicrobial stewardship program at CHOP and assistant professor of Pediatrics and Epidemiology at Penn, joined Ebbing Lautenbach, MD, MPH, MSCE, chief of the division of Infectious Diseases at Penn, as co-principal investigator for the Penn-CHOP site.

Innovation and improvement in antimicrobial stewardship — practices to ensure that the right drugs get to the right patients in the right dose and delivery — are a particular strength of the Penn-CHOP site.

"The idea is to find a way to preserve the effectiveness of these often curative and sometimes lifesaving drugs, but not to lose them," Dr. Gerber said. "The overall goal is to optimize antimicrobial use, which is not just rationing or restriction, but designing systems to ensure that people select the drugs that work best to help fight infections while limiting unnecessary exposure that leads to antimicrobial resistance and adverse drug effects."

The broad collaboration across CHOP and Penn capitalizes on investigators' expertise in fields ranging from infectious diseases, critical care, pulmonary medicine, emergency medicine, epidemiology, biostatistics, bioinformatics, health economics, and microbiology. In addition to their emphasis on antimicrobial stewardship, they will focus on areas including risk factors and outcomes for healthcare-associated viral infections in hospitalized children and adults, and use of biomarkers to inform antimicrobial prescribing.

Read more about some of the CHOP-Penn Epicenter site's unique strengths on the Cornerstone blog.



BEVERLY DAVIDSON, PHD, NAMED CHOP'S FIRST CHIEF SCIENTIFIC STRATEGY OFFICER

Ensuring that a world-leading pediatric research enterprise is positioned for ongoing growth and preeminence is a weighty task that demands an accomplished leader. In February 2016, Beverly Davidson, PhD, took on such a critical role as Chief Scientific Strategy Officer (CSSO) at Children's Hospital of Philadelphia. In this newly created position, Dr. Davidson serves as an integral member of the CHOP Research Institute senior leadership team, has overall accountability for the implementation of the research strategic vision, oversees space and resources allocation, assists in recruitment of researchers, and works with development to ensure philanthropic support of CHOP's research mission. She also has key role in coordinating scientific alignment of CHOP with the Perelman School of Medicine at the University of Pennsylvania.

Dr. Davidson remains the director of the Raymond G. Perelman Center for Cellular and Molecular Therapeutics. She holds the Arthur V. Meigs Chair in Pediatrics at CHOP, and is a professor in the department of Pathology and Laboratory Medicine at Penn Medicine. Her research is focused on inherited brain disorders and the development of novel therapies to treat these fatal diseases. She is a fellow of the American Association for the Advancement of Science and has served as co-chair for study sections and review committees for the National Institutes of Health and as a member of the national advisory council of the National Institute of Neurological Disorders and Stroke, among numerous other honors and leadership positions.

"Dr. Davidson brings to the CSSO position a wealth of scientific expertise, a stellar track record of scientific innovation and leadership, an exciting vision for CHOP research, and exceptional qualities as a mentor and role model," said Bryan A. Wolf, MD, PhD, Chief Scientific Officer and director of the CHOP Research Institute, in appointing her to this new role.

KATHERINE YANG-IOTT TAKES NEW RESEARCH NAVIGATOR ROLE

Research at Children's Hospital of Philadelphia has a new helping hand from Katherine Yang-Iott, who became the first person in the newly defined role of Research Navigator in February 2016. The new Navigator role is intended to serve as the point of contact for investigators and the research community to listen to and address any questions and concerns about doing research at CHOP. Services include facilitating research processes, providing and connecting contacts, and coordinating opportunities for improvement wherever it is needed. As Navigator, Yang-Iott works in CHOP's Clinical Research Support Office and serves the entire CHOP Research Institute.

Yang-Iott has a background in basic laboratory research and has worked at CHOP since 2006. Her work in the lab of Craig Bassing, PhD, in the department of Pathology and Laboratory Medicine, focused on cancer pathobiology. In 2015, she completed the Research Administration Fellowship, a six-month program designed to give interested research personnel a broad overview of leadership in CHOP Research Administration with administrative directors in their areas of interest.

"My goal is to be an advocate for research faculty and staff," Yang-Iott said. "My job is to work with research administration as a resource to find ways to make researchers' jobs easier so that scientists can focus on their studies and discoveries."

Read more about Yang-Iott and the Navigator's role in her blog post on Cornerstone.

KAI TAN, PHD, FUSES CANCER BIOLOGY, AND BIOINFORMATICS

Too much information can be a bad thing if no one is able to interpret it. As next-generation sequencing methods have begun generating vast quantities of data about cancer and other diseases, there is a growing and urgent need for scientists who can find meaningful signals in the noise, such as identifying the specific genes or pathways that are most promising to target with new therapies.

Kai Tan, PhD, a cancer genomics and bioinformatics researcher who joined Children's Hospital of Philadelphia in January 2016, has pioneered the development of novel computational strategies and systems biology to identify molecular events that drive cancers. As a faculty member in the division of Oncology and in the department for Biomedical and Health Informatics at CHOP, and an associate professor of Pediatrics at the Perelman School of Medicine at the University of Pennsylvania, Dr. Tan collaborates with CHOP clinicians and engages with the robust cancer and genomic research communities at both CHOP and Penn Medicine.

His bioinformatics lab, which includes a team that came with him from the University of Iowa, develops algorithms to analyze next-generation sequencing data and gene network data to generate hypotheses about molecular targets for new treatments. In addition, he is beginning to develop algorithms to interpret data now available from analyses of single cells. Dr. Tan also studies the development pathways of hematopoetic stem cells (blood stem cells) in his work as a bench scientist, comparing mechanisms that regulate gene expression in both healthy and cancerous cells to gain insight into cancer's differences — and its weaknesses.

"CHOP's cancer center is one of the best, so I'm excited to apply our basic science skills to really do something that can eventually lead to new therapeutics," Dr. Tan said. "That's what really excites me."

Read more about Dr. Tan on the Cornerstone blog.

DANIEL RADER, MD, LEADS REUNITED DIVISION OF HUMAN GENETICS DIVISION

"Human genetics isn't bounded by children or adults; it's really one big continuum. Families are also a huge part of human genetics research, including families of all different ages," said Daniel Rader, MD, a professor and chair of the department of Genetics at the Perelman School of Medicine at the University of Pennsylvania.

The family principle was front and center with Dr. Rader's selection as the chief of the division of Human Genetics in the department of Pediatrics at Children's Hospital of Philadelphia. Since assuming this role in March 2016, Dr. Rader has been working to strengthen the family bonds within the CHOP division itself and between pediatric and adult genetics programs on the CHOP-Penn campus. The former divisions of Genetics and Metabolism were merged upon Dr. Rader's appointment to his new role, restoring a previous arrangement at CHOP that reflects the shared training and overlapping expertise among the individuals practicing in each specialty. Dr. Rader hopes to develop the division into a hub of genetics activities at CHOP that others from across the institution can consult for genetics-related questions and projects. At the same time, he aims to strengthen collaborations with adult genetics specialists at Penn to engage entire families of all ages in research and clinical care across the lifespan.

"We're fortunate to have attracted Dan to this position, in particular given his stature as a leader and a physician-scientist in the field of genetics," said Joseph St. Geme III, MD, CHOP's physician-in-chief and chair of the department of Pediatrics at CHOP and Penn. "His concurrent roles as chief of the division of Human Genetics at CHOP and chair of the department of Genetics at Penn create an exciting opportunity to unify the genetics community across the Penn and CHOP campuses, stimulating greater collaboration and increased progress in understanding and treating genetic diseases."

DENNIS DURBIN, MD, MSCE, EXPANDS LEADERSHIP ROLE IN CLINICAL RESEARCH

Dennis Durbin, MD, MSCE, was appointed Assistant Vice President and Chief Clinical Research Officer at Children's Hospital of Philadelphia in July 2016. This newly created role expands on Dr. Durbin's longstanding leadership responsibilities in CHOP's clinical research that include serving as the CHOP site principal investigator of the Clinical and Translational Science Award with the University of Pennsylvania, where he is also a professor of Pediatrics in the Perelman School of Medicine. Dr. Durbin served most recently as the director of the Office of Clinical and Translational Research at CHOP.

"One of Dennis' primary responsibilities is to promote institutional alignment by serving as the point of intersection among clinical operations, faculty affairs, research, and hospital administration," said CHOP Chief Scientific Officer and Research Institute Director Bryan A. Wolf, MD, PhD, in announcing Dr. Durbin's expanded role. "An important component of this rests with overseeing clinical research operations at CHOP, a major initiative stemming from our strategic planning process."

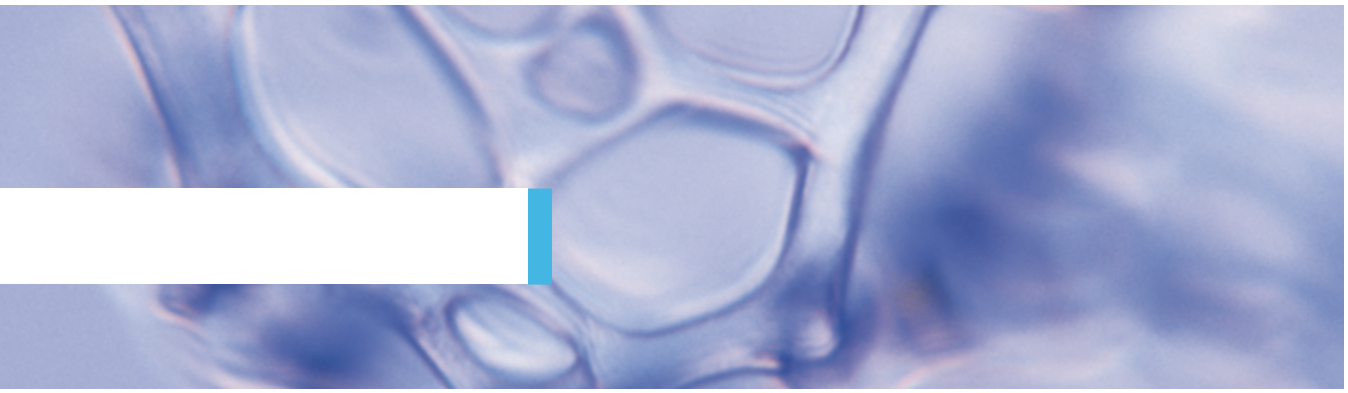
Dr. Durbin serves as a key member of Dr. Wolf's CSO Leadership Team, and in his expanded role as Chief Clinical Research Officer he partners with leaders across the CHOP enterprise and the University of Pennsylvania to support CHOP's research mission. He also participates in the development, communication, implementation, and organizational engagement of the Research Institute's strategy. While holding this growing leadership role, he continues to maintain his own clinical responsibilities and his role as a co-investigator on injury prevention research projects.

NEW LEADERSHIP KEEPS RESEARCH CORES PROGRAM ROBUST AS SCIENCE EVOLVES

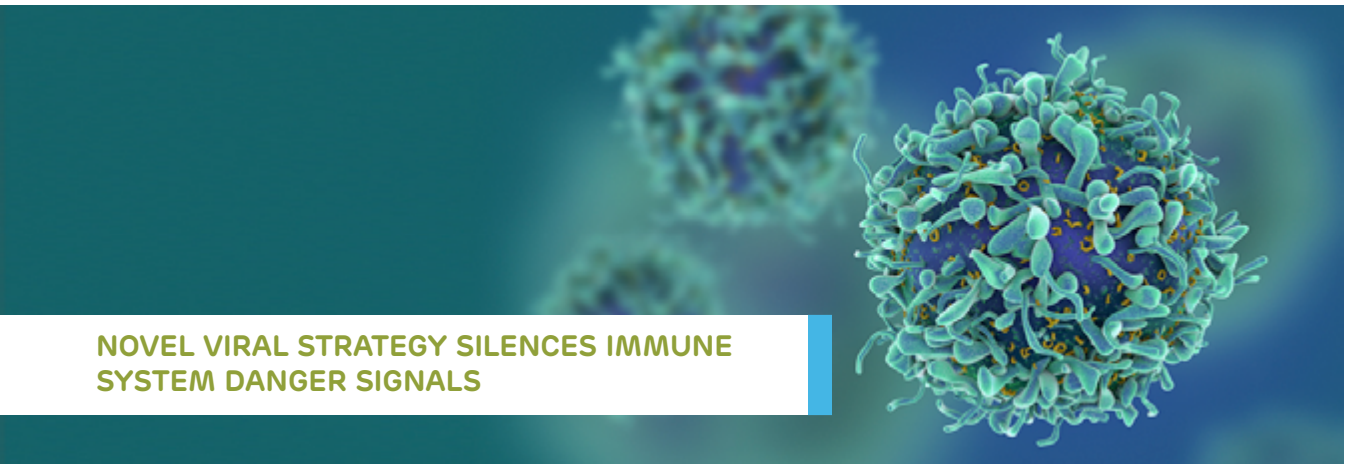
A pool of shared resources and expertise within a complex research organization is vital to support discovery that is convenient, affordable, and efficient. Hence, research institutions such as Children's Hospital of Philadelphia invest in research cores to provide centralized equipment, services, and technical staff in key scientific areas — allowing individual research laboratories and teams to use these resources without each bearing the potentially prohibitive cost of developing them independently.

As science evolves, ensuring that these core capabilities remain robust and up to date with researchers' contemporary needs is essential. At CHOP, Harry Ischiropoulos, PhD, recently took on this key responsibility. Dr. Ischiropoulos, an investigator whose research program focuses on the biological chemistry and molecular mechanisms of nitric oxide signaling, has been with CHOP since 1999. He was named scientific director for the cores at the CHOP Research Institute in February 2016. In this role, he chairs the Institutional Core Advisory Committee, advises CHOP Chief Scientific Officer and Research Institute Director Bryan A. Wolf, MD, PhD, directly on matters concerning the cores, and serves as a liaison with the University of Pennsylvania.

"The CHOP Research Institute cores are committed in providing state-of-the-art technologies, technical expertise, and education to support the research missions of our investigators," said Dr. Ischiropoulos, who is also a research professor of Pediatrics at the Perelman School of Medicine at Penn. "We are instituting transparent oversight and evaluation procedures, implementing measures to determine success, and empowering investigators to work with cores leaders to develop new technologies and drive innovation. We will continually evaluate technologies and service needs of our researchers as well as improving our collaborative efforts with core resources at Penn."



INSPIRATION ›



NOVEL VIRAL STRATEGY SILENCES IMMUNE SYSTEM DANGER SIGNALS

Scientists at Children's Hospital of Philadelphia revealed a surprising way that adenovirus uses a viral protein to prevent infected cells from releasing a danger signal from the nucleus to alarm the immune system.

WHY IT MATTERS

The novel mechanism the researchers discovered that enables this common human virus to evade the immune system establishes new connections within the fields of virology, immune signaling, and chromatin biology. Knowledge of these molecular interactions could lead to new strategies to control unwanted inflammation in other diseases such as cancer and severe infections such as sepsis.

KEY CHOP INVESTIGATORS

Daphne C. Avgousti, PhD, CHOP postdoctoral fellow; Matthew Weitzman, PhD, CHOP virologist and associate professor of Pathology, Pediatrics and Microbiology at the Perelman School of Medicine at the University of Pennsylvania; G. Scott Worthen, MD, CHOP neonatology researcher and professor of Pediatrics at Penn.

HOW THEY DID IT

Since the adenovirus protein known as protein VII has a role on the compacted viral genome, the study group applied research techniques and principles that are typically used to study histones, the proteins that condense a cell's DNA into chromatin (the collection of chromosomes). They tested whether protein VII could mimic histones and disrupt the structure of cellular chromatin in cell culture, in human lung tissue in the laboratory, and in mouse models — and found that it did. They also found that this viral protein actually retains the molecule HGMB1, an important danger signal, within the nucleus, and as a result suppresses the recruitment of immune cells.

QUICK THOUGHTS

"We have learned a new way that this virus evades the immune system, and this insight suggests a potential method of exploiting the process to control immune responses for patient benefit," Dr. Weitzman said.

NEXT STEPS

The scientists will continue to investigate other viral proteins to determine whether they act similarly, in hiding alarm signals from the immune system.

WHERE IT WAS PUBLISHED

Nature

FUNDING SOURCES

The National Institutes of Health supported this study (grants CA115299, GM112414, and CA097093, and others).

READ MORE

See the Cornerstone blog post.

INVESTIGATORS IDENTIFY 15 GENETIC INFLUENCES ON CHILDHOOD OBESITY

The largest genetic study to date of childhood body mass index (BMI) identified 15 gene locations associated with childhood BMI, three of which were novel.

WHY IT MATTERS

The genetics of childhood BMI has remained largely unknown. The crucial novel insight into the biology of obesity this study provides may also lead to opportunities for generalized therapeutic intervention.

KEY CHOP INVESTIGATORS

Struan F.A. Grant, PhD, CHOP genomics researcher and associate professor of Pediatrics at the Perelman School of Medicine at the University of Pennsylvania; Jonathan Bradfield, bioinformatics specialist.

HOW THEY DID IT

The researchers performed a meta-analysis that covered 33 genome-wide association studies, including a total of more than 45,000 children, all of European ancestry. Of that total, there were 35,668 children from 20 studies in the discovery phase, and 11,873 children from 13 replication studies. In all, they found that 15 risk-susceptibility loci account for 2 percent of the variance in childhood BMI.

QUICK THOUGHTS

"As we continue to identify gene variants implicated in pediatric obesity and body mass, we are laying a foundation for research that could provide useful biological targets for better treating childhood obesity, and its negative health consequences," Dr. Grant said.

NEXT STEPS

Further research may determine whether the three novel loci the study group discovered influence BMI only in childhood, or whether their effects are stronger during childhood.

WHERE IT WAS PUBLISHED

Human Molecular Genetics

FUNDING SOURCES

The National Institutes of Health (grant HD056465) and the Cotswold Foundation funded CHOP's involvement in this study.

READ MORE

See the CHOP press release.

FILLING IN GAPS IN KNOWLEDGE ABOUT PEDIATRIC CONCUSSIONS

Researchers from CHOP suggest that the U.S. may be underestimating the incidence of pediatric concussions because those counts currently are based solely on emergency department (ED) visits or organized high school and college athletics data.

WHY IT MATTERS

The investigators provided a better estimate of the scope of the problem by examining concussion visits across an entire pediatric health care network, which will allow clinicians to more effectively prevent and treat concussions. In particular, the findings demonstrate that the primary care setting is an integral part of concussion care management.

KEY CHOP INVESTIGATORS

Kristy Arbogast, PhD, co-scientific director of CHOP's Center for Injury Research and Prevention and research associate professor of Pediatrics at the Perelman School of Medicine at the University of Pennsylvania; Christina Master, MD, CHOP pediatric sports medicine specialist and associate professor of Clinical Pediatrics at Penn.

HOW THEY DID IT

Using the CHOP electronic health record, the study team retrospectively analyzed more than 8,000 concussion diagnoses over a four-year period (July 2010 – June 2014), among children up to 17 years who received their primary care within the CHOP regional pediatric network. During that period, primary care visits as the point of entry increased 13 percent, with a corresponding 16 percent decrease in point-of-entry ED visits. Among the study participants, 82 percent had their first concussion visit with a primary care pediatrician, 12 percent went to the ED, 5 percent first saw a specialist (sports medicine, neurology, trauma), and 1 percent were admitted directly to the hospital.

QUICK THOUGHTS

"We learned two really important things about pediatric concussion healthcare practices," Dr. Arbogast said. "First, four in five of this diverse group of children were diagnosed at a primary care practice — not the emergency department. Second, one-third were under age 12, and therefore represent an important part of the concussion population that is missed by existing surveillance systems that focus on high school athletes."

NEXT STEPS

Researchers will continue to explore the large and diverse electronic health record at CHOP to answer many questions about the natural history of pediatric concussion and apply this knowledge to many other clinical effectiveness issues.

WHERE IT WAS PUBLISHED

JAMA Pediatrics

FUNDING SOURCES

The U.S. Centers for Disease Control and Prevention funded this research.

READ MORE

See the CHOP press release, and check out the infographic.

PREVENTIVE CARE LAGS WHEN FAMILIES MISS WELL VISITS

Adherence to a well-visit schedule is a priority for preterm infants because they are at increased risk for medical complications and lifelong health problems. That is why this study's findings were disconcerting to researchers at CHOP: Only 43 percent of preterm infants received all expected health supervision visits during the first 18 months of life.

WHY IT MATTERS

Missing well visits can make a substantial difference in health outcomes for premature infants, according to this retrospective study. In addition to not getting vaccinations, the babies were less likely to receive screening tests and developmental assessments on time.

KEY CHOP INVESTIGATOR

Scott Lorch, MD, MSCE, an attending neonatologist at CHOP and an associate professor of pediatrics at the Perelman School of Medicine at the University of Pennsylvania

HOW THEY DID IT

The study team looked at outpatient data from a retrospective cohort of 1,854 preterm infants born between 2005 and 2009 who received care at CHOP's primary care network. Upon analyzing the data, the researchers identified two primary reasons why families missed the well visits. Sometimes they showed up for a well visit, but baby was not feeling well that day, so it became a sick visit. Other times they came in for a sick visit and then cancelled their next well visit. In both scenarios, the well visits were never rescheduled, and families did not receive the preventive care that normally would have occurred during those sessions.

QUICK THOUGHTS

"This is one of the first studies to provide documented evidence that there are health consequences for missing well visits," Dr. Lorch said. "It shows how difficult it is for providers to get caught up with the services that these visits provide to patients."

NEXT STEPS

In future research, Dr. Lorch and his study team will take a closer look at some of the potential barriers to families' attendance at well visits. They also will investigate factors that could improve continuity of care and determine ways to avoid delays in immunizations and help close gaps in health monitoring.

WHERE IT WAS PUBLISHED

Pediatrics

FUNDING SOURCES

National Institutes of Health grant R01 HD057168 supported this study.

READ MORE

See the Cornerstone blog post.

PROGRAM AIMS TO PUT THE BRAKES ON ALLERGIC RESPONSE

Researchers at CHOP describe how two small adapter proteins, Ndfip1 and Ndfip2, contribute to the braking system that keeps T cells from instigating hyperactivity of the immune system and producing proinflammatory cytokines that are involved in ramping up inflammation.

WHY IT MATTERS

T cells are the immune system's watchdog to recognize serious threats. But sometimes T cells can be too zealous and set in motion a signaling cascade that can cause allergic reactions to everyday things and even attack your body's healthy cells by mistake. CHOP scientists learned more about what is occurring at a basic cellular level to drive inappropriate immune cell responses.

KEY CHOP INVESTIGATORS

Claire O'Leary, PhD, then a postdoctoral fellow at CHOP and Paula Oliver, PhD, an investigator in the Cell Pathology Division

HOW THEY DID IT

The researchers discovered how this molecular braking system works in two distinct stages. Ndfip1 comes on early when the immune system perceives a substance as being foreign or dangerous, and its expression skyrockets as T cells are stimulated. When the T cells are re-exposed to the antigen and stimulated a second time, they initiate a more aggressive and rapid memory response that requires both Ndfip1 and Ndfip2 to be activated in order prevent an overly exuberant immune response. They also found that when Ndfip1 and Ndfip2 were not functioning, it halted degradation of a protein called Jak1, which is essential for signaling via certain types of cytokine receptors. Without appropriate down regulation of Jak1, expansion and survival of pathogenic effector T cells increased. The study authors suggest that Ndfip1 and Ndfip2 work together to regulate the cross talk between the T cell receptor and cytokine signaling pathways to prevent inappropriate T cell responses.

QUICK THOUGHTS

"We think of these proteins as being negative regulators of inappropriate activation," Dr. O'Leary said. "In the absence of these proteins, the cells are accelerating immune reactions without a lot of guidance. They become self-directed and differentiate toward a path that is highly proliferative. They produce a lot of Th2 type cytokines associated with allergic disease."

NEXT STEPS

As scientists learn more about the basic mechanisms of T cells' negative regulatory pathways, these findings could point the way to future drug therapies.

WHERE IT WAS PUBLISHED

Nature Communications

FUNDING SOURCES

Funding for this work came from the American Asthma Foundation and the National Institute of Allergy and Infectious Disease.

READ MORE

See the Cornerstone blog post.

LINKING CONGENITAL HEART DISEASE, NEURODEVELOPMENTAL ABNORMALITIES

A team of researchers from the Pediatric Cardiac Genomics Consortium studying the role of genetics in congenital heart disease (CHD) confirmed their longstanding suspicion: Some of the same gene defects underlie certain cases of congenital heart malformations and neurodevelopmental disorders.

WHY IT MATTERS

CHD is the most common type of birth defect in the U.S. and one of the leading causes of infant death. These findings may allow researchers to tailor future treatments to children based on their personal genetic risk for neurodevelopmental disorders. Clinicians may be able to intervene earlier on, when the brain is still developing, which could improve developmental outcomes for children with CHD.

KEY CHOP INVESTIGATORS

Elizabeth Goldmuntz, MD, FAAP, FACC, a cardiologist at CHOP, and professor at the Perelman School of Medicine at the University of Pennsylvania

HOW THEY DID IT

Researchers sequenced the whole exome, or expressed part of the genome, from 1,213 family trios (a child with CHD and the mother and father), to identify spontaneously arising (de novo) mutations in the child's genes that did not come from either parent. These damaging mutations disproportionately occurred in genes for developmental processes that are highly expressed in the developing heart and brain.

QUICK THOUGHTS

"Congenital heart disease is the most frequent serious birth defect, so as we discover more of these gene alterations, we will be better able to provide genetic counseling and refine patient care for many families and children," Dr. Goldmuntz said.

NEXT STEPS

Follow-up research must be done before the findings could be used in early screening tests. Also, further analysis of these mutated genes may help researchers to identify new biological pathways critical to the heart and brain's development. Ultimately, these pathways might eventually be targeted with specific drugs, but such targeted therapies will require more research.

WHERE IT WAS PUBLISHED

Science

FUNDING SOURCES

The National Institutes of Health provided grant support for this study.

READ MORE

See the Cornerstone blog post.

STUDY MAPS EARLY CONNECTIVITY NETWORKS IN NEWBORN BABIES' BRAINS

Scientists at CHOP are beginning to glimpse exactly how a gestating infant's developing brain forms important connections. Before and during these critical weeks, brain development patterns emphasize early, efficient connectivity within the primary sensorimotor cortex.

WHY IT MATTERS

The findings help establish a normal reference for how connectivity patterns develop in the brain. The emphasis on developing the primary sensorimotor cortex early prepares a baby to handle the basic needs of sensation and movement after birth.

KEY CHOP INVESTIGATOR

Hao Huang, PhD, investigator in radiology at CHOP and research associate professor at the Perelman School of Medicine at the University of Pennsylvania

HOW THEY DID IT

The researchers used resting-state functional magnetic resonance imaging scans to map the functional connectivity in the brains of 40 infants soon after their birth at various preterm ages, from as early as 31 postmenstrual weeks, up to full-term, or 42 postmenstrual weeks. Even the youngest preterm babies' brains had a characteristic called "small worldness" in their entire brain connectivity, a feature of networks that offer easy navigation from one area to another. But as gestational age increased, so did a quality called rich club structure, characterized by nodes of densely connected regions that make signaling more efficient within areas of the brain.

QUICK THOUGHTS

"In certain periods, some brain regions develop at faster rates," Dr. Huang said. "Although it's heterogeneous, it's not random. There is a well controlled, organized pattern at work."

NEXT STEPS

Dr. Huang has subsequently been awarded a new National Institutes of Health (NIH) grant to study infant brain connectivity changes from ages one month to two years, and to establish a quantitative Penn-CHOP infant brain image atlas. Ultimately, he hopes to identify infant brain biomarkers of atypical connectivity that may occur in various conditions, ranging from autism spectrum disorder to cerebral palsy. If these brain indicators can allow earlier identification of these conditions, children could potentially begin early intervention services sooner and grow up with fewer impairments related to their condition. He also plans to study connectivity development from birth through adolescence.

WHERE IT WAS PUBLISHED

Cerebral Cortex

FUNDING SOURCES

The NIH (grants R01MH092535, U54HD086984, and R01MH092535-S1), National Science Fund for Distinguished Young Scholars (grant 81225012), the Natural Science Foundation of China (grants 91432115 and 31221003), the 111 Project (grant B07008), and the Open Research Fund of the State Key Laboratory of Cognitive Neuroscience and Learning (grant CNLYB1407) supported this study.

READ MORE

See the Bench to Bedside article.

POSSIBLE 'CENTRAL HUB' PROTEINS FOUND IN CANCER CELL GROWTH

A team of scientists at CHOP discovered a mechanism by which proteins that are essential for cell division in healthy cells can drive excess growth and proliferation in cancer cells. They found that when there is an excess quantity of a protein called E2f1, which normally activates the expression of various genes for the cell cycle of reproduction, this protein binds to a molecular complex of proteins that unzip adjacent DNA strands and allow other E2f proteins to amplify the activity of many other genes. In particular, some of these other genes regulate a long-known process of rewiring the energy metabolism in cancer cells for rapid growth, known as the Warburg effect.

WHY IT MATTERS

Scientists have known that E2f1 is overexpressed in the late stages of many pediatric and adult cancers and is linked to poor prognoses, but they did not know why having more of this protein was bad news for cancer patients. Now they have linked a molecular activity of this protein to other known mechanisms of cancer cell growth.

KEY CHOP INVESTIGATOR

Patrick Viatour, PharmD, PhD, investigator at CHOP and assistant professor of Pathology and Laboratory Medicine at the Perelman School of Medicine at the University of Pennsylvania

HOW THEY DID IT

Most of this work was done in a mouse model of hepatocellular carcinoma, a form of liver cancer primarily affecting adults. In addition, Dr. Viatour and his team performed further experiments using human cell lines from multiple types of pediatric and adult cancers. In just over half of these human cell experiments, they found the same complex of the DNA-unzipping proteins Pontin and Reptin binding with E2f1, suggesting that the same mechanism may occur in many human cancers.

QUICK THOUGHTS

"This finding really expands what's been considered textbook material," Dr. Viatour said. "We thought E2f was mostly promoting cancer growth through aberrant cell cycle activity. If you only have a little E2f activity, it is just the cell cycle. But if you have a lot of E2f activity, as you have in cancer, it's way more than that. These factors promote cancer progression by actually activating multiple gene programs."

NEXT STEPS

The team's next phase of research will seek to better understand this mechanism of amplified gene expression to determine whether it is not only associated with cancer progression, but truly critical to it. If so, Dr. Viatour said, there is potential to pursue cancer treatments that would target the E2f1/Pontin/Reptin complex in cancer cells to stop excessive gene expression before it starts. Targeting protein-protein interactions has been successful in other cancer therapies.

WHERE IT WAS PUBLISHED

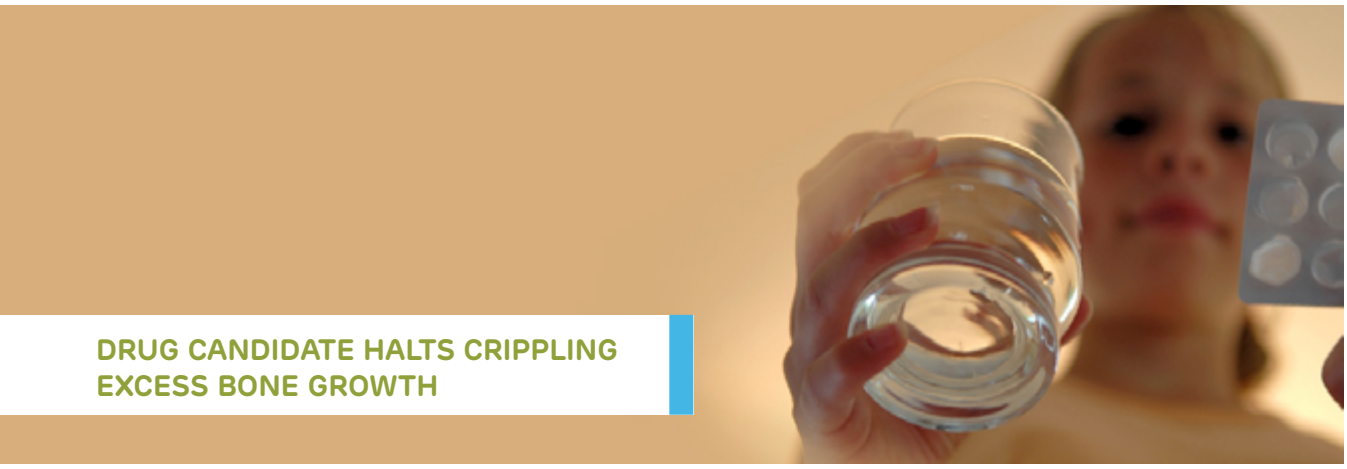
Nature Communications

FUNDING SOURCE

Dr. Viatour's funding from the W.W. Smith Charitable Trust Fund, the Stand Up to Cancer, Alex's Lemonade Stand, and the Canuso Foundations, and start-up funds from the Center for Childhood Cancer Research at CHOP supported this research.

READ MORE

See the Cornerstone blog post.



DRUG CANDIDATE HALTS CRIPPLING EXCESS BONE GROWTH

New research in laboratory animals at CHOP suggests that the drug Palovarotene may prevent multiple skeletal problems caused by a rare but extremely disabling genetic skeletal disease, and may even be a candidate for use in newborn babies with the condition.

WHY IT MATTERS

Currently untreatable and painful, Fibrodysplasia Ossificans Progressiva (FOP) often causes death early in adulthood. In this disease, cartilage and bone form and accumulate in muscles and other tissues where they do not belong, starting in early childhood. This pathological process, collectively called heterotopic ossification (HO), causes progressive loss of skeletal motion and hampers skeletal growth, joint function, breathing and swallowing.

KEY CHOP INVESTIGATOR

Maurizio Pacifici, PhD, developmental biologist and director of Orthopedic Research in the Division of Orthopedic Surgery at CHOP and a professor of Orthopaedic Surgery at the Perelman School of Medicine at the University of Pennsylvania; Masahiro Iwamoto, DDS, PhD, research associate professor in Orthopaedic Surgery at CHOP and Penn.

HOW THEY DID IT

The extra bone that occurs in FOP appears first as cartilage before becoming fully mature bone cells, and Palovarotene was identified as a drug candidate because it selectively targets a regulatory pathway involved in cartilage formation. The current study extended previous research by Drs. Iwamoto and Pacifici showing that the drug inhibited HO in mouse models of genetic HO and injury-induced HO. In mice carrying the genetic mutation that causes most cases of FOP, the drug had potent effects, preventing HO and preserving limb motion and normal bone growth in young mutant mice. Nursing mouse mothers given the drug were also able to pass on its benefits to their offspring with the mutation.

QUICK THOUGHTS

"If these results translate to humans, we may be able to treat children with FOP early in life, before the disease progresses," Dr. Pacifici said.

NEXT STEPS

Clementia Pharmaceuticals is currently conducting phase 2 clinical trials in individuals with FOP. The international study is being done at three sites, including the FOP Center at Penn Medicine, and is testing whether Palovarotene is safe and effective in reducing or preventing HO in children and adults experiencing disease flare-ups.

WHERE IT WAS PUBLISHED

Journal of Bone and Mineral Research

FUNDING SOURCES

Funds for the CHOP researchers were from the National Institutes of Health (grants AR056837 and AR41916) and the U.S. Department of the Army (contract W81XWH-07-1-0212). Funds for collaborating scientists at Penn were from the International Fibrodysplasia Ossificans Progressiva Association, the Penn Center for Musculoskeletal Diseases, the Ian Cali Endowment for FOP Research, the Whitney Weldon Endowment for FOP Research, and the Penn Center for Research in FOP and Related Disorders.

READ MORE

See the CHOP press release.

ABNORMAL GENE IS A TRIPLE THREAT IN DRIVING PEDIATRIC BRAIN TUMORS

An international team of oncology researchers led by CHOP and Dana-Farber Cancer Institute has discovered that an abnormal fused gene that drives pediatric brain tumors poses a triple threat, operating simultaneously through three distinct biological mechanisms — the first such example in cancer biology.

WHY IT MATTERS

This finding potentially offers triple benefits as well — more accurate diagnoses, clues for more effective treatments and new insights into molecular processes underlying other types of cancer.

KEY CHOP INVESTIGATORS

Adam Resnick, PhD, neuro-oncology researcher in the Division of Neurosurgery at CHOP and the Department of Neurosurgery at the Perelman School of Medicine and the co-director of the Center for Data-Driven Discovery in Biomedicine at CHOP; Payal Jain, University of Pennsylvania graduate student.

HOW THEY DID IT

Scientists investigated pediatric low-grade gliomas (PLGGs), a varied group collectively representing the most common pediatric brain tumor. Drawing on multiple consortia and previously uncurated datasets, they analyzed the largest amount of data available for PLGGs, representing the genomes of 249 such tumors. In one class of these tumors (angiocentric gliomas, of which there were 19), virtually all had two genes, MYB and QKI, fused together. They investigated this fused gene and found that it acts in three ways: The rearranged gene expresses truncated, constitutively active fusion proteins that give rise to cancer; the fusion protein is abnormally expressed in brain tissues due to the movement of enhancer regions during the fusion event, and this abnormal expression leads to a feedback loop that drives cell proliferation; and the fusion gene disrupts QKI's protective role as a tumor suppressor.

QUICK THOUGHTS

"The study expands our current understanding of cancer, by focusing attention on the multiple mechanisms occurring simultaneously, and bringing into relief how gene fusions may give rise to epigenomic dysregulation," Dr. Resnick said. "Gene fusions occur in many other cancers in both children and adults, so our findings may apply more broadly to other cancers."

NEXT STEPS

Identifying the MYB-QKI fusion gene as a defining event in angiocentric glioma may allow oncologists to better diagnose this subtype of tumor, guiding them toward directed therapies less likely to overtreat or undertreat children. Better understanding the mechanisms involved in this gene fusion can lead to treatment strategies targeting any of these mechanisms, including potential drugs that may be effective against the type of epigenomic dysregulation seen in these tumors.

WHERE IT WAS PUBLISHED

Nature Genetics

FUNDING SOURCES

CHOP's collaborative low-grade glioma discovery work is supported by A Kids' Brain Tumor Cure Foundation/ Pediatric Low-Grade Astrocytoma Foundation, Voices Against Brain Cancer, Thea's Star of Hope, and Why Not Me Inc. Multiple additional grants from the National Institutes of Health and more than 20 foundations also supported this research across partnering institutions.

READ MORE

See the CHOP press release.

GENE SITES SHARED ACROSS MULTIPLE PEDIATRIC AUTOIMMUNE DISEASES

An international study team led by researchers from CHOP's Center for Applied Genomics focused on 10 autoimmune diseases that begin in childhood and found that they indeed have some shared genetic underpinnings.

WHY IT MATTERS

Autoimmune diseases occur when they body's immune system attacks and destroys healthy body tissue by mistake. As much as 7 to 10 percent of the Western Hemisphere's population is affected. Identifying the biological mechanisms that underlie these disorders, and especially shared pathways, can lead to targeted therapeutic approaches for multiple related diseases.

KEY CHOP INVESTIGATORS

Hakon Hakonarson, MD, PhD, director of the Center for Applied Genomics at CHOP and professor of Pediatrics at the Perelman School of Medicine at the University of Pennsylvania; Yun (Rose) Li, MD, PhD, then a graduate student at the Perelman School of Medicine.

HOW THEY DID IT

Researchers performed a meta-analysis including a case-control study of 6,035 subjects with autoimmune disease and 10,700 controls, all of European ancestry. The research encompassed 10 pediatric autoimmune diseases: type 1 diabetes, celiac disease, juvenile idiopathic arthritis, common variable immunodeficiency disease, systemic lupus erythematosus, Crohn's disease, ulcerative colitis, psoriasis, autoimmune thyroiditis, and ankylosing spondylitis. The investigators found 22 genetic loci that were shared by at least two of the autoimmune diseases, and 19 of these were shared by at least three diseases. The team then studied the pathogenic roles of the shared genes, focusing on how these genes upregulated gene expression in specific cell types and tissues to find patterns that were directly relevant to specific diseases.

QUICK THOUGHTS

"Our approach did more than finding genetic associations among a group of diseases," Dr. Hakonarson said. "We identified genes with a biological relevance to these diseases, acting along gene networks and pathways that may offer very useful targets for therapy."

NEXT STEPS

Identifying specific autoimmune diseases' genetic architecture gives researchers opportunities to better target potential therapies, including the possibility of repurposing existing drugs available for the treatment of other diseases.

WHERE IT WAS PUBLISHED

Nature Medicine

FUNDING SOURCES

The National Institutes of Health, the Wellcome Trust, the Paul and Daisy Soros Fellowship for New Americans, the Crohn's & Colitis Foundation of America, the Juvenile Diabetes Research Foundation, the Lupus Research Institute, and Institutional Development Funds from CHOP supported this research.

READ MORE

See the story on the Cornerstone blog.

CELL'S POWERHOUSE PLAYS ROLE IN MIND-BODY INTERACTIONS

Mitochondria, the tiny structures inside our cells that generate energy, may also play a previously unrecognized role in mind-body interactions. Researchers led by a pioneer of mitochondrial medicine at CHOP found that relatively mild alterations in mitochondrial genes have large effects on how mammals respond to stressful changes in their environment.

WHY IT MATTERS

This insight may have broad implications for human psychology and for the biology of psychiatric and neurological diseases, including implications for the hereditary basis of neuropsychiatric diseases and for the role of stress in human health. It lends support to the idea that an important reason for our limited progress in understanding the genetic and biologic basis of psychology is our lack of appreciation for the importance of systematic alterations in energetic metabolism.

KEY CHOP INVESTIGATORS

Douglas C. Wallace, PhD, director of the Center for Mitochondrial and Epigenomic Medicine at CHOP and professor of Pathology and Laboratory Medicine at the Perelman School of Medicine at the University of Pennsylvania.

HOW THEY DID IT

Researchers subjected mice to a standardized psychological stress: placing them in restraint for a brief period. They then measured the effects of this stressor on the animals' neuroendocrine, inflammatory, metabolic, and gene transcription systems. In humans, all of these systems are involved in behavioral responses to stress and long-term susceptibility to stress-related diseases. They found that in the mice, relatively mild mutations in mitochondrial genes produced unique whole-body stress-response signatures, indicated by physiological and gene expression patterns.

QUICK THOUGHTS

"Our recent papers strongly suggest that by reorienting our investigations from the anatomy of the brain and brain-specific genes to the mitochondria and the bioenergetics genes, we may have a more productive conceptual framework to understand neuropsychiatric disease," Dr. Wallace said. "If so, this will spawn a whole new generation of neuropsychiatric therapeutics."

NEXT STEPS

While much more research remains to be done on the role of mitochondria on human behavior, identifying the altered mitochondrial states associated with neuropsychiatric diseases may help suggest new therapies. These may permit physicians to more effectively ameliorate the effects of environmental stressors on human health.

WHERE IT WAS PUBLISHED

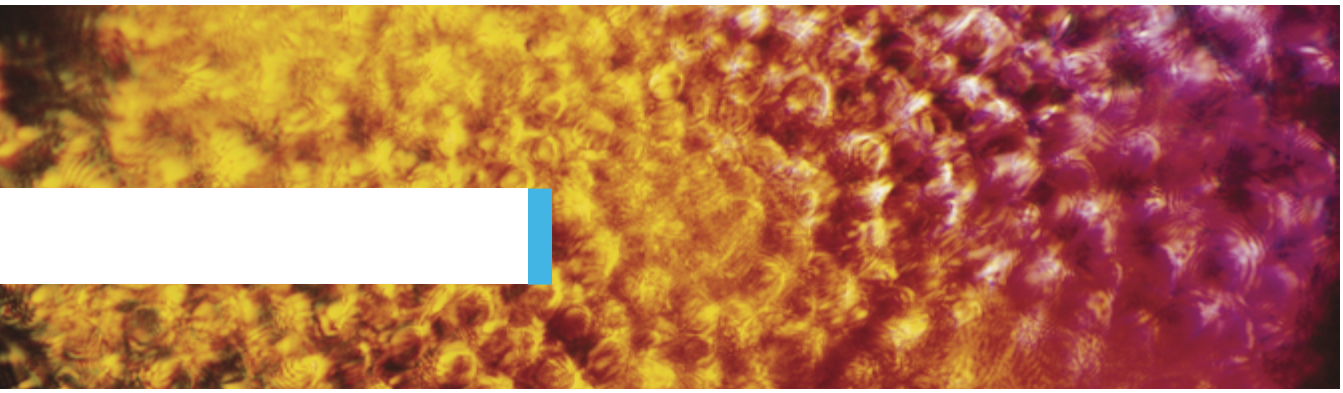
Proceedings of the National Academy of Sciences

FUNDING SOURCES

The Simon Foundation and the National Institutes of Health (grants NS21328, DK73691, and CA143351) supported this research.

READ MORE

See the CHOP press release.



FACTS & FIGURES ›

CHOP'S INNOVATIVE SPINA BIFIDA FETAL SURGERY GROWS UP

Under a sunny sky and surrounded by their families, a few teenage boys threw a football around on a grassy patch in a garden in Cleveland. Such an ordinary scene could happen any day, anywhere in America. But these three boys and their families are a miracle in triplicate.

A worker behind that miracle, N. Scott Adzick, MD, Surgeon-in-Chief and director of the Center for Fetal Diagnosis and Treatment at Children's Hospital of Philadelphia, was watching that football toss between three of his former patients. It took place during a regional reunion for the Center's patients and their families. When they meet at CHOP Fetal Family Reunions — the 20th of which was celebrated in 2016 — it is an opportunity to reflect on the many ways remarkable innovations in fetal intervention have changed lives, to thank the Center, and to simply have fun in celebration.

Katherine Mulligan, whose son Sean was one of those boys, was watching Dr. Adzick.

"I could see how touched he was, seeing these three boys that all had spina bifida, and I was just thinking, wow, three months before they were supposed to be born, he helped them and then put them back in to cook some more," recalled Katherine. "It just brings tears to your eyes, knowing what could have been, and knowing how this man and this team saved all of us from a very different lifestyle."

If not for Dr. Adzick and the team at CHOP, Sean would have waited until after birth to have surgery to repair his improperly formed spinal column. This procedure for the most severe form of spina bifida, myelomeningocele (MMC), was the standard treatment long before Katherine's pregnancy in 2000, and continues to be an option for some patients. But much of the damage to the developing spinal cord has already occurred before birth. If he had surgery as a newborn, Sean would still have had a high risk of lifelong neurological disabilities, major motor impairments including potentially the inability to walk, significant bowel and bladder problems, and the need for a shunt tube in the brain to drain excess fluid that accumulates in a complication called hydrocephalus.

Instead, Sean was born, in Katherine's words, "kicking and screaming," two months after being one of the earliest of the now nearly 300 spina bifida patients to have fetal surgery for MMC at CHOP. Katherine and her husband traveled from their home in Ohio for the then-experimental surgery soon after receiving Sean's diagnosis at Katherine's 20-week ultrasound.

The CHOP team led by Dr. Adzick pioneered this surgery through preclinical research and began performing it in patients in 1998. The idea behind it was that closing the fissure in the spinal column during gestation would reduce the spinal cord's continued exposure to the ravaging neurotoxic effects of amniotic fluid and potentially prevent some of MMC's most disabling symptoms. At the time of the Mulligans' choice, there were anecdotal reports that, among the approximately two dozen babies born after fetal surgery at CHOP, few had hydrocephalus that required a shunt to be surgically implanted in the brain. But the procedure was too new to know more.

"We had no idea what the outcome of the fetal surgery would even be like for a 1-year-old or 2-year-old," Katherine recalled. "But, we thought, if we don't have to be playing around in our child's brain, that alone has to alleviate a lot of issues. We were thrilled that, within weeks, we were watching the hydrocephalus disappear on the MRIs and other scans."

BIRTH AFTER FETAL SURGERY IS JUST THE BEGINNING

The joyous moment of welcoming a healthy baby after fetal surgery is one that the Center knows well. These moments, and the journeys parents go through to reach them, were on display in the three-part documentary series called "TWICE BORN: Stories from the Special Delivery Unit," that aired on PBS in 2015. The series won an Emmy award for Outstanding Science and Technology Programming.

But these happy endings are the beginning of longer stories, too. In the 16 years since Sean's birth, he and many other early fetal surgery patients have been growing up living outwardly ordinary lives. At the same time, the procedure that offered them that dramatically changed trajectory has grown up in parallel.

"Establishing fetal surgery for spina bifida as a standard of care option was one of the most exciting developments in the history of the treatment for birth defects, and one that our CHOP team has spent years helping to pioneer," Dr. Adzick said.

Like most children, but unlike many with severe spina bifida, young Sean learned to walk, talk, and run. Before Sean was old enough to begin preschool, CHOP and several other leading fetal centers that were performing fetal surgery for MMC joined forces for an ambitious study. They aimed to compare outcomes between prospectively enrolled patients who were randomized to receive either prenatal surgery or postnatal surgery. They sought to verify whether the early successes they saw in children like Sean indeed reflected benefits of the fetal procedure — not just the rigorous selection process families went through to qualify for it. The trial (Management of Myelomeningocele Study, or MOMS) was partially funded by the Eunice Kennedy Shriver Institute of Child Health and Human Development and co-led by members of the team at CHOP.

Over the eight years the MOMS study was underway, Sean grew steadier on his feet, developed loves of baseball and fishing, and enjoyed the adoration of three little brothers. He began attending school, where other students had no idea he had a disability unless he told them.

In 2011, the results of the MOMS study were published in the *New England Journal of Medicine* with Dr. Adzick the first author of the publication. This study showed conclusively that fetal surgery improved short-term neurological outcomes compared to surgical repair after birth. It improved young children's ambulation, and it reduced the need for ventricular shunting in the first year. The findings were clear: Fetal surgery showed enough benefits in the first few years of life to be a standard care option for eligible patients.

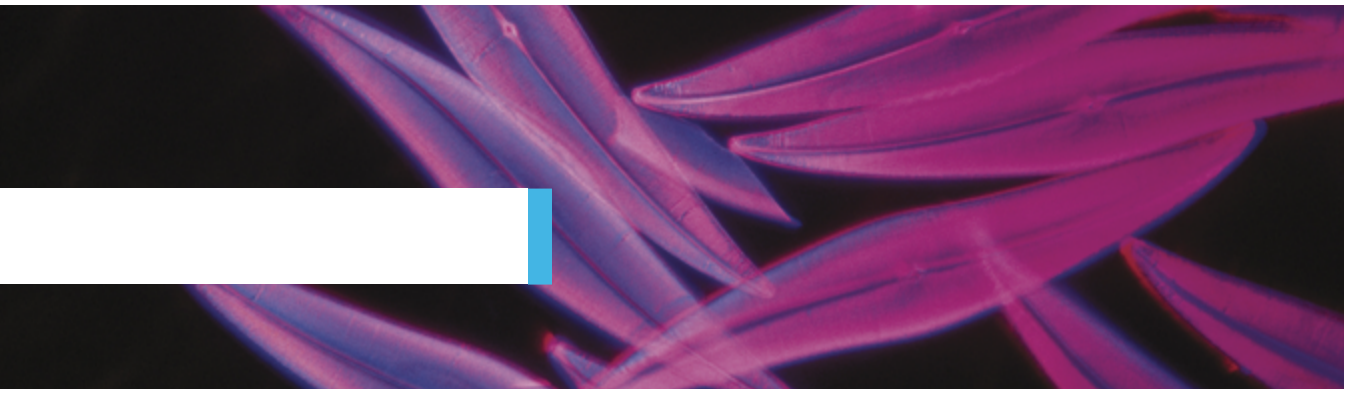
LIVING IN A BRIGHTER FUTURE

Sean spent last summer bicycling around town with his friends, capturing Pokémon. This fall, he got his temporary driver's license, and he is doing well in school. He needs to give extra attention to certain bladder health concerns related to his spina bifida but is generally healthy and well-adjusted. He knows he had fetal surgery, and he knows his life might have been different without it, but he rarely thinks about that.

Although it is too soon to have full results of the long-term follow-up of the MOMS study in a controlled study population, MOMS2, Sean's experience seems typical of many of the earliest, pre-MOMS fetal surgery patients. A CHOP research team conducted surveys of 42 families who had fetal MMC surgery at CHOP before 2003 and published their results in February 2016 in the *American Journal of Obstetrics and Gynecology*. They reported that one-third of the children have normal bowel and bladder function at all times, compared to only 10 percent of children who have postnatal repair of MMC. They found that 79 percent of these children and teens were ambulatory in the community, and another 9 percent were ambulatory at home. And two-thirds of the children participate in sports activities, either special-needs or typical, ranging from baseball to ballet and, of course, touch football.

"It is so rewarding to see patients, who before even being born received grave diagnoses, growing up healthy and strong," Dr. Adzick said. "It's important to be open and honest with families and to be clear that while fetal surgery is not a cure for spina bifida, it has the potential to drastically improve the patient's life. It has been our pleasure to give families hope for their baby's future, and we look forward to continuing to treat more and more children."

Read more about Dr. Adzick and the Patient Impact Award he received in honor of his pioneering work.



FINANCIALS

$362,548,763

TOTAL RESEARCH OPERATING EXPENSES

$220,558,794

EXTERNAL GRANTS AND CONTRACTS

$113,100,105

632 AWARDS

2,128

PUBLICATIONS


$220,558,794
EXTERNAL FUNDING
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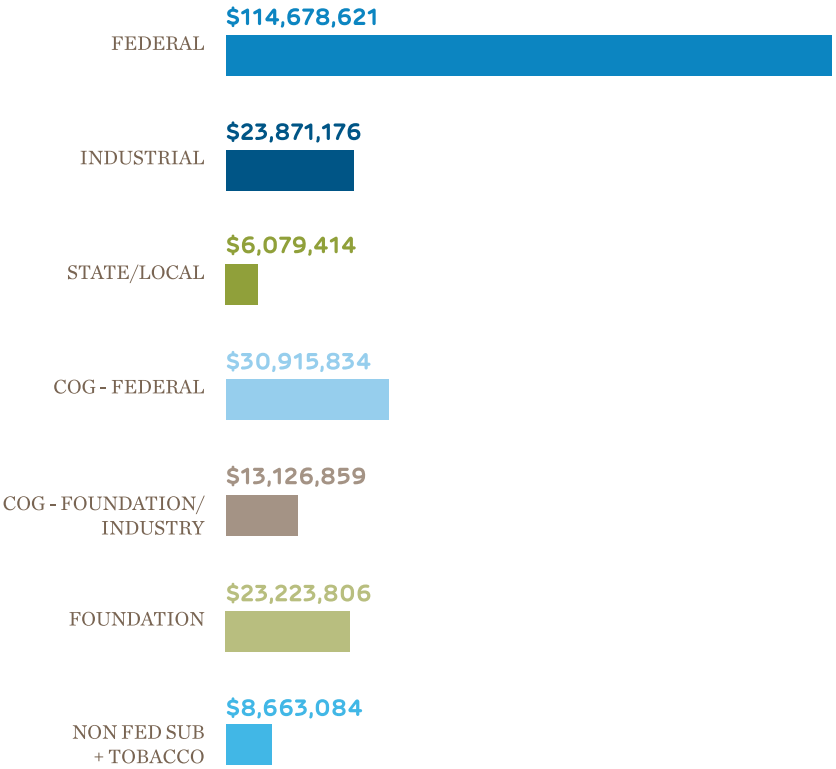
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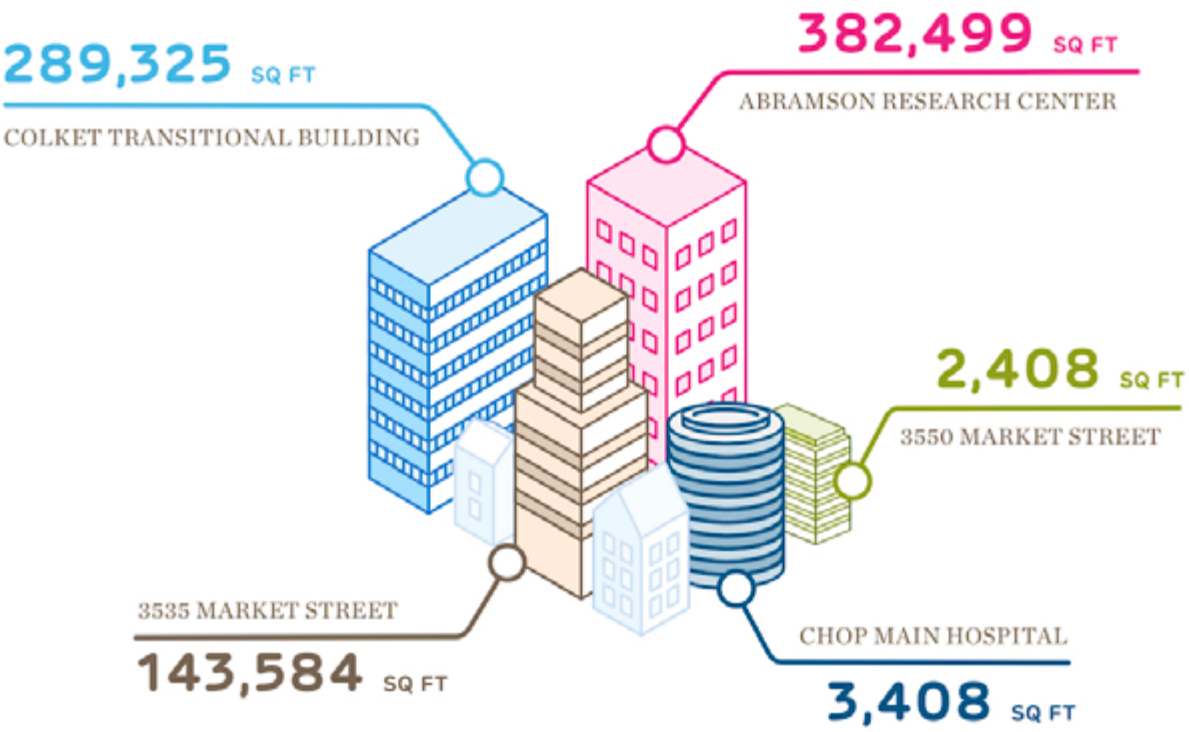
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- Children's Hospital of Philadelphia Research Institute Website
- *Cornerstone*, CHOP Research Institute's blog
- CHOP Research Institute Press Releases
- *Bench to Bedside*, CHOP Research's Monthly Online Newsmagazine
- CHOP Research Institute's Facebook Page
- CHOP Research Institute's Twitter Feed
- CHOP Research Institute's LinkedIn Page
- CHOP Research Institute's YouTube Channel
- Children's Hospital of Philadelphia Website
- Children's Hospital of Philadelphia YouTube Channel
- Children's Hospital of Philadelphia Foundation Website

CHOP Research Institute's department of Research Communications produced the 2016 Research Annual Report.