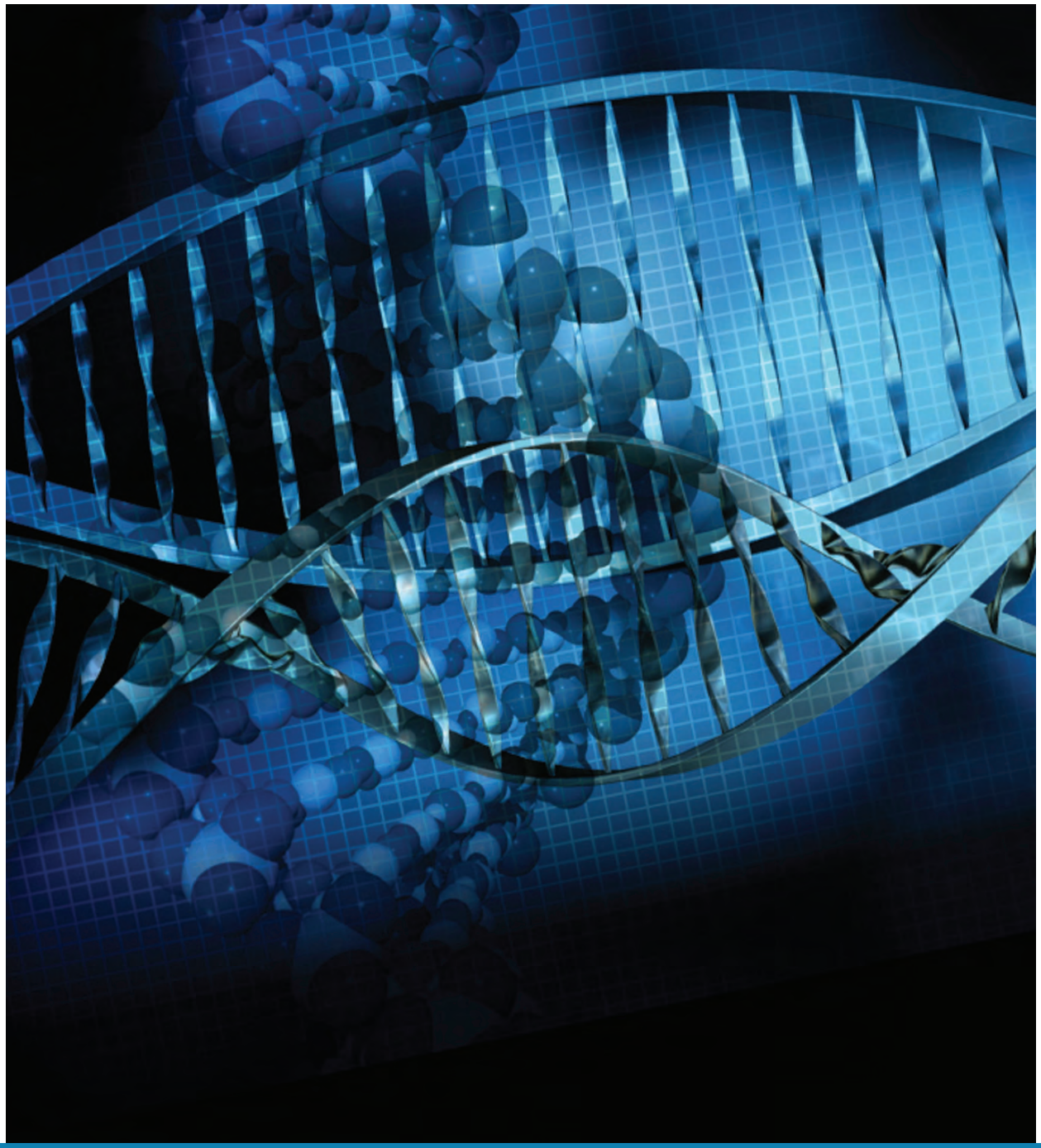

2010 ANNUAL REPORT

The Children's Hospital of Philadelphia®
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01.INNOVATION

Clinical Effectiveness During a Healthcare Crisis: Determining the Best Practices in Patient Care

The costs of medical care in the United States continue to escalate, putting severe financial strain on patients, employers, providers, and payers, and leading many to question whether healthcare can be provided in a more cost-effective manner.

A growing body of literature suggests that different providers and health systems have varying approaches to treating the same condition, and that considerable savings and improved outcomes could be achieved by reducing this variation. Much of the variation in practice seen today stems from differences in local culture and tradition,rather than differences in patient disease or presentation. The variation means that some patients are getting unnecessary care, while others are not getting the care they need.

So which diagnostic and treatment strategies for a particular disease and particular patients are best? What are the benefits and potential harms of each therapeutic approach? And how can we make sure that patients get the most value for their healthcare dollars?

These issues have formed the basis of an emerging – and critical – field of investigation, called comparative effectiveness research (CER). Recognizing the importance of this field, the federal government allocated more than $1.1 billion under the American Recovery and Reinvestment Act to this initiative and formed a Federal Coordinating Council specifically for CER.

The Children's Hospital of Philadelphia Research Institute is taking a leading role in this initiative through the Center for Pediatric Clinical Effectiveness (CPCE), which promotes research on how to best manage pediatric illnesses, disseminates knowledge gained from these investigations, and collaborates to establish best practices to improve the healthcare of children everywhere.

Led by Ron Keren, MD, MPH, this Center of Emphasis at the CHOP Research Institute facilitates the performance of CER, partners to improve the care of children, and educates the next generation of comparative effectiveness investigators.

"Comparative effectiveness research is just one part of a larger issue around how we will respond to the nation's healthcare crisis," says Dr. Keren. "CPCE provides an essential link between determining what the best practices actually are and making sure that they are implemented in clinical care."

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Building a Solid Evidence Base for Best Clinical Practices: Ron Keren, MD, MPH

Medicine has come a long way in the last century. Thanks to advances in techniques, cutting-edge research on diseases and their processes, new therapeutics, and advanced technologies, we are continuously gaining a greater understanding of disease and ways to improve health.

As a result, we now have longer life expectancies in the United States. And some diseases that were once considered life-threatening, or at least life-limiting, are now more effectively managed as chronic conditions.

It may come as a surprise that, despite these advances, healthcare providers still question the effectiveness of some of the treatments routinely provided for common ailments and conditions. Even more surprising is that some of the treatments we receive – and have come to expect – may not actually be ideal and often vary from one institution to another.

That's where the question of comparative effectiveness research (CER) comes in, and Ron Keren, MD, MPH, director of the CHOP Research Institute's Center for Pediatric Clinical Effectiveness, is leading the effort to look at how medical facilities evaluate and treat pediatric diseases and conditions, the treatment differences among those institutions, and what the most effective and appropriate therapeutic approaches are.

"While some pediatric diseases and conditions may be common, their treatment approaches often vary widely," says Dr. Keren, "and may be based largely on tradition and anecdotal evidence. Clinicians can hardly be faulted, though. The evidence base for pediatrics is not as good as it should be, and we are trying to make it better."

Dr. Keren has been involved in CER for several years. His research focuses on the effectiveness and cost-effectiveness of treatments for common problems in general pediatrics including the prediction and prevention of newborn hyperbilirubinemia and kernicterus, the therapeutic and radiological management of children with urinary tract infections, and the epidemiology and economics of influenza.

Dr. Keren is a co-principal investigator in a landmark, multicenter National Institutes of Health-sponsored clinical trial evaluating the effectiveness of daily preventive antibiotics in children who have had a urinary tract infection (UTI) and are found to have urinary reflux – a condition in which urine goes back up to the kidneys during urination. Despite the intuitive appeal of this approach for preventing UTI recurrences, the strategy had been untested in properly designed clinical trials until now. When the trial is completed in 2013, it might show that clinical intuition was right after all, or it might show that daily antibiotics are not effective for preventing recurrent UTIs, a finding that may lead many doctors to reconsider the appropriate strategy for managing children with urinary reflux.

Dr. Keren recently received a $9 million grant from the Agency for Healthcare Research and Quality to help build the clinical data infrastructure needed to perform high quality CER. Working with medical informatics experts from the University of Utah, the Pediatric Research in Inpatient Settings research network, and the Child Health Corporation of America (CHCA), he is leading an effort to build a database that receives clinical data from six of the largest children's hospitals in the country, and to use those data to complete several CER studies.

This clinical database will be an extension of the existing data-sharing collaboration of the Pediatric Health Information System (PHIS), an administrative database created by CHCA for 42 of North America's leading children's hospitals. The expanded database containing clinical data will be called PHIS+.

Since 1999, PHIS has collected administrative data on 20.5 million patient encounters from a full spectrum of ages, races, ethnicities, and geographic regions in the United States. Augmenting PHIS's detailed administrative data with clinical data from a variety of clinical settings will enable researchers to generate new high quality evidence on the comparative effectiveness of healthcare interventions for children. The data will also be useful for measuring and improving the quality of pediatric healthcare.

The grant will allow Dr. Keren and his colleagues to learn more about the effectiveness of treatments commonly used in pediatric hospital care. The study team will compare the effectiveness of antibiotics in children hospitalized with community-acquired pneumonia, gastroesophageal reflux disease treatments in neurologically impaired children, single versus multi-drug antibiotic treatments after surgery for advanced appendicitis, and antibiotics with and without MRSA activity for acute osteomyelitis.

A War Against Microbes and Superbugs: Taking a Closer Look at Antibiotic Use: Theoklis Zaoutis, MD, MSCE

A cough. A fever. A possible infection. You take your child to the doctor's office and leave with a prescription for an antibiotic to treat it. That's the most effective treatment strategy, isn't it? Maybe not.

It's a problem you've likely heard and read about in the national news: bacteria are becoming more resistant to antibiotics, rendering us less able to fight off infection. There is a war raging against microbes and superbugs, and much of the media attention has focused on antibiotic use and misuse.

It's also a focus of groundbreaking research at CHOP Research Institute, where Theoklis Zaoutis, MD, MSCE, associate chief of the Division of Infectious Diseases and associate director for the Center for Pediatric Clinical Effectiveness Research, is looking at the excessive use and overprescription of antibiotics.

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According to Dr. Zaoutis, antibiotics are prescribed inappropriately 50 percent of the time, and investigators have additional questions about the length of time a patient who needs antibiotics should actually take them. Couple that with the fact that few new antibiotic agents have become available in recent years, and a major public health issue emerges.

Antibiotic overprescription and inappropriate use have allowed bacterial strains to evolve and find ways around our most effective treatments. Patients who experience antibiotic resistance don't fare as well as others do. As a result, these patients experience a significant increase in morbidity and mortality as well as lengthier and costlier hospital stays.

"Despite widespread use, many clinicians believe there is no harm to overprescription or misuse," says Dr. Zaoutis. "But in reality, we're seeing more and more drug-resistant bacteria and we're looking at a very costly public health problem from that overprescription or misuse."

To delve further into the issue, Dr. Zaoutis is looking at antibiotic use in children with urinary tract infections, or UTIs. Although highly treatable, these infections represent the most common disorder of the kidneys and urinary tract in early childhood. The six-year, $14 million federal grant supporting this research comes from the National Institute of Allergy and Infectious Diseases, which has made the reduction of antibiotic resistance a research priority. In one of the largest studies of its kind, Dr. Zaoutis and his colleagues are comparing a short course versus the standard course of antimicrobial treatments for UTIs in children.

"Our goals are to determine the optimal duration of antimicrobial treatment for UTIs," says Dr. Zaoutis. "This information will allow doctors to improve pediatric care while reducing the unnecessary use of these drugs."

Seeking a Not-So-Complicated Treatment Approach to Complicated Pneumonia: Samir Shah, MD, MSCE

There are an estimated 150 million new cases of pediatric pneumonia each year, making it the most common form of community-acquired infection in children. Some of these cases can be treated through antibiotics or over-the-counter remedies. However, up to 200,000 cases of pneumonia may be severe enough to require hospitalization, and some of these children may have more complicated forms of pneumonia that require surgery to drain the fluid in the lungs.

With such a high number of new cases every year, it would seem logical that there are standardized treatment strategies among hospitals and healthcare providers for diagnosing and treating children with complicated forms of pneumonia.

Unfortunately, this isn't necessarily the case, according to Samir Shah, MD, MSCE, a pediatric infectious disease physician with a vibrant research program aimed at understanding the pathogenesis of severe childhood pneumonia.

Some of Dr. Shah's ongoing pneumonia-related research projects center on developing predictive models to identify high-risk children with community-acquired pneumonia, using observational study designs and administrative data to determine optimal treatment approaches for children with pneumonia-related complications, and identifying process measures for children with pneumonia in both the outpatient and inpatient settings.

"Approximately 15 percent of children hospitalized for pneumonia have infection-associated complications like empyema," a collection of pus between the lung and the covering of the lung, Dr. Shah says. "To date, there have only been a handful of single-hospital studies that have conducted and published randomized trials on how complicated pneumonia is diagnosed and treated."

But those few studies were not designed to shed light on the discrepancies among hospitals in the treatment strategies for children with complicated pneumonia. A larger, more thorough and in-depth study was just what the doctor ordered.

Using a comparative effectiveness approach, Dr. Shah is heading a consortium of children's hospitals to look at four commonly used treatment strategies for draining the fluid in the lungs of children with complicated forms of pneumonia. The procedures being compared are thoracentesis, which requires inserting a hollow needle into the thorax to remove fluid or air from the lungs; chest tubes for drainage; video-assisted thoracic surgery; and thoracotomy, which requires an incision into the pleural space to gain access to the lung and other organs.

The research team is using data from 40 pediatric hospitals that contributed data to the Pediatric Health Information System from 2004 through 2009. The investigators are reviewing patient records to validate the diagnosis of complicated pneumonia, and have identified 3,500 children with complicated pneumonia who had their lung fluid drained.

From there, the team is looking at the variations in outcomes across the hospitals based on the different treatments used. Some of the critical factors of this analysis are the length and cost of hospital stays, and a patient's need for multiple lung drainage procedures.

"Our team's findings will shed some light on key differences in the approach to treating complicated pneumonia," says Dr. Shah. "This, in turn, should one day lead to a more standardized – or 'best practice' – approach."

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Research With an Eye on Better Choices, Better Outcomes: Chris Feudtner, MD, PhD, MPH

New treatments and therapeutics must undergo rigorous testing and evaluation before they are approved for use in patients. Historically, however, many of those clinical tests involve comparing the proposed new treatment with a placebo, a substance with no active medication. Rarely are there head-to-head studies to determine if one medication or treatment is better than a competing one.

It's like comparing apples to oranges, rather than apples to apples. And when it comes to patient care and prescribing the most effective treatment course, how can you be sure one medication is better than another?

"Once a medication is approved and becomes available, post-marketing surveillance typically does not give enough information for hospitals, physicians, and consumers to make wise choices," says Chris Feudtner, MD, PhD, MPH, director of the Department of Medical Ethics at Children's Hospital and holder of the Steven D. Handler Endowed Chair in Medical Ethics. "But conducting high-quality head-to-head studies of two competing treatments that may be distinguished by a small difference between their effects it isn't so easy to do — or even desirable in many cases."

Furthermore, while one drug may do a little more than another, does the patient really benefit from the small difference? Is a small increased benefit worth a potentially much higher cost? And if one drug turns out to be the best, why use any of the others? It all comes down to what you really want — and need — to know.

"Scientifically, there is a deep issue here about what knowledge we really want to have to guide healthcare choices," says Dr. Feudtner. "It's a matter of exploring the differences in the impact of various treatments that will actually make a difference – a difference that really matters to that patient."

Comparative effectiveness research (CER) offers a unique approach to this conundrum by allowing investigators to compare treatment strategies to one another — not just to a placebo — and to do it in a way that allows physicians to provide the best possible treatment based on a individual's unique needs.

Through CER, investigators can conduct observational studies of similar patients who have the same underlying medical condition and are affected by the disease to the same degree yet, for no discernable reason, are given two different treatments. Sometimes this happens because doctors in one area of the country or one set of hospitals like to use treatment A, but other doctors prefer to use treatment B, even though their patients are essentially the same. With this data, Dr. Feudtner and other researchers in the field can look back several years and create more of a head-to-head comparison of medications to discern with greater accuracy the outcomes of those different treatments.

"Comparative effectiveness research provides an important, alternative way of obtaining information that is useful for decision-makers," says Dr. Feudtner, whose primary research focuses on medical ethics and strategies to improve the quality of life for children and families dealing with complex chronic diseases.

Among his current projects, Dr. Feudtner is leading a nationwide study aimed at providing critical data that will guide future efforts to advance pharmaceutical effectiveness and safety. Using several large existing national databases, the research team is looking a multitude of variables, including clinical data, hospitalization records, and drug exposure information — all with an eye on improving patient outcomes through the more informed use of medications.

"This comprehensive project will provide information that is of relevance to consumers, clinicians, and policy makers, and can be translated into targeted programs to improve outcomes," he says.

Steroid Use in Vasculitis: To Treat or Not to Treat: Pamela Weiss, MD, MSCE

Henoch-Schönlein purpura (HSP) represents the most common forms of vasculitis, or inflamed blood vessels, in children, affecting approximately 10 out of 100,000 children each year. Causing abdominal and joint pain, rashes, and potentially chronic renal disease, healthcare providers usually see an upswing in the number of HSP cases in the early fall, often after a patient has experienced an upper respiratory infection.

However, despite accounting for half of the pediatric vasculitis cases in the United States, healthcare providers continue to debate the appropriate treatment strategy for children with this painful and potentially serious condition.

The main topic of disagreement has centered not only on how but if HSP should be treated, particularly with steroids that are not currently part of the standard of care for inpatient management of HSP.

New Center for Pediatric Clinical Effectiveness faculty member Pamela Weiss, MD, MSCE, Division of Rheumatology, conducted a groundbreaking study looking at the children who are at risk for more severe problems stemming from HSP in an effort to determine the effect of steroid therapy.

Conducting a systematic meta-analysis of HSP and corticosteroid efficacy, Dr. Weiss found that patients treated early with steroids experienced resolution of their severe abdominal pain in 24 hours and reduced their odds of developing chronic renal disease.

In a subsequent study she used the Pediatric Health Information Systems database to look at the ways in which children with HSP were being treated across the country, with particular attention

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to steroids, narcotics, and other pain medications. She found significant differences in the use of these medications across children's hospitals.

"The discrepancy across the country on how kids were being treated with steroids set the stage for a large comparative effectiveness study," says Dr. Weiss, whose comparative effectiveness research (CER) study assessed the risk of surgery, abdominal imaging, and need for intravenous nutrition in children who did and did not receive steroids during the first days of hospitalization. She and her colleagues demonstrated that children who received steroids fared significantly better in regards to these outcomes. This CER study was recently published in *Pediatrics*.

"Data from these studies provide evidence to support treatment with steroids early in the course of HSP for those sick enough to require hospitalization," says Dr. Weiss. "Future studies to further improve these patients' outcomes, particularly the chronic renal disease, will need to focus on predictive models, risk stratification, and trials of additional immunomodulatory or renal-protective treatments."

Dr. Weiss has extended her CER endeavors to a form of juvenile arthritis called enthesitis-related arthritis (ERA). Poorly controlled ERA can cause growth disturbances, joint contractures, joint destruction, and functional limitation in children. A subset of children with ERA will progress to ankylosing spondylitis, a condition characterized by spinal and back pain, stiffness, and eventual fusion of the vertebra.

There are a variety of drugs used to control the inflammation from ERA but, similar to HSP, there is also significant disagreement on which combinations of drugs work best.

"In the juvenile arthritis realm we have wonderful drugs, but most of them have the potential for significant toxicities," says Dr. Weiss. "So it comes down to trying to provide the best treatment with the least amount of toxicity."

Training the Next Generation of CER Investigators

An intensive focus on comparative effectiveness research (CER), while a relatively new area of investigation, is essential to understanding which treatments and therapeutic interventions are actually necessary and for developing strategies aimed at optimizing treatment while eliminating unnecessary costs.

The Children's Hospital of Philadelphia is leading the way not only in research but also in training the next generation of investigators to pursue research in this innovative – and critical – field.

The Center for Pediatric Clinical Effectiveness (CPCE) is helping to lead the way in training physicians in CER. In the fall of 2009 it coordinated the submission of two training grants to the National Institutes of Health to fund the training of pediatric fellows in outcomes, epidemiology, and pharmacoepidemiology research. Both training grants were selected for funding, and in the fall of 2010, the first cohorts of fellows were enrolled in the Pediatric Hospital Epidemiology and Outcomes Research Training Program and the Pediatric Pharmacoepidemiology Training Program.

The Pediatric Hospital Epidemiology and Outcomes Research Training Program is a two-year research fellowship designed to train clinical scientists in research methods used to evaluate quality, safety, and costs in the care of hospitalized children. Through the program's combination of formal coursework and mentored research projects, trainees will develop expertise in CER, quality measurement, severity adjustment, and economic evaluation as they relate to pediatric hospital care.

The Pediatric Pharmacoepidemiology Training Program is preparing pediatricians to be rigorous, independent, academic investigators able to use the range of approaches available in epidemiology to study the use and effects of medications in pediatric patients. The program provides highly motivated, clinically trained individuals with intensive training in the methods of clinical epidemiology in pediatric populations, including biostatistics, pharmacokinetics, and pharmacogenetics.

Together, the national expertise of CPCE investigators, the commitment to advancing innovative areas of investigation, and the programs in place to support further training and mentoring help ensure that CPCE and CHOP Research will continue to lead the way in CER.

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02.TRAILBLAZERS

An Illuminating Year of Research Innovation

Research saves lives. At CHOP Research we think about this reality every day. It is the thought that drives the engine of discovery, the immutable force that compels investigators to push against the edges of knowledge and expand our concept of medical innovation. Our competitive nature pushes us to the forefront of translational medicine, where basic and clinical research meet to make the impossible a reality and to create new ways of identifying and treating pediatric disease.

Our insistence on being the best has lead to an enormous level of success, which will serve the needs of patients at Children's Hospital and around the globe. CHOP Research investigators published more than 750 articles during the fiscal year, work that communicates, validates, and challenges the discoveries our investigators have made. Our research was published in many influential journals that reach a wide, diverse audience, such as *Nature*, *Nature Genetics*, and the *Journal of Clinical Investigation*, and prestigious specialty journals that communicate directly with leading subject-matter authorities, including *Pediatrics* and *Brain*.

The phenomenal research findings from CHOP Research are possible because of our high level of fiscal support. The number of grant awards to CHOP Research increased 75 percent over the last fiscal year and the Institute remains a leader in pediatric funding from the National Institutes of Health.

Browse through a collection of some of our top research findings published this year, selected from the accomplishments of more than 450 investigators.

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Understanding of Neuroblastoma Risk Enhanced

Two studies looking at the genetic causes of neuroblastoma have unlocked much of the mystery surrounding why it arises in some children and not in others. This complex and puzzling cancer is the most common solid cancer of early childhood, causing 15 percent of all childhood cancer deaths. Pulling from the strengths of the CHOP Research powerhouses the Center for Applied Genomics and the Center for Childhood Cancer Research, the studies used DNA samples collected from around the world by the Children's Oncology Group to better define the genetic landscape of neuroblastoma.

In the largest pediatric oncology gene study ever conducted, led by John Maris, MD, chief of the Division of Oncology and director of the Center for Childhood Cancer Research, the team performed a genome-wide association study to compare DNA from neuroblastoma patients with DNA from healthy children. The team found that common variants in the gene *BARD1* increase a child's susceptibility to a high-risk form of neuroblastoma. Published in *Nature Genetics*, this study has opened the door for research to understand the mechanism by which *BARD1* gene variants act on developing nervous system cells to give rise to cancer during fetal or early development.

A second genome-wide study, spearheaded by Sharon Diskin, PhD, Division of Oncology, and published in *Nature*, found that an inherited copy number variation (CNV) – a missing stretch of DNA – along a structurally weak location on chromosome 1 plays an important role in the development of neuroblastoma. The chromosome region where the CNV is located, 1q21.1, contains a large family of genes that are involved in the development of the nervous system. The CNV identified in the study changes how much of one particular gene is made within normal nerve and neuroblastoma cells. In addition to the impact this has on neuroblastoma research, this study is notable in the field of genome-wide analysis as a whole, as it was the first to show a specific CNV predisposes people to cancer and has set the stage for studies to identify the mechanisms of how CNVs may increase the risk of cancer.

Capasso M, Devoto M, Hou C, Asgharzadeh S, Glessner JT, Attiyeh EF, Mosse YP, Kim C, Diskin SJ, Cole KA, Bosse K, Diamond M, Laudenslager M, Winter C, Bradfield JP, Scott RH, Jagannathan J, Garris M, McConville C, London WB, Seeger RC, Grant SF, Li H, Rahman N, Rappaport E, Hakonarson H, Maris JM. Common variations in BARD1 influence susceptibility to high-risk neuroblastoma. *Nat Genet.* 2009 Jun;41(6):718-723.

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Second Dose of Gene Therapy Safe in Animal Studies

Using gene therapy that produced dramatic restoration of eyesight in 12 children and young adults who were treated in one eye for a severe inherited blindness, investigators have shown in an animal study that a second injection of genes into the opposite, previously untreated eye is safe and effective. These findings suggest that patients who benefit from gene therapy for Leber's congenital amaurosis (LCA), a retinal disease that progresses to total blindness by adulthood, may experience similar benefits from treatment in the other eye.

Led by director of the Center for Cellular and Molecular Therapeutics, Katherine High, MD, HHMI, and her colleagues at the University of Pennsylvania, the research team treated 10 animals with a normal version of the gene missing in LCA packaged inside a genetically engineered vector, adeno-associated virus (AAV). The vector delivers the gene to cells in the retina, where the gene produces an enzyme that restores light receptors. Although the virus does not cause human disease, it previously set off an immune response that cut short the initial benefits of gene therapy. Researchers who conducted the human trial for LCA exercised caution by treating only one eye.

The team found no evidence of toxic side effects in the blood or the eyes of the animals — four monkeys and six dogs — that received the gene therapy by injection in the right eye and 14 days later by injection in the left eye. All six dogs, bred to have congenital blindness, had improved vision in addition to showing no toxic effects. Monkeys, like humans, generate neutralizing antibodies against AAV; however, these antibodies did not prevent the injected gene from producing the desired enzyme. These results provide encouraging indications that immune responses will not interfere with human gene therapy in both eyes and that patients with antibodies against AAV in their blood, excluded from the initial human gene therapy trial, may be candidates for this treatment.

Subjects from the human trial, all of whom experienced partially restored eyesight in their treated eyes, were eager to receive the same treatment in the other eye. This animal study, published in *Science Translational Medicine*, advances that possibility. The research team is planning a new clinical trial of LCA therapy, which may include some of the subjects from the first group.

Amado D, Mingozzi F, Hui D, Bennicelli JL, Wei Z, Chen Y, Bote E, Grant RL, Golden JA, Narfstrom K, Syed NA, Orlin SE, High KA, Maguire AM, Bennett J. Safety and efficacy of subretinal readministration of a viral vector in large animals to treat congenital blindness. *SciTransl Med.* 2010 Mar 3;2(21):21ra16.

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New Map of Genomic Variation Constructed

Genetics researchers studying human illnesses look at differences between the DNA of healthy people and people with a disease to determine which changes might play a role in the formation of disease. Copy number variations (CNVs) are DNA deletions, duplications, and insertions that contribute to genetic diversity and disease and often change the action of genes. In order to pinpoint a CNV that is the cause of a disease, it is critical to identify CNVs that are part of the spectrum of normal variation in the human genome. A CHOP Research team, led by Peter White, PhD, director of the Center for Biomedical Informatics, and Tamim Shaikh, PhD, Division of Human Genetics and Molecular Biology, established a resource that provides a uniform baseline standard to indicate which CNVs represent normal variation.

The study team analyzed DNA from more than 2,000 healthy children and their parents to create a map of CNVs throughout the genome, one of the largest and highest resolution maps to date. The study, published in the journal *Genome Research*, cataloged more than 50,000 CNVs, three quarters of which were "non-unique," meaning they occur in multiple unrelated individuals. A majority of the non-unique CNVs were newly discovered.

Gene researchers worldwide can freely search the CNV database and compare specific CNVs to those collected in public data repositories from other institutions. The site has quickly emerged as a standard reference for genomic research worldwide, with more than 1 million Web hits to date. The accompanying manuscript has already been cited by more than 40 subsequent studies.

To demonstrate the clinical usefulness of the database in rapidly diagnosing rare diseases, the study's authors looked at DNA from a child with multiple congenital problems and were able to quickly identify CNVs found in healthy controls and form a strong conclusion about the CNV that played a role in the child's disease. The resource is now used for clinical diagnostic tests given to all children with suspected genetic disorders at Children's Hospital. In addition to its use in diagnosis, the database may also assist researchers studying molecular evolution, such as how genetic variations occurred as human populations spread across continents.

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Animal Findings May Guide Epilepsy Treatment

Children who experience infantile spasms, a type of seizure, often suffer from lifelong epilepsy and varying degrees of mental retardation. Finding an improved therapy for this difficult-to-treat condition could prevent some of the problems children encounter later in life. A research team led by Jeffrey Golden, MD, pathologist-in-chief, developed a line of mice that lack the *Arx gene* – known to be mutated in humans with infantile spasms – as a tool to help scientists test treatments that may benefit children.

Removing *Arx* in a type of cell that inhibits electrical firing in brain circuits called interneurons, led to overexcited brain cells and seizures in the mice resembling human infantile spasms as well as abnormal brain waves on an EEG that are similar to abnormalities seen in EEGs from children with this disorder. This new animal model, the first for a developmental epilepsy resulting from the mutation of a known human infantile spasms gene, adds to the understanding of the biological mechanism of infantile spasms, which may lead to treatments that are more specific.

Additionally, because the mutation occurs on the X chromosome, the team expected female mice with the mutation to be unaffected carriers, which was not the case, prompting the investigators to look at human families with an infantile spasms patient and find relatives with varying degrees of neurological problems. These findings, described in the journal *Brain*, will immediately change the evaluation and testing of women with mental retardation and epilepsy and assist genetic counselors in advising parents who have a child with an *Arx* mutation.

Marsh E, Fulp C, Gomez E, Nasrallah I, Minarcik J, Sudi J, Christian SL, Mancini G, Labosky P, Dobyns W, Brooks-Kayal A, Golden JA. Targeted loss of Arx results in a developmental epilepsy mouse model and recapitulates the human phenotype in heterozygous females. *Brain*. 2009 Jun;132(Pt 6):1563-76.

Protein Disrupts Gene Function in Rare Disorder

Cohesion, a protein complex known to control chromatids, the long strands chromosomes form when they copy their DNA, also plays an important role in regulating genes, according a study led by Ian Krantz, MD, Division of Human Genetics and Molecular Biology. Using a genome-wide analysis of cell lines from patients with a severe form of the rare disorder Cornelia de Lange syndrome (CdLS), Dr. Krantz's team found that the cells had mutations in the *NIPBL* gene, which plays a role in moving cohesin on and off chromosomes and was found in a previous study by Dr. Krantz to cause CdLS. The current study, published in the journal *Public Library of Science Biology*,

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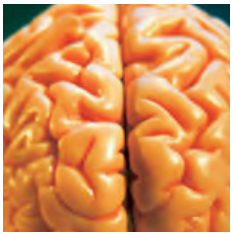
detected gene expression profiles that are unique to CdLS and corresponded to the severity of the disease. These findings, the first in human cells to identify genes that are dysregulated when cohesion does not work properly, could be used to develop a diagnostic tool for CdLS and a variety of other developmental disorders.

Liu J, Zhang Z, Bando M, Itoh T, Deardorff MA, Clark D, Kaur M, Tandy S, Kondoh T, Rappaport E, Spinner NB, Vega H, Jackson LG, Shirahige K, Krantz ID. Transcriptional dysregulation in NIPBL and cohesin mutant human cells. *PLoS Biol.* 2009 May 5;7(5):e1000119.

Studying Altered Brain Cells Sheds Light on Epilepsy

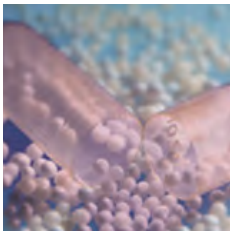


In patients with epilepsy, the delicate balance between electrical brain signaling and inhibition required for healthy brain function is not working properly. Investigators led at CHOP Research by Douglas Coulter, PhD, Division of Neurology, isolated the molecular and electrical events that occur when this balance is disrupted by focusing on reactive astrocytosis, a condition known to occur in many neurological diseases. In this condition, brain cells called astrocytes swell to a large size and change the expression levels of a number of proteins. Using a mouse model, the team found that changes in reactive astrocytes profoundly reduced inhibitory control over brain signals.

Published in *Nature Neuroscience*, this study showed reactive astrocytosis reduces the supply of glutamine synthetase, an enzyme that is key to producing a neurotransmitter that generates electrical signals in the brain. The reduced neurotransmitter supply decreases inhibition and allows neurons to fire out of control. The investigators also found that glutamine, an amino acid that is depleted because of reduced glutamine synthetase activity, restored normal neuronal signaling. These findings may help improve treatments for epilepsy and other conditions that involve disrupted inhibition, including many psychiatric disorders, traumatic brain injury, and neurodegenerative disorders such as Parkinson's disease.

Ortinski PI, Dong J, Mungenast A, Yue C, Takano H, Watson DJ, Haydon PG, Coulter DA. Selective induction of astrocyticgliosis generates deficits in neuronal inhibition. *Nat Neurosci.* 2010 May;13(5):584-91.

Magnetic Fields Deliver Drug-Loaded Nanoparticles



The latest in a series of studies at CHOP Research led by Robert Levy, MD, the William J. Rashkind Endowed Chair in Pediatric Cardiology, demonstrated that magnetically guided nanoparticles delivered drug to metal stents in injured blood vessels, preventing blockages better than conventional non-magnetic stent therapy. The team found that treatment with magnetized nanoparticles and stents led to a higher volume of nanoparticles in stented arteries and significantly lower reobstruction rates 14 days following treatment in rats with carotid artery stents when compared to control rats that received the stents and nanoparticles but were not exposed to the magnetic field. This approach, published in *Proceedings of the National Academy of Sciences*, could potentially be used to deliver a broad range of effective therapeutic agents.

Chorny M, Fishbein I, Yellen BB, Alferiev IS, Bakay M, Ganta S, Adamo R, Amiji M, Friedman G, Levy RJ. Targeting stents with local delivery of paclitaxel-loaded magnetic nanoparticles using uniform fields. *Proc NatlAcadSci* U S A. 2010 May 4;107(18):8346-51.

Family Therapy Helps Teens With Suicidal Thoughts

A CHOP Research team led by Guy Diamond, PhD, director of the Center for Family Intervention Science, found that adolescents with severe suicidal thinking treated with Attachment-Based Family Therapy (ABFT) were at least four times more likely to have no suicidal thinking at the end of treatment or three months after treatment than patients treated in the community were. Patients in ABFT also showed a more rapid decrease in depression symptoms and remained in treatment longer than in community care, even with additional supports provided by the study. Published in the *Journal of the American Academy of Child and Adolescent Psychiatry*, this is the first treatment study for teen suicidal ideation to show robust and statistically significant improvement over treatment as usual.

Diamond GS, Wintersteen MB, Brown GK, Diamond GM, Gallop R, Shelef K, Levy S. Attachment-based family therapy for adolescents with suicidal ideation: a randomized controlled trial. *J Am Acad Child Adolesc Psychiatry*. 2010 Feb;49(2):122-31.

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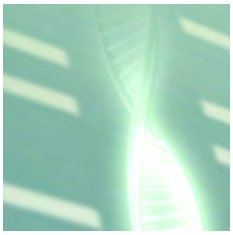
Diabetes Gene Raises Odds of Lower Birth Weight



Investigators led by Struan Grant, PhD, a member of the Center for Applied Genomics, found a gene involved in the development of type 2 diabetes also predisposes children to having a lower birth weight. Drawing on a cohort of DNA from 5,700 Caucasian children in an ongoing genome-wide association study of obesity, Dr. Grant and his team investigated 20 gene locations previously shown to be associated with type 2 diabetes and compared the occurrence of the variants in these genes with birth weight. They found that a variant, in a gene called *CDKAL1,* had a strong association with lower birth weight, which is known to increase the risk of type 2 diabetes later in life.

This finding, published in *Diabetes*, reinforces a smaller European study that implicated *CDKAL1* in both lower birth weight and type 2 diabetes and sheds light on a possible genetic influence on how prenatal events may set the stage for developing diabetes in later childhood or adulthood. Dr. Grant's team at CHOP Research subsequently joined forces with multiple groups worldwide to uncover two additional genes involved in birth weight, results published in *Nature Genetics*.

Zhao J, Li M, Bradfield JP, Wang K, Zhang H, Sleiman P, Kim CE, Annaiah K, Glaberson W, Glessner JT, Otieno FG, Thomas KA, Garris M, Hou C, Frackelton EC, Chiavacci RM, Berkowitz RI, Hakonarson H, Grant SF. Examination of type 2 diabetes loci implicates CDKAL1 as a birth weight gene. *Diabetes*. 2009 Oct;58(10):2414-8.

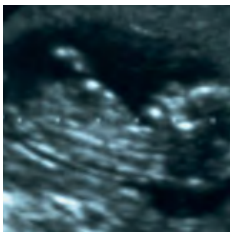
Freathy RM, Mook-Kanamori DO, Sovio U, Prokopenko I, Timpson NJ, Berry DJ, Warrington NM, Widen E, Hottenga JJ, Kaakinen M, Lange LA, Bradfield JP, Kerkhof M, Marsh JA, Mägi R, Chen CM, Lyon HN, Kirin M, Adair LS, Aulchenko YS, Bennett AJ, Borja JB, Bouatia-Naji N, Charoen P, Coin LJ, Cousminer DL, de Geus EJ, Deloukas P, Elliott P, Evans DM, Froguel P; Genetic Investigation of ANthropometric Traits (GIANT) Consortium, Glaser B, Groves CJ, Hartikainen AL, Hassanali N, Hirschhorn JN, Hofman A, Holly JM, Hyppönen E, Kanoni S, Knight BA, Laitinen J, Lindgren CM; Meta-Analyses of Glucose and Insulin-related traits Consortium, McArdle WL, O'Reilly PF, Pennell CE, Postma DS, Pouta A, Ramasamy A, Rayner NW, Ring SM, Rivadeneira F, Shields BM, Strachan DP, Surakka I, Taanila A, Tiesler C, Uitterlinden AG, van Duijn CM; Wellcome Trust Case Control Consortium, Wijga AH, Willemsen G, Zhang H, Zhao J, Wilson JF, Steegers EA, Hattersley AT, Eriksson JG, Peltonen L, Mohlke KL, Grant SF, Hakonarson H, Koppelman GH, Dedoussis GV, Heinrich J, Gillman MW, Palmer LJ, Frayling TM, Boomsma DI, Davey Smith G, Power C, Jaddoe VW, Jarvelin MR; Early Growth Genetics (EGG) Consortium, McCarthy MI. Variants in ADCY5 and near CCNL1 are associated with fetal growth and birth weight. *Nat Genet.* 2010 May;42(5):430-5.

Eliminating Cell Receptor Prevents Infections

By using mice genetically engineered to lack the coxsackievirus and adenovirus receptor (CAR) in heart and pancreas cells, a study team led by Jeffrey Bergelson, MD, the Stanley Plotkin Endowed Chair in Pediatric Infectious Diseases, prevented infection by Group B coxsackieviruses, common viruses that occasionally cause severe infections in the heart, brain, and pancreas. This finding builds on a series of research studies following Dr. Bergelson's identification of CAR in 1997. The current study, published in *Cell Host and Microbe*, found that mice that did not form CAR in their pancreas or heart had virus levels a thousand times smaller in these organs and significantly less tissue damage and inflammation than control animals. These findings indicate CAR is the receptor used by coxsackieviruses to infect the heart and pancreas and to cause injury to tissues, a basic finding that suggests the potential for drugs and treatments that could prevent viruses from using the receptor to gain entry to cells and cause infection.

Kallewaard NL, Zhang L, Chen JW, Guttenberg M, Sanchez MD, Bergelson JM. Tissue-specific deletion of the coxsackievirus and adenovirus receptor protects mice from virus-induced pancreatitis and myocarditis. *Cell Host Microbe.* 2009 Jul 23;6(1):91-8.

Mother's Immune System Blocks Fetal Therapies



In utero hematopoietic cell transplantation (IUHCT) introduces donor cells to a fetus to establish a tolerance for later organ or cellular transplant to treat blood diseases, but the tolerance to later transplants is often inconsistent, suggesting an immune barrier sometimes acts against transplanted cells. An animal study led by Alan Flake, MD, the Ruth M. and Tristram C. Colket Jr. Endowed Chair in Pediatric Surgery, found that while mice nursed by foster mothers retained healthy donor cells transplanted using IUHCT, mice nursed by their biological mothers lost the transplanted donor cells. Published in the *Journal of Clinical Investigation*, the study shows that the mothers whose fetuses received the donor cell transplants had developed antibodies against the transplanted cells and transmitted the antibodies to their pups through breast milk. Although additional research is needed to understand how these findings apply to humans, this study suggests that transplant techniques that avoid the maternal immune response may allow scientists to treat blood diseases before birth.

Merianos DJ, Tiblad E, Santore MT, Todorow CA, Laje P, Endo M, Zoltick PW, Flake AW. Maternal alloantibodies induce a postnatal immune response that limits engraftment following in utero hematopoietic cell transplantation in mice. *J Clin Invest.* 2009 Sep;119(9):2590-600.

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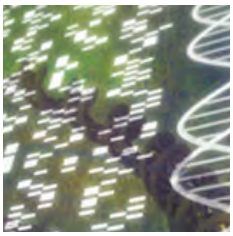
Mitochondrial Gene Defects Impair Life Functions



Defects in mitochondria, structures within cells where energy is generated, result in a wide array of debilitating, multi-system diseases and contribute to complex disorders ranging from Parkinson's disease and Alzheimer's disease to epilepsy and diabetes. For such crucial biological actors, much remains unknown about how mitochondria function. Researchers led by Marni J. Falk, MD, director of the CHOP Mitochondrial-Genetics Diagnostic Clinic and co-leader of the Mitochondria Research Affinity Group, used a small worm called *Caenorhabditis elegans* as a model organism in which to study a biological pathway called the respiratory chain, specifically the first large multi-subunit complex of the chain, which is the most common culprit in human mitochondrial disease. The team found one subset of genes impairs the ability of mitochondria to consume oxygen and another group affects how the worms react to anesthesia, findings that help to suggest specific gene candidates that may cause mitochondrial disease in individual patients and clarify the biology of how specific genes may cause disease. This study was published in *PLoS ONE*.

Falk MJ, Rosenjack JR, Polyak E, Suthammarak W, Chen Z, Morgan PG, Sedensky MM. Subcomplex Ilambda specifically controls integrated mitochondrial functions in Caenorhabditis elegans. *PLoS One*. 2009 Aug 12;4(8):e6607.

Link Between Metabolic Syndrome and Liver Disease

A research team led by Rose Graham, MD, found a strong association between metabolic syndrome – a complication of obesity – and elevated levels of alanine aminotransferase (ALT) – a liver enzyme associated with a potentially severe disease called nonalcoholic fatty liver disease (NAFLD). In a nationally representative sample of 1,323 U.S. adolescents aged 12 to 19, the link between metabolic syndrome and elevated ALT levels was present in adolescent males but not in adolescent females. Among Hispanic males this association was largely explained by obesity measured by body mass index. However, among non-Hispanic males metabolic syndrome and high ALT levels were associated with each other independent of obesity, suggesting that obesity is not the only risk factor for NAFLD among boys with metabolic syndrome. This finding, published in the *Journal of Pediatric Gastroenterology and Nutrition*, suggests that treating NAFLD may require more than just weight loss, the only currently known treatment.

Graham RC, Burke A, Stettler N. Ethnic and sex differences in the association between metabolic syndrome and suspected nonalcoholic fatty liver disease in a nationally representative sample of US adolescents. *J Pediatr Gastroenterol Nutr.* 2009 Oct;49(4):442-9.

Brain's Magnetic Fields Reveal Language Delays in Autism

Children with autism spectrum disorders (ASDs) process sound and language a fraction of a second slower than typically developing children, according to research led by Timothy Roberts, PhD, vice chair of research the Department of Radiology and holder of the Oberkircher Family Endowed Chair in Pediatric Radiology. The research team used magnetoencephalography to detect magnetic fields in the brain of 25 children with ASDs and 17 typically developing children and found that the children with ASDs had an average delay of 11 milliseconds when compared to control subjects. This finding, published in *Autism Research*, suggests that the auditory system may be slower to develop and mature in children with ASDs and the delays these children experience may cascade as a conversation progresses, causing them to lag behind their peers. While more work is needed, the magnetic signals that mark this pattern of delayed brain response may be refined into a standardized way to diagnose autism.

Roberts TP, Khan SY, Rey M, Monroe JF, Cannon K, Blaskey L, Woldoff S, Qasmieh S, Gandal M, Schmidt GL, Zarnow DM, Levy SE, Edgar JC. MEG detection of delayed auditory evoked responses in autism spectrum disorders: towards an imaging biomarker for autism. *Autism Res.* 2010 Feb;3(1):8-18.

ADHD Genes Found, Also Act in Neurodevelopment

In the first study to investigate the role of genetic changes known as copy number variations (CNVs) in attention deficit hyperactivity disorder (ADHD), a team led by Josephine Elia, MD, Division of Child and Adolescent Psychiatry, and Peter White, PhD, director of the Center for Biomedical Informatics, analyzed and compared the genomes of 335 ADHD patients and their families to genomes of more than 2,000 unrelated healthy children. The study team expected to find a handful of genes that predispose a child to ADHD but found 222 inherited CNVs in ADHD patients and their families that were not present in healthy subjects. A significant number of these CNVs were in genes previously identified in other neurodevelopmental disorders including autism, schizophrenia, and Tourette syndrome, and genes important in learning, behavior, brain function, and neurodevelopment. These findings, published in *Molecular Psychiatry*, provide the first statistically supported evidence that ADHD has a substantial genomic contribution, and suggest that many gene factors likely play a role in ADHD risk. In addition, they may help to explain why children with ADHD often have slightly different symptoms and may eventually guide researchers to better targets for early ADHD intervention.

Elia J, Gai X, Xie HM, Perin JC, Geiger E, Glessner JT, D'arcy M, deBerardinis R, Frackelton E, Kim C, Lantieri F, Muganga BM, Wang L, Takeda T, Rappaport EF, Grant SF, Berrettini W, Devoto M, Shaikh TH, Hakonarson H, White PS.

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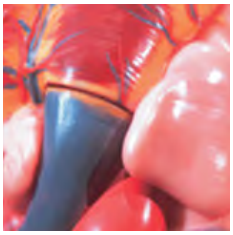
Rare structural variants found in attention-deficit hyperactivity disorder are preferentially associated with neurodevelopmental genes. *Mol Psychiatry*. 2010 Jun;15(6):637-46.

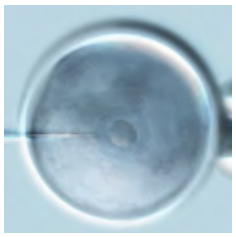
First Common Gene Found for Congenital Heart Disease



Peter J. Gruber, MD, PhD, Division of Cardiothoracic Surgery, has advanced the understanding of the genetic causes of congenital heart disease (CHD) – the most common major birth defect – by leading the first collaboration to discover a common genetic variant that strongly raises the risk of CHD. Dr. Gruber's previous research found that a gene on chromosome 5 called *ISL1* was crucial in regulating the development of human cardiac stem cells. In the current study, published in the journal *Public Library of Science One*, Dr. Gruber's team investigated *ISL1*'s involvement in CHD during the earliest period of the heart's development using DNA from 1,344 children with CHD and 6,135 healthy children. The team found seven gene variants in or near the *ISL1* gene that raised the risk of CHD. The variants were alternative spellings in DNA bases called single nucleotide polymorphisms, or SNPs. Further analysis found that one SNP raised the risk for white children, and a different SNP in the same gene increased the risk for African-American children.

Stevens KN, Hakonarson H, Kim CE, Doevendans PA, Koeleman BP, Mital S, Raue J, Glessner JT, Coles JG, Moreno V, Granger A, Gruber SB, Gruber PJ. Common variation in ISL1 confers genetic susceptibility for human congenital heart disease. *PLoS One*. 2010 May 26;5(5):e10855.

Grants Advance Stem Cell Research for Blood Disorders



Following the decision to permit federally funded researchers to use new lines of human embryonic stem cells, CHOP Research investigators were awarded two large federal grants that will advance the frontiers of research into cellular therapies. Human embryonic stem cells – derived from human embryos fertilized in *in vitro* fertilization clinics and donated for research purposes – are capable of developing into every type of cell and tissue in the body. Both grants support programs engineering these cells to potentially treat patients suffering from blood diseases, cancer, and a range of other disorders.

Led by Mortimer Poncz, MD, chief of the Division of Hematology, one grant focuses on platelets, naturally occurring blood cells that help control bleeding and assist in wound healing but that are depleted following chemotherapy and bone marrow transplantation. This seven year, $16.8 million grant from the National Heart, Lung, and Blood Institute (NHLBI) uses human embryonic stem cells to generate platelet supplies for hematology and oncology patients and to use platelets to deliver customized proteins to injured blood vessels. Awarded jointly to CHOP Research and the Fred Hutchinson Cancer Research Center at the University of Washington, the grant funding will be used to conduct a complimentary approach that builds upon the team's expertise with generating platelets and precursor cells from stem cells, transplanting stem cells, and using platelets as a drug delivery vehicle.

The second grant, a two-year, $997,000 Grand Opportunity Grant funded by the American Recovery and Reinvestment Act, is part of an NHLBI program to support novel research designed to quickly advance an area of biomedicine in significant ways. Awarded to hematologist Mitchell Weiss, MD, PhD, the Jane Fishman Grinberg Endowed Chair in Stem Cell Research, the grant capitalizes on the ability to reprogram most of the body's cells into induced pluripotent stem cells (iPSCs), which have the capacity to develop into other types of human cells. The study team is developing iPSCs into hematopoietic, or blood forming, cells and will evaluate iPSCs as a model system for understanding how blood disorders develop. Dr. Weiss' team, partnered with scientists at Pennsylvania State University and the Coriell Institute for Medical Research, also plans to reprogram patient cells into iPSCs and develop them into tissue banks to model and perhaps treat specific blood diseases.

Both projects are strengthened by the newly launched Human Embryonic Stem Cell Core at CHOP Research, directed by gene therapy pioneer Katherine High, MD, HHMI. The projects illustrate the promising future that stem cell biology holds for a wide range of diseases that currently have suboptimal therapies.

Genomic Research Projects Funded by Stimulus Grants

Hakon Hakonarson, MD, PhD, who directs the Center for Applied Genomics (CAG), is the principal investigator (PI) on three grants awarded from the National Institutes of Health's stimulus funding. The grants hinge upon the genotyping technology of CAG, used to identify genetic variants that play a role in disease, such as single nucleotide polymorphisms (SNPs) – single base pair variations in DNA – and copy number variations (CNVs) – segments of DNA consisting of deleted, duplicated, or rearranged genetic material. Totaling $22 million, the grants seek to enhance the understanding of genetic factors that contribute to epilepsy, juvenile idiopathic arthritis, and mental illness, in order to facilitate the development of more effective diagnoses and treatments.

Under the epilepsy grant, Dr. Hakonarson and his team of investigators from CHOP Research, the Veteran's Affairs Medical Center, University of Pennsylvania, The Ohio State University, and Thomas Jefferson University are uncovering genes and genetic variants that predispose individuals to common forms of epilepsy, a common cause of childhood disability. Using DNA collected

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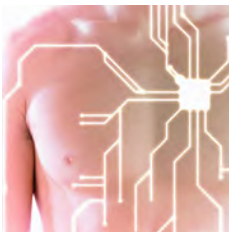
from 2,000 epilepsy patients and 4,000 healthy controls, the team is identifying genetic variants that associate with epilepsy and subsequently testing them in a new group of 1,000 epilepsy patients and 1,000 unrelated healthy controls for additional confirmation of their roles in epilepsy. To further validate and refine these findings, the team will genotype 10 to 20 candidate SNPs in DNA samples from 250 African-American epilepsy patients and 1,000 African-American controls, a population of different genetic background, to help pinpoint the key disease genes involved. Additionally, the team will conduct a fine-mapping analysis of the variants that are most significant and affect genes that have a compelling biological role in epilepsy to prioritize genes that will be further evaluated as targets for new therapies.

Dr. Hakonarson and co-PI Terri H. Finkel, MD, PhD, chief of the Division of Rheumatology, were awarded a stimulus grant from the National Institute of Arthritis and Musculoskeletal and Skin Diseases to target arthritis. Their team will use the funds to identify genes that work together to predispose children to juvenile idiopathic arthritis (JIA), another common and disabling disease of childhood. The team is genotyping DNA from 1,500 JIA patients and 4,000 matched controls. Similar to the epilepsy study, the disease genes identified will then be validated in an independent cohort of 1,000 JIA patients and 2,000 controls to ensure the genes discovered are causative of JIA. This research is expected to identify 10 to 20 candidate genomic regions that predispose patients to JIA and should be evaluated further in studies aimed at developing new therapeutic treatment approaches.

In the project focused on mental illnesses, which emerge in a large number of children and adolescents, Dr. Hakonarson's team will assess the behavioral dimensions – such as anxiety, mood, and substance abuse – of 10,000 children and adolescents who have already been genotyped by CAG to identify which factors indicate vulnerability to mental illness. These 10,000 children will undergo a comprehensive neurocognitive assessment through a battery of computerized tests to determine which genes play a key role in normal development and how mutations in these genes may lead to disease. These children will also undergo neuroimaging to look at brain structure, white matter connectivity, cerebral blood flow, and cerebral activation of neural circuits implicated in major mental illnesses. A database combining these data with a genome-wide analysis of methylation, a DNA modification that alters the expression of genes, will link genetics, epigenetics, and brain systems that regulate behavior and psychopathology, a resource that will be made available to the scientific community at large.

Award Supports Commercializing a Therapeutic Delivery Platform



Robert Levy, MD, the William J. Rashkind Endowed Chair in Pediatric Cardiology, received an award from the University City Science Center's QED Proof-of-Concept Program to support his efforts toward developing and commercializing a new delivery system that magnetically targets therapeutic agents to catheter-deployed stents. Called vascular magnetic intervention (VMI), the therapy could become a major platform technology for delivering drugs, cells, and other agents to specific sites in diseased or injured blood vessels. The QED award provides a 12-month, $200,000 grant for early-stage research and development that includes matching funds from CHOP Research, business advice from an advisor with a background in project development and implementation, and guidance from industry and investment experts.

VMI builds upon existing stent technology by directing biodegradable nanoparticles loaded with an antiproliferative drug, paclitaxel, to stents using uniform field magnetization. Dr. Levy's team first established the VMI mechanism and demonstrated that VMI effectively prevented restenosis in the stented carotid arteries of rats and provided sustained drug release over the course of a 14-day study. Current investigations by the QED Award include a preclinical proof-of-concept study that evaluates the distribution of paclitaxel when administered using VMI and that compares restenosis in animals treated with stents and VMI to deliver paclitaxel and those treated with bare metal stents and no paclitaxel. The model for this study has been used in other preclinical studies submitted to the Food and Drug Administration for Investigational New Drug Applications.

VMI could potentially treat the 9 million patients with symptomatic peripheral arterial disease (PAD), a buildup of plaque that can harden and narrow the arteries. In children, who do not commonly suffer from PAD, VMI could eventually be used to deliver drugs to improve outcomes in a number of stent-based interventions in pediatric cardiology for conditions such as peripheral pulmonary artery stenosis, coarctation of the aorta, and atrial septal defects. Unlike existing drugeluting stent technology that delivers one fixed dose, VMI offers the possibility of providing a variable initial dose based upon the extent of disease and can be readministered for either redosing or treatment with a different agent. Additionally, because the magnetic effect concentrates its delivered agent at the specific site of a stent, VMI could be used to achieve stronger effects with lower overall doses of a given agent than is possible with existing routes of administration.

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Grant Funds New Growth Charts for Children With Down Syndrome

Growth charts are a screening tool used by pediatricians to identify children who may have underlying health conditions. CHOP Research investigators led by Babette Zemel, PhD, director of the Nutrition and Growth Laboratory, are developing updated growth charts for children with Down syndrome, who tend to grow more slowly and are considerably shorter than most other children.

Major advances in the medical care and life expectancy of children with Down syndrome have been achieved in the 25 years since data was collected for the current growth charts. In addition, the demographics of the general U.S. population have changed and children are taller, but also more overweight.

Under a four-year, $1.2 million grant from the Centers of Disease Control and Prevention (CDC) the study team will recruit about 600 children with Down syndrome from birth to 20 years of age in Southeastern Pennsylvania, New Jersey, and Delaware. The study team, composed of experts in growth and nutrition, Down syndrome, and general pediatrics, will measure patients' growth and body dimensions, and collect data about their health, dietary patterns, and physical activities during regularly scheduled follow-up visits.

The growth charts developed by the study will be broadly distributed free of charge. In addition to developing more representative growth charts, the study team also expects to develop a screening tool for identifying children at risk for overweight and obesity, common concerns for adolescents and young adults with Down syndrome, and to better understand what factors may contribute to growth-related problems in children with Down syndrome.

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03.INVESTING FOR SUCCESS

Innovation is crucial to our mission of advancing the health of children around the world. Bringing innovation to life requires stepping away from the standard way of getting things done – bold moves that are risky, and often expensive, but can lead to breakthroughs that have value beyond measure. In an environment where every dollar is critical, CHOP Research makes calculated investments to support innovations that are truly revolutionizing the way pediatric research is conducted.

CHOP Research investments have armed the research community with the facilities, tools, and support to capitalize on opportunities that will strengthen the Institute, fortify our community of research professionals, enhance the productivity of research in action, and contribute to the broad pursuit of scientific knowledge. Taking these critical steps today will lead to a healthier tomorrow for millions of children.

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Center for Applied Genomics Continues to Provide Key Insight Into the Genetics of Childhood Diseases

Four years ago, The Children's Hospital of Philadelphia Research Institute saw the potential to lay the foundation for personalized medicine. With a substantial investment in state-of-the-art equipment and highly trained and innovative personnel, the Institute opted to pursue a then-novel path aimed at finding ways to more effectively manage or even prevent diseases from occurring – all based on a person's genetic predisposition.

It was an investment in research that continues to pay off exponentially in terms of contributing to the collective scientific knowledge about the genetic cause of numerous diseases and conditions affecting children across the globe.

Today, through the work from the high-throughput genotyping technology used by the Institute's Center for Applied Genomics (CAG), investigators and healthcare providers have a greater understanding of the genetic basis for autism, attention deficit hyperactivity disorder, asthma, obesity, diabetes, inflammatory bowel disease, and cancer, among others.

Led by Hakon Hakonarson, MD, PhD, CAG has stayed true to its goals of working toward new diagnostic tests for childhood diseases and using this knowledge to guide physicians to the most appropriate therapies. The group has also played a pivotal role in biomedical research by refining tools that may accelerate how quickly investigators can pinpoint genes that cause disease.

CAG, one of nearly a dozen Centers of Emphasis at the CHOP Research Institute, has proven to be one of the most prolific research programs in the country, frequently publishing its findings in many of the top-ranked biomedical journals, including *Nature*, the *New England Journal of Medicine*, and *Nature Genetics*.

"Through our discoveries we are achieving a greater understanding of the major gene networks that cause some of the most common and devastating diseases in children," says Dr. Hakonarson. "By identifying gene mutations that perturb gene function, we now have a way of diagnosing these children and are better positioned to develop new and novel therapies."

The following are some of the highlights from CAG's groundbreaking research in fiscal year 2010 alone.

2010 CAG Highlights

Autism

Dr. Hakonarson and his colleagues in CAG put in place more pieces to the complex autism inheritance puzzle by identifying 27 genetic regions where rare copy number variations (CNV) – missing or extra copies of DNA segments – were found in the genes of children with autism spectrum disorders (ASDs). The study results stemmed from a refinement of previous research reported in *Nature*, in which Dr. Hakonarson and his team identified the first common gene variants in ASDs as well as copy number variations in two major neuronal gene networks that raise the risk of having an ASD.

Collaborating with colleagues from several other institutions, the CAG research team also uncovered two novel genes in which variations were found – *BZRAP1* and *MDGA2* – both of which are believed to be important in synaptic function and neurological development, respectively.

Neuroblastoma

In studies published in *Nature* and *Nature Genetics*, two of the most prestigious biomedical journals, Dr. Hakonarson and his CAG collaborators worked with John Maris, MD, director of the Division of Oncology at Children's Hospital on a genome-wide association study that discovered common variants in the gene *BARD1* increase a child's susceptibility to a high-risk form of neuroblastoma. The effort represented the largest gene study to date in pediatric oncology.

A second genome study found that a CNV along a structurally weak location on chromosome 1 plays an important role in the development of neuroblastoma, the most common solid cancer of early childhood that is responsible for 15 percent of all childhood cancer deaths.

The study was the first to identify a specific CNV that predisposes people to cancer and has opened up a new area for investigators studying how these variations may increase the risk for cancer.

Asthma

In one of the largest gene studies to date on asthma, reported in the *New England Journal of Medicine*, investigators from CAG identified a novel gene involved in this common, yet complex, respiratory disease. The gene, called *DENND1B*, affects cells and signaling molecules thought to be instrumental in the immune system overreaction that occurs in asthma.

Numerous genes are involved in asthma, and most of them remain undiscovered. Not only do these genes interact with one another, they mingle with environmental factors to produce the

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wheezing, coughing, and shortness of breath that are the primary characteristics of asthma.

The discovery of a novel gene by Dr. Hakonarson and his team in CAG may therefore have singled out an important target for new treatments.

Inflammatory Bowel Disease

As part of an extensive international research team, work by CAG played a primary role in the discovery of five new genes related to inflammatory bowel disease (IBD), a painful, chronic inflammation of the gastrointestinal tract.

Most gene analyses of IBD have focused on adult-onset disease, but CAG concentrated on the form that arises in childhood, which tends to be more severe than that experienced by adults. Evaluating the DNA of more than 15,000 children, the team identified five new gene regions that raise the risk of early-onset IBD, on chromosomes 16, 22, 10, 2, and 19.

The most significant finding was at chromosome locus 16p11, which contains a gene that carries a specific signaling protein that acts on a biological pathway that causes intestinal inflammation.

The findings have given investigators critical clues on how IBD develops, and will lead to further studies aimed at developing new therapeutic treatment approaches.

In a separate study, Dr. Hakonarson and his team analyzed DNA variations in type 1 diabetes and IBD and found a complex interplay of genes. Some of the genes have opposing effects, raising the risk of one disease while protecting against the other. In other cases, a gene variant may act in the same direction, raising the risk for both diseases.

These opposing effects may suggest a possible "genetic switch" of some biological pathways involved in both IBD and type 1 diabetes.

Schizophrenia

CAG analyzed the genomes of patients with schizophrenia and discovered numerous CNVs that increase the risk of developing the disorder. Of particular note, many of these variations occur in genes that affect signaling among brain cells.

In addition, Dr. Hakonarson and his co-investigators found that the genes and signaling systems linked to schizophrenia had some overlap with those for autism and for attention deficit hyperactivity disorder. In fact, the study found deletions in the same region of chromosome 16 as those found in a study of autism spectrum disorders that Dr. Hakonarson led in 2009.

Future studies will delve into how these and other CNVs may alter brain function. A better understanding of signaling pathways in the brain may eventually enable investigators to develop drugs that can selectively act on biological pathways involved in schizophrenia, with better efficacy and fewer side effects for patients.

Food Allergies

Dr. Hakonarson and his CAG team identified the first major gene location responsible for a severe, often painful type of food allergy called eosinophilic esophagitis (EoE). This disease, which doctors are diagnosing with greater frequency, may cause weight loss, vomiting, heartburn, and swallowing difficulties. As a result, a patient may be unable to eat a wide variety of foods.

The CAG team found EoE was linked to a region of chromosome 5 that includes two genes. The likely culprit is the gene *TSLP*, which has higher activity levels in children with EoE compared to healthy subjects. In addition, *TSLP* has been previously linked to allergic inflammatory diseases, such as asthma and the skin inflammation atopic dermatitis.

Several other discoveries are on the horizon at CAG, including discoveries of gene variants that predispose to anorexia nervosa, attention deficit hyperactivity disorder, and dysregulated lipid levels in children, to name a few.

PROSPER Formed to Serve the Clinical Research Community, Strengthen Research Programs

Running a clinical research study is an enormous undertaking. Principal investigators are faced with designing and overseeing the study, establishing funding, safeguarding clinical research participants, collecting data, reporting adverse drug effects, and publishing results, often while managing other research projects and attending to clinical responsibilities.

Investigators often turn to the expertise of clinical research coordinators (CRCs) to address the complexities of the day-to-day management of clinical studies. Investigators rely on CRCs to help them with all aspects of clinical research studies, often delegating responsibility for several components of a study to the CRC. Adding to the challenge, CRCs are often assigned to help with multiple studies.

To support the individuals who serve in this complex and demanding role, members of the CHOP Research community have developed an organization to serve as a resource for all clinical research staff in the CHOP Research community. Called PROSPER, based on its intention to be a **PRO**fessional **S**ociety for **PE**diatric Clinical **R**esearch, the society offers ongoing support for new and seasoned research personnel and serves as an avenue for clinical research interactions. Since its launch in 2008, PROSPER has gathered more than 250 members and has assembled multiple committees that work on shared education, communication, and planning goals.

CHOP Research CRCs include clinical research staff representing a diverse range of departments, divisions, and centers.

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PROSPER creates a community where all CRCs can interact and gain support in common areas of interest and concern. In one such effort toward this goal, PROSPER has built a robust Web site, available on the CHOP Research intranet, that serves as a centralized information source of what it takes to conduct research at CHOP.

Information provided on the PROSPER site includes education on federal regulations governing clinical research, the human subjects protections overseen by the Institutional Review Board, research billing requirements and implications, and the Hospital's clinical management systems. Augmenting PROSPER's educational efforts are the events the society holds, which have a dual purpose of education and networking. At PROSPER events, new and experienced CRCs can learn from each other and make connections for shadowing and mentoring opportunities in which knowledge can be shared to enhance the CRC experience.

PROSPER is also addressing the expanded scope of the CRC's role, recognized nationally as an issue that challenges research organizations. Traditionally, CRCs were assigned to oversee the clinical management of patients enrolled in a clinical study and ensure human subject protection. Today, the expectations of a CRC's role are broader and include many sophisticated tasks requiring expertise in regulatory compliance, research administration, study sample and drug processing, marketing, and financial management.

PROSPER is working to create a standardized job description for CRCs and establish new job categories within the CHOP Research infrastructure to relieve CRCs from tasks that detract from their ability to carry out core responsibilities. PROSPER plans to use the restructured job categories to develop a career ladder for the CRC pool in an effort to retain experienced, talented employees who facilitate and expedite the research process.

In addition to serving the CRC community, the resources PROSPER provides benefit the Research Institute as a whole. CRCs are in the unique position of navigating the clinical research process for both investigators and research participants, with great implications for the Institute's research program and reputation. By improving the information provided to CRCs, PROSPER is increasing the general understanding of complex issues clinical researchers face, which in turn, is improving the clinical research CRCs manage.

PROSPER's work toward a new employment structure for CRC will also have a beneficial effect on research studies. CRCs with clear career paths and advancement opportunities will continue to work within the CHOP Research Institute, enhancing and continuing CHOP Research's cadre of experienced and dedicated CRC professionals.

With leadership from Lisa Speicher, PhD, Denise DePaul, RN, and an active steering committee, PROSPER is positioned to continue toward its goal of supporting the research community by focusing on continued outreach and education efforts. In the coming year, PROSPER will coordinate with other CHOP Research organizations and with a similar society at the University of Pennsylvania to enhance the educational resources available to CRCs and other members of the clinical research community at CHOP Research.

Mobile App Provides Rapid Access to Side Effect Information, Advancing Care of Patients in Clinical Trials

Participation in clinical research studies involves an element of risk, including the risks of side effects, which can vary in both frequency and intensity. Swiftly accessing side effect information and maintaining accurate records of these effects is critical not only to patient care but also to improving future clinical studies. When a patient experiences a side effect, how can you sift through the hundreds of classifications for the symptom and accurately report it?

The answer may be in the palm of your hand.

Physicians and other healthcare practitioners have always been challenged with absorbing – as well as retaining and calling to mind in an instant when needed – rapidly evolving information on treatments and side effects for a multitude of diseases and disorders.

This can be a daunting task, given the ever-changing nature of healthcare and research suggesting better treatment approaches, new therapeutics, complex drug interactions, and FDA warnings.

At the bedside, there is sometimes a small window of opportunity – a mere moment – to assess what is happening and move forward on an appropriate treatment course.

And that small moment can have a huge impact on saving lives.

Healthcare-related mobile applications for devices like the iPhone® have emerged as an intriguing tool in caring for and sometimes treating patients, and in allowing healthcare practitioners to immediately access up-to-date information that may advance their practice and improve the health of patients.

More than a quarter million iPhone® applications are now available in a multitude of categories, including a category designed for medical purposes, and the number of applications grows daily. With the touch of a finger, healthcare practitioners can access information critical to saving lives. Monitoring the safety of treatments used in clinical trials is crucial to providing the best results for current and future patients.

The Center for Biomedical Informatics (CBMi) at The Children's Hospital of Philadelphia Research Institute has helped advance the care of individuals participating in clinical trials. With a few touches of an iPhone® or iPod touch®, physicians and nurses can now keep more accurate records of adverse events for those taking part in clinical trials.

The National Cancer Institute (NCI) classifies adverse events to help standardize the record keeping of side effects experienced by study participants. In the printed form of its current version, the NCI's Common Terminology Criteria for Adverse Events (CTCAE) spans almost 200 pages.

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CBMi took the wealth of information in the NCI's reference materials and converted it into a free, innovative, easy-to-use software application for the iPhone® or iPod touch®.

From an alphabetized list of symptoms, healthcare providers can tap in any side effect and the app will display a definition and grade the problem – mild, moderate, or severe. By using these categories, care providers and clinical trial investigators can log data into the trial's records to be shared with other hospitals and physicians who have patients participating in the same trial. Users can also bookmark adverse events and categories that are most frequently accessed.

While the CTCAE classifications originated in oncology research, they have a broad application in clinical trials for other conditions and provide rapid, point-of-care information that can improve the efficiency and effectiveness of clinical research. Investigators may incorporate the CTCAE information as a rubric in their protocols as a means of protecting patients through standardized record keeping.

The benefits of using the CTCAE mobile application, which has already been downloaded more than 2,300 times, do not end with clinical investigators. Attending physicians, medical students, and others involved in healthcare can use the app as a valuable and readily available information resource.

"This app is one example of mobile health development, in which we are assisting healthcare staff in accessing the next generation of information technologies," says CBMi Director Peter White, PhD. "Besides the immediate benefits for efficiency, we feel that using this type of technology has significant potential for standardizing care delivery, reducing error, and improving both quality of care and patient safety."

Supporting the Development of Postdocs, Building a Pipeline of Innovators

TheScientist 2010 BEST PLACES TO WORK POSTDOCS

World-class researchers are in a constant pursuit of knowledge. One step in this lifelong journey is a postdoctoral fellowship. Many investigators take advantage of a postdoctoral position as a unique, short-term training opportunity, designed to extend, refine, and enhance skills necessary to transition to a permanent career position.

Affectionately called "postdocs," this group of researchers is an essential part of the CHOP Research community; postdocs make indispensible contributions in almost every lab and research group, including the programs of the most high-achieving scientists.

A postdoc position also helps young investigators, who face incredible competition to become an independently funded investigator. The resources, mentoring, and support postdocs receive hones their scientific skills and helps them become more competitive in the world of academic research.

CHOP Research invests considerable resources into the postdoc community, not only to strengthen the careers of individual investigators and today's leading research programs, but also to build a pipeline of innovators who will advance scientific investigations at CHOP Research, and possibly even other institutions, working toward a common goal of eradicating disease.

CHOP Research was included in the eighth annual "Best Places to Work for Postdocs" survey from *The Scientist*, a magazine for life science professionals. The Institute was ranked among the top 15 U.S. institutions that support the values and needs of their postdocs according to 11 categories that encompass the quality of training and mentoring, facilities and infrastructure, funding and compensation, and work-life balance.

CHOP Research's investment in the next generation of research scientists at Children's Hospital is led by the Office of Postdoctoral Affairs, a dedicated administrative resource that maintains materials and programs to assist postdocs as they prepare for a well-rounded career. The office provides a number of venues in which postdocs can gain support, such as the newly launched CHOP Research Trainee Web Portal.

Investments into our postdoc program have made CHOP Research a leading center for training new scientists who will lead the next generation of research and will continue CHOP Research's history of successfully identifying critical clinical targets and supplying innovative solutions through translational research.

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04.CATALYSTS FOR CHANGE

In the pursuit of improving the health of children, the ideal return on every research investment is change. By its very nature, the Institute's mission to turn scientific discovery into medical innovation necessitates changes so great they can revolutionize pediatric medicine. New information, new approaches, and new techniques are the building blocks that will help bridge the gap between research and clinical applications, the core of translational research.

CHOP Research Institute investigators are never content with standing still or accepting the status quo. By evoking change in research policies, methods, and agendas, our investigators are accelerating the pace of discovery and establishing new standards that are optimizing investigations at CHOP Research and throughout the world. Continuing to capitalize on these changes will ensure pediatric research is efficient, effective, and focused on the most urgent needs of children.

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Setting the Agenda for Pediatric Cancer Research: Cure Is Not Enough

When it comes to pediatric cancer, exciting news is emerging from the research world, but it is tempered by some stark realities of current day cancer treatments.

First, the good news: the cure rates for all forms of cancer have improved dramatically over the past five decades. For example, a child born in the 1960s who developed acute lymphoblastic leukemia, the most common form of childhood cancer, had perhaps a 5 percent chance of being cured; the cure rate for those born in the 1990s now exceeds 80 percent.

That's the encouraging news, and a testament to the dedication of oncology investigators to find therapeutic approaches that allow children to live cancer-free lives.

The downside is that current oncology treatment protocols often expose children to severe and sometimes life-threatening side effects that can affect every system in the body. And too many children carry side effects later into their life.

As the scientific understanding of childhood cancers continues to improve, an increasing challenge in pediatric oncology will be how best to develop new, tailored treatments that not only cure children of cancer but also allow them to grow and lead long, healthy lives.

Peter C. Adamson, MD, director of Clinical and Translational Research at the CHOP Research Institute, is uniquely positioned to set the priorities for the international approach to pediatric cancer clinical-translational research.

As incoming chair of the Children's Oncology Group (COG), the cooperative group for pediatric cancer clinical trials, Dr. Adamson is working to restructure the existing system to allow for a more rapid and streamlined process for developing new anti-cancer treatments.

"Progress in curing children with cancer has slowed over the last 10 years. Pediatric oncologists have gotten as much mileage out of the anti-cancer drugs available today as they possibly can," says Dr. Adamson, noting that most of today's drugs have been available for 30 or more years. "Moreover, curing children of cancer is not enough; we need to give them long, healthy lives with a high quality of life."

Dr. Adamson is an internationally recognized leader in pediatric cancer drug development and will serve for at least five years as chairman of COG, which unites more than 5,000 experts in childhood cancer at leading children's hospitals, universities, and cancer centers across North America, Australia, New Zealand, and Europe in the fight against childhood cancer.

He previously led a 21-site phase 1 consortium through COG that involved evaluating drugs being developed to treat cancer in children. During the eight years that Dr. Adamson led this effort, the collaborating sites conducted more than 25 studies focused on the initial testing of novel anti-cancer drugs in children.

His experiences working with investigators from multiple disease areas and industry partners through his involvement with COG, his own research efforts, and his membership on key advisory committees for the National Cancer Institute, give Dr. Adamson a unique perspective on the nationwide challenges facing the cancer clinical trial system.

As the head of COG, Dr. Adamson hopes to increase the collaborative efforts needed to create therapies for cancer that are more effective than existing treatment options. Since it can take many years to begin a new cancer trial, creating targeted therapies for children with cancer requires a better pathway for moving from the bench to the bedside, which Dr. Adamson will lead through expanding COG's role at Children's Hospital and fostering new and enhanced collaborations with COG sites throughout the world.

Dr. Adamson's influence and vision with respect to pediatric oncology clinical trials was evident in his recent participation in a Childhood Cancer Summit on Capitol Hill, where he shared his experience about developing new treatment approaches for children battling cancer.

He has asked lawmakers to support greater investment in pediatric cancer research as part of an increase in funding for the National Institutes of Health, and to increase incentives to the biopharmaceutical industry to develop new anti-cancer drugs. During his advocacy visit to the nation's capital, Dr. Adamson was accompanied by his patient Mollie Ward and her family. Mollie is now-healthy child who was successfully treated with an experimental cancer drug as part of phase 1 clinical trial.

"The next five to 10 years will usher in an era of unprecedented discovery in pediatric cancer," according to Dr. Adamson. "We must take those discoveries and turn them into better treatments for all children with cancer." Fostering a research environment focused on discoveries and enhancing collaboration among COG institutions will lead to more cures for children like Mollie.

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You Really Can Learn a Lot From a Dummy: Pediatric Biomechanics Key to Reducing Crash-Related Injuries

In the mid-1980s, the Ad Council, in conjunction with the National Highway Traffic Safety Administration, launched a series of public service announcements encouraging drivers and motor-vehicle occupants to "buckle up." The campaign introduced two "spokespeople" to drive the message home – crash-test dummies.

These models have been used for decades in simulated crashes, which look at velocity, force, and other variables, and are used by investigators and the auto industry to analyze the potential physical effects of crashes on occupants and predict the likelihood of injuries.

But vehicle safety doesn't end with buckling up. As it turns out, it's only a beginning to understanding the ways to reduce or eliminate crash-related injuries.

The pediatric crash-test dummies traditionally used do not account for the significant and critical differences in bone and tissue structure and body composition between children and adults. Oftentimes, the child versions of the models are merely scaled-down versions of the adults models used.

The result is that vehicle testing may ultimately provide greater safety for adults involved in a crash but might not optimally protect children who may be more vulnerable and susceptible to injury.

To help remedy the disparity, investigators from the Center for Injury Research and Prevention (CIRP) are working with industry leaders to create more true-to-life crash-test dummies for children, which are called child anthropometric test devices (ATDs).

Center leader Flaura Winston, MD, PhD, and her colleagues are international experts in pediatric biomechanics, having studied real-world crashes for more than a decade to understand how children's bone structure and soft tissues respond to crash forces differently than fully developed adults.

The center's work in this area revolves around preventing head and brain injuries; protecting the spine, chest, and rib cage; understanding the potential injuries to a child's legs and feet in a crash; and preventing abdominal injuries from seat belts.

A specific focus is the head and brain – injuries to this part of the body are the most common and the most deadly. The CIRP team, along with colleagues from the University of Pennsylvania's Department of Bioengineering, is developing brain injury criteria for children ages 6 to 10 years that will lead to a method for more accurately predicting the likelihood of brain injury in a motor vehicle crash for children in this age range.

In developing new ATDs, the investigators have also paid significant attention to the effects of crash forces on children's spines. Using a test device designed to mimic the impact of amusement park bumper cars, the investigators determined that children's spines are more flexible than adult's spines and were able to quantify the effect of this increased flexibility on head movement. These research findings will fuel an industry initiative to design better restraint devices specifically for children that will minimize the forward movement or excursion of the head.

In addition, the investigators and CIRP engineers have used a collaborative research approach with academic and industry colleagues from University of Virginia, Ford Motor Company, and Takata Corporation to create a prototype of an accurate pediatric abdomen-pelvis that gauges the loading forces around the abdomen when seat belts are engaged.

"This is a critical component to making the pediatric ATDs more true-to-life, since abdominal injuries are the second most common trauma experienced by children in vehicle crashes and current ATDs are unable to accurately detect those injuries," says Dr. Winston.

The pediatric abdomen insert is now undergoing tests by the Society of Automotive Engineers, with the goal of making it available for broad use in government-mandated crash tests. The research findings may also lead to the development of novel restraint designs to prevent seat belt-related injuries.

Moreover, CIRP investigators – with support of the National Highway Traffic Safety Administration and Laerdal Corporation – have highlighted the dramatic biomechanical differences between the ability of the adult and pediatric chest and rib cage to resist force. These data have been collected during cardiopulmonary resuscitation of real pediatric patients through a novel partnership with the Hospital's Division of Critical Care Medicine.

CIRP researchers, with funding from its National Science Foundation sponsored Center for Child Injury Prevention Studies, are also applying a novel approach aimed at developing an age-equivalent model for pediatric long bones. Data gathered by CIRP will serve as the foundation for future research examining mechanisms of lower extremity injury and exploring injury treatments and counter measures, research that will impact the fields of biomechanics, clinical care, nutrition, and bone health.

"In order for the auto industry to innovate beyond just 'buckle up' to keep kids safe in crashes, we need better tools, such as accurate child crash test dummies; but we've been lacking the basic data we need to create those tools," says Kristy Arbogast, PhD, CIRP director of engineering. "The research being conducted by biomechanics research centers around the world and here at CHOP delivers the critical data on how children move in a crash and the tolerance of their bodies to injury. This information is needed to determine how cars can be made safer for children in the future."

CIRP and the Association of International Automobile Manufacturers released a joint report detailing the center's groundbreaking work with industry and academia to develop more accurate child ATDs. The full 2010 Child Passenger Safety Issue is available on the CIRP Web site at http://www.research.chop.edu/programs/injury.

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Early Career Award Propels Research on Immune System Malfunction in Arthritis, Autoimmune Disease

Scientists and physician-scientists continuously pursue funding and opportunities to advance their research interests. Some of the endeavors involving pressing research questions can lead to prestigious awards for investigators whose programs are at the cutting edge of their field or show promise in advancing an institution's priorities.

Biomedical research is an increasingly competitive field, and young investigators vie against those with firmly established research programs for limited funding. But some of these awards are specifically aimed at giving promising new investigators needed support to rapidly propel their own research programs.

The Early Career Physician-Scientist Award from the Howard Hughes Medical Institute (HHMI) is one such award. It's designed to help investigators get their first National Institutes of Health grant, with the hope it is a step in a long career of research that influences public health.

Since physician-scientists in their first permanent academic position often experience pressure to spend more time in the clinic and less time doing research, they often lack sufficient funding to collect data for an effective grant proposal. The Early Career Physician-Scientist Award provides funding to accelerate data collection and analysis and requires that awardees spend at least 70 percent of their time doing research.

Edward Behrens, MD, Division of Rheumatology, received the award for his research on how the immune system provokes autoimmune diseases by attacking its own tissues.

Dr. Behrens, an alumnus of the HHMI Medical Fellows Program, focuses his research on dendritic cells, which initiate the immune system's response to foreign invaders and trigger autoimmune or autoinflammatory disorders if improperly activated. He investigates proteins inside dendritic cells called toll-like receptors and how activation of these proteins leads to a life-threatening rheumatic disease of children called macrophage activation syndrome (MAS).

His research has led to discoveries about how the immune system malfunctions in MAS and raised the possibility of novel therapies that might improve the treatment of children with this disease. This work is being presented as a featured plenary session talk at this year's national American College of Rheumatology Scientific Meeting and is currently being reviewed for publication in a scientific journal.

Dr. Behrens is one of 11 promising physician-scientists from across the country who received the award in fiscal year 2010 to support work on a variety of pressing research questions. The award provides recipients with a $375,000 grant, distributed over five years, to help them launch and develop innovative research programs at a critical stage of their careers.

"The HHMI award has been crucial in supporting my efforts to understand this enigmatic disease. I needed to develop an entirely new system from scratch to perform this work, and the HHMI made this possible through their support," Dr. Behrens says of the award. The result of this funding is already beginning to snowball, as the data he generated from his initial work has led to additional funding from an Arthritis Foundation Innovative Research Grant.

Measuring Health From Children's Own Perspectives

Why do children say they are healthy? Is it a lack of physical symptoms or emotional distress? Is it a positive state of happiness? Do friendships, family, and school play a role? How are the physical, mental, and social aspects of health connected?

These questions, and many more, are being addressed by a new research program led by Christopher B. Forrest, MD, PhD, the Mary D. Ames Endowed Chair in Child Advocacy, with a $4.4 million grant from the National Institutes of Health through the Patient Reported Outcomes Measurement Information System (PROMIS) network.

Most of us know what we think of as "healthy," but a common framework for measuring health in children has eluded scientists.

"Measuring only how the body is functioning fails to capture the breadth of factors that affect children," says Dr. Forrest, "especially those that are part of a child's personal experience, such as symptoms, feelings, well-being, and a sense of belonging in family and school."

Evaluations of medical care have traditionally focused on clincal end points, but many outcomes of healthcare are known only to the patient, and can be different for everyone. And, because parents and children provide complementary views of child health, the perspective of the child and the child's parents are needed to gather the information that is required to optimally manage disease.

To complicate matters, as children grow and develop, their interactions with their parents and environments change. As these changes happen, factors that can cause stress – like how children perceive their interpersonal relationships – become more important.

The goal of PROMIS is to provide researchers and clinicians access to efficient, precise, valid, and responsive adult- and child-reported measures of health and well-being. Dr. Forrest is extending the work of PROMIS by developing a set of developmentally appropriate measures to capture children's health through self-reported responses from children as young as 8 years of age. He is also developing an edition for parents, whose assessments of their child's health may be merged with the

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child's own assessment to provide a richer evaluation of health that is more predictive of future outcomes than either assessment would be alone.

"Children's self-assessed health is the foundation for being able to embrace their childhood and take part in activities that stimulate their development and allow them to flourish," says Dr. Forrest. "Figuring out how children use physical, mental, and social resources to successfully adapt to the demands of their environment and overcome illness may lead to improved research and clinical practices that address the factors that matter most to children and their families, and may help clinicians promote health throughout a patient's life. As this effort matures, PROMIS measures are likely to become part of the electronic health record, because they will be important outcomes that clinicians, patient, and families will want to monitor in response to treatments."

Dr. Forrest's group will use the patient-reported outcome tool to better understand pediatric perceived health in inflammatory bowel disease (IBD), one of the most common pediatric chronic diseases. IBD can lead to symptoms like abdominal pain, weight loss, and growth delay, and can cause children to need to visit the bathroom more frequently than their peers.

IBD symptoms can be embarrassing and socially limiting, especially in situations that are not readily accessible to the bathroom like trips to the mall or participating in sports. Additionally, common steroid treatments can have negative side effects like facial swelling, acne, and depression, all of which may have negative implications for children and adolescents.

"Considering the physical, mental, and social challenges associated with IBD and the rapid changes in therapy for this disorder, the need for tools that measure outcomes in pediatric patients is acute," says Dr. Forrest. "By using IBD as a model, we will develop tools for pediatric chronic diseases that will advance the science of pediatric clinical trials and translational research, while uncovering previously unknown effects of pediatric healthcare."

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05:TECHNOLOGY

Windows of Opportunity: Commercialization of Technologies, Discoveries

Making significant discoveries in research – be it a new therapeutic application, device, or technology – yields little influence over future healthcare if those advances don't make their way to a patient's bedside.

The challenges of unlocking the secrets of diseases and developing novel therapeutic approaches and tests are one part of the equation leading to better healthcare around the globe. The other part involves a thorough understanding of the applicability of a discovery, the nuances and trends of the industry, and finding a common ground that will optimize the unique characteristics and utility of the discovery.

However, the road to bring those discoveries from the laboratory to the marketplace can be difficult to navigate. The Office of Technology Transfer at the CHOP Research Institute guides investigators and research teams to traverse the often complex paths to commercialization.

Technology Transfer provides myriad services to investigators and their teams, all aimed at minimizing the time researchers spend on commercialization matters. This approach allows investigators to focus more attention on what they do best – finding the causes and developing new treatments for pediatric diseases and disorders.

With the assistance of specialized services provided by Technology Transfer, Children's Hospital investigators were awarded several patents during fiscal year 2010, introducing technologies and approaches that have the potential to improve the health of children everywhere.

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The following patents were issued during fiscal year 2010 for technologies developed by CHOP Research investigators:

US Patent Number 7,589,070

Robert Levy, MD, Ivan Alferiev, PhD, and Ilia Fishbein, MD, PhD, have developed therapeutic agents that can be targeted to a specific area of a patient's body with a magnetized metallic stent. Non-magnetic formulations can also be used. The cardiology applications provide an immediate, high-impact market. Other applications include therapy in the esophagus, urinary tract, bile duct, and skeletal system. Therapeutic agents can include siRNA, small molecule compounds, proteins, cells, and gene therapy vectors embedded within, or attached to, biodegradable polymers.

US Patent Number 7,635,734

Robert Levy, MD, and colleagues Ivan Alferiev, PhD, Michael Chorny, PhD, Ilia Fishbein, MD, PhD, Benjamin Yellen, PhD, and Darryl Williams, PhD, were awarded a patent closely related to the one above. Therapeutic agents can be targeted to implantable metallic devices by attaching the agents to a biodegradable nanoparticle containing iron oxide. A uniform magnetic field forms high-field gradients around the metallic device and the injected magnetic nanoparticles are drawn to the device. Nonmagnetic versions of the nanoparticles can also be formulated, and a wide variety of therapeutic agents can be used in conjunction with the nanoparticles. An MRI machine, commonly available in most hospitals, can be used to induce the uniform magnetic fields around the metallic device.

US Patent Number 7,589,174

This technology, developed by Yair Argon, PhD, Tali Gidalevitz, PhD, and Chhanda Biswas, PhD, covers methods and compositions for stimulating an immune response against malignant tumor cells or cells that are infected with viruses. GRP94 is coupled to a tumor-specific or virus-specific antigen, forming a complex that can stimulate cytotoxic T cells to mount a response against the tumor or virus.

US Patent Number 7,617,000

Cochlear implants have to be fitted and adjusted for each individual. The adjustments are made by clinicians based on patient feedback. However, very young users may not be able to communicate effectively with the clinician. The technology developed by Kevin Franck, PhD, MBA, is a software-based method of programming a cochlear implant that allows the patient to make adjustments for sound level and quality rather than requiring the clinician to interpret the patient's feedback. The technology has a cartoon-based graphical interface that can be used by small children and that transmits the information to the implant in order to make the correct adjustments.

43 Active Licenses

30 New U.S. Patents Filed

50 Invention Disclosures Received

5 U.S. Patents Issued

US Patent Number 7,629,122

Cornelia de Lange syndrome (CdLS) is a clinically heterogeneous developmental disorder that can be difficult to diagnose because the abnormalities seen in the disorder overlap with those seen in other disorders. This technology, developed by Ian Krantz, MD, and Laird Jackson, MD, covers the first molecular diagnostic for the disorder. It includes the discovery that the *NIPBL* gene, when mutated, gives rise to CdLS. However, different mutations can result in a more or less severe manifestation of the disorder. Accurate diagnosis can aid clinicians in determining which interventions are appropriate. Additionally, the test can be used for genetic counseling and prenatal testing.

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06.TALENT

The success of CHOP Research is entirely dependent upon the talent of our investigators and staff. With the right doctors and investigators working side by side within CHOP Research's environment of promoting discovery, amazing ideas and innovations can flourish. The stakes are high – to be the best, we have to attract and retain the best employees, who are often in the sights of other organizations that realize top talent is the key to success.

CHOP Research's battle to bring together the best and the brightest is constant, and consistently successful. By maintaining an unrelenting focus on recruiting and mentoring talented investigators, and providing support and recognition for outstanding research leaders, CHOP Research is building new areas of expertise, bolstering the strength of programs that are already preeminent, and forging new paths of discovery that are advancing the understanding of, and potential treatments for, a multitude of disorders and diseases.

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Understanding Mitochondria: A Shifting Paradigm for How Diseases are Treated and Prevented

The mitochondrion is the cellular power plant and a key supplier of the energy needed for the multiple functions of our cells such as metabolism, signaling, growth, reproduction, and even death. These organelles, of which there are hundreds in each cell, play a pivotal role in human health and disease.

Mitochondria contain their own DNA, called the mitochondrial DNA (mtDNA). While the DNA in a cell's nucleus encodes the structure of both the cell and the mitochondria, the mtDNA encodes the wiring diagram for the cellular power plants.

As is the case in a metropolitan brown out, when the mitochondrial power plants of our cells become damaged the energy output for the body's cells and tissues progressively declines. And since certain tissues have higher energy demands than others, one organ after another begins to malfunction as that critical mitochondrial energy decreases. The organs with the highest requirement for mitochondrial energy are those in the central nervous and endocrine systems, and the heart, muscle, and kidneys – the same organs that are most commonly affected in diseases and aging.

The realization that systemic energy defects can lead to organ-specific symptoms provides a striking alternative to the traditional Western medical perspective that organ-specific symptoms are due to organ-specific defects. Determining the inner workings of the mitochondria therefore promises to provide a major new approach to understanding and developing therapies for myriad rare and common diseases in children and adults.

The mitochondrion is a powerhouse, indeed.

Investigators are starting to take a closer look at the mitochondrion and its energy, and Children's Hospital is leading this unique field of study that could one day shift our most fundamental biomedical paradigms.

The role of mitochondrial energy in human health and disease has long been the investigative focus of Douglas Wallace, PhD. In 2010, he moved his pioneering, world-renowned research program to The Children's Hospital of Philadelphia Research Institute to join the already vibrant group of physicians and scientists at the Hospital and the University of Pennsylvania who are pursuing the highly promising new field of mitochondrial medicine.

More than 35 years ago, Dr. Wallace and his colleagues founded the field of human mitochondrial genetics by demonstrating that the human mitochondria encode genetic traits that are separate from those of the nucleus. He subsequently linked these traits to the mtDNA and demonstrated that the genetic rules of the mtDNA are very different from those of the nuclear DNA. The mtDNA is inherited exclusively from the mother and is present in thousands of copies per cell, unlike the traditional two copies of each gene in the nuclear DNA, so cells can have different percentages of damaged and normal mtDNA.

Knowledge of these novel genetic rules and the realization that the mtDNA encodes the central energy genes has permitted a growing number of biomedical scientists around the world to link mitochondrial dysfunction to a wide range of metabolic and degenerative diseases as well as cancer and aging.

Demonstration of the exclusive maternal inheritance of the mtDNA also permitted Dr. Wallace and his colleagues to reconstruct the origin and ancient migrations of women based on the realization that the number of mutational differences between two individuals is directly proportional to the time since they shared a common mother. These seminal studies have revealed that humans arose in Africa approximately 200,000 years ago; that women left Africa about 65,000 years ago to colonize Eurasia; and from Siberia, they crossed the Bering land bridge starting around 20,000 years ago to populate the Americas.

Dr. Wallace continues his groundbreaking research at Children's Hospital as the Michael and Charles Barnett Chair in Pediatric Mitochondrial Medicine and Metabolic Diseases and directs a new Center of Emphasis at CHOP Research – the Center for Mitochondrial and Epigenomic Medicine.

By shifting the medical perspective from the anatomy of disease and nuclear genetics to the energetics of disease and non-nuclear genetics, Dr. Wallace and his team are providing a mechanistic understanding of holistic medicine. This is providing a bridge between the medical traditions of the West and East.

"Because energy flow is central to all life processes, mitochondria play a central role throughout the life cycle," says Dr. Wallace, the first CHOP Research investigator who is a member in the prestigious National Academy of Sciences. "Therefore, our findings in age-related diseases help us to better understand how mitochondria dysfunction contributes to pediatric diseases, and vice-versa."

He adds that the potential is great for contributing knowledge of mitochondrial medicine to the innovative clinical and research programs at Children's Hospital and the University of Pennsylvania.

"These institutions have numerous outstanding physicians and scientists, and a strong tradition of interest in mitochondrial energy production through the leadership of Professor Britton Chance," notes Dr. Wallace. "If we are successful in bringing the clinical and mitochondrial communities together, CHOP and Penn will be at the epicenter for an exciting new way to look at the disease processes, which promises to restructure medical thinking and lead to the prevention and treatment of a broad spectrum of human illnesses."

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Pediatric Oncologist Honored With Prestigious Institute of Medicine Membership

An international leader in pediatric oncology research, and a key leader at The Children's Hospital of Philadelphia Research Institute, has been elected to the prestigious Institute of Medicine (IOM), an honorific association for scientists at the top of their fields.

Tom Curran, PhD, FRS, who serves as the deputy scientific director for CHOP Research, received the honor in late 2009 in connection with his research on the molecular biology of the brain's growth and development. His prominent program at Children's Hospital centers on finding new treatments for childhood brain tumors.

More specifically, Dr. Curran and his colleagues are exploring the molecular basis of normal and neoplastic growth in the developing nervous system. By establishing a greater understanding of the normal processes that govern the formation of the brain, they hope to uncover new approaches for the treatment of rare but devastating pediatric brain tumors.

Dr. Curran's research combines basic approaches with genomics and translational science in a broad-based effort, using experimental strategies that include various disease models, cell culture, genomics, human tumor samples, imaging, and a range of molecular techniques.

His groundbreaking research led to the opening of a clinical trial in January 2009 to test a new treatment of the pediatric brain tumor medulloblastoma.

Dr. Curran serves on the editorial boards of numerous scientific journals. He has also presented hundreds of invited lectures around the world and authored more than 250 peer-reviewed publications. He was ranked fourth in the world among high-impact researchers in molecular biology between 1988 and 1992 by the Institute for Scientific Information, and is currently listed as a Highly Cited Scientist in three distinct fields – neuroscience, molecular biology and genetics, and microbiology.

He has served as president of the American Association for Cancer Research and on the Board of Scientific Advisors of the National Cancer Institute. In 2005, he was elected a Fellow of the Royal Society, the national scientific academy of the United Kingdom.

In addition to serving as deputy director for the CHOP Research Institute – one of the nation's largest pediatric research programs – Dr. Curran is a professor of Pathology and Laboratory Medicine, professor of Cell and Developmental Biology, and associate director of Translational Genomics, Penn Genome Frontiers Institute, all at the University of Pennsylvania.

Established in 1970 by the National Academy of Sciences, the IOM elects members for their excellence and professional achievement in a field relevant to the institute's mission and for their willingness to participate actively in its work. For those at the top of their field, membership in the IOM reflects the height of professional achievement and commitment to service.

Renowned Investigators Leading World-Class Oncology Program

Over the past several decades, the cancer research program at the CHOP Research Institute has unraveled some of the most perplexing questions about the nature and progression of cancer. Oncology investigators have taken this critical information to the next level, developing therapeutic strategies and treatments aimed at eradicating a multitude of pediatric cancers.

The world-renowned oncology research program at Children's Hospital was bolstered in 2009 when two nationally prominent pediatric oncologists were appointed to serve in key leadership roles in the Hospital's Division of Oncology.

John M. Maris, MD, was named chief of the division, and Frank M. Balis, MD, joined the Hospital as director of clinical research for the division. Dr. Balis also was named director of clinical research for the Hospital's Center for Childhood Cancer Research, directed by Dr. Maris.

A member of the Oncology Division staff since 1995, Dr. Maris became acting chief of the division in 2008 and holds the Giulio D'Angio Endowed Chair in Neuroblastoma Research. He is an associate professor of pediatrics at the University of Pennsylvania School of Medicine, where he is also a member of the Abramson Family Cancer Research Institute.

Dr. Maris is an expert on the molecular genetics and treatment of neuroblastoma, the most common solid cancer in children. In 2008, he led an international team that identified for the first time common DNA variants that are the genetic origin of neuroblastoma. He is the principal investigator of numerous National Institutes of Health-funded grants focused on the disease, and chairs the Neuroblastoma Disease Committee of the Children's Oncology Group, a national cooperative research organization.

As Oncology Division chief, Dr. Maris succeeds Garrett M. Brodeur, MD, also a nationally prominent expert in neuroblastoma, who remains in the division as an attending physician and researcher.

Dr. Maris notes that "Dr. Brodeur led the division through a decade-long period of dramatic expansion, with tremendous growth in both the clinical and research programs."

Dr. Balis came to Children's Hospital from a 27-year career at the National Cancer Institute, where he was most recently the institute's clinical director. His research program has focused on

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drug development for childhood cancers. He is most prominent for his seminal contributions to intrathecal administration, a method of delivering anti-cancer drugs directly to the spinal fluid that has allowed doctors to abandon the use of craniospinal radiation in treating most children with acute lymphoblastic leukemia.

Dr. Maris, who led the effort to recruit Dr. Balis to Children's Hospital, says, "As we seek to re-engineer how we develop drugs for children with cancer, we recognized the need for a national leader in the area of clinical research to spearhead our efforts. It became clear very quickly that Dr. Balis was the ideal candidate." In this newly created position, Dr. Balis oversees all aspects of clinical research on pediatric cancer.

Children's Hospital cares for more children with cancer than any other general pediatric hospital in the United States. Dr. Maris adds that Dr. Balis will expand existing strong clinical research programs in neuroblastoma, brain tumors, and leukemia, while establishing additional clinical research programs in pediatric sarcomas and lymphomas.

Jeffrey Golden, MD, Named Hospital's Pathologist-in-Chief

The timely and accurate diagnosis of diseases and conditions is critical to the care and treatments children receive.

Leading this effort at Children's Hospital is Jeffrey A. Golden, MD, who was appointed as pathologist-in-chief after an extensive national search.

A staff neuropathologist since 1996, Dr. Golden has held several leadership roles, including chief of the Hospital's Division of Developmental Biology. His personal research has focused on patterning and cell migration in the developing nervous system.

Dr. Golden is a leader in his field, with more than 90 published research articles, and has been honored with numerous awards for his research. He currently holds three National Institutes of Health grants and is the Evelyn Willing Bromley Endowed Chair in Pathology and Clinical Laboratories at Children's Hospital.

Dr. Golden is the past president of the American Association of Neuropathologists and holds positions on several editorial boards including being the associate editor for the *Journal of Neuropathology and Experimental Neurology*.

The Department of Pathology and Laboratory Medicine at Children's Hospital, which Dr. Golden leads, includes nationally and internationally recognized experts who provide diagnostic services and consultation in all areas of pathology and laboratory medicine.

The field also plays a critical role in the growing translational research program at The Children's Hospital of Philadelphia Research Institute.

Pathology "stands at the crossroads between basic science and clinical care," Dr. Golden says. His department engages in both basic and translational research aimed at understanding the pathogenesis of childhood disease and instituting novel methods for earlier and more precise diagnoses that will result in enhanced and tailored therapy.

"We are currently experiencing an exhilarating growth in our understanding of the fundamental molecular and cellular mechanisms of disease and our faculty, by virtue of their unique position bridging the clinical and basic sciences, are at the forefront of applying this new knowledge to medical practice," he says.

Focusing on Our Future

CHOP Research focuses on innovations of the future, and the future of innovation. To that end, the Institute strives to attract the best and brightest new investigators, who open windows of discovery that would otherwise remain unexplored and augment the pool of investigators who will become tomorrow's leaders.

The investigators featured here, while new to CHOP Research, are experts in their field of study. They represent the success CHOP Research has in attracting and retaining exceptional investigators, nurturing innovative ideas, and producing revolutionary results. With their help, and the help of scores of other motivated and gifted people, the Institute will continue on its path toward eradicating pediatric disease.

Clyde J. Wright, MD

Hyperoxia - Preterm birth affects more than half a million children in the United States every year and, despite advances in maternal and perinatal care, the rate of preterm birth continues to rise. Many preterm babies need help transitioning from the in utero environment to the outside world, treatment that often includes supplemental oxygen and mechanical ventilation through a breathing tube. While these interventions are lifesaving, the high levels of oxygen they provide can damage the delicate preterm lung, ultimately resulting in a disease called bronchopulmonary dysplasia (BPD), which affects more than

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15,000 babies every year.

Clyde J. Wright, MD, Division of Neonatology, focuses his research on how the cells of the preterm lung sense and orchestrate a response to high levels of oxygen, a scenario often called hyperoxia. His research looks at the role of the transcription factor NF-(kappa)B in mediating the cellular response to hyperoxia. NF-(kappa)B regulates the cellular response to inflammatory and oxidative stress and is highly conserved among multiple organisms, from sea sponges to human beings, which suggests that it has a functional value maintained throughout evolution. In a recent study published in the *American Journal of Physiology*, Dr. Wright found a unique pathway of NF-(kappa)B activation in fetal lung cells exposed to hyperoxia that may prevent steps necessary for normal lung development. Through a better understanding of how NF-(kappa)B responds to hyperoxia, Dr. Wright's team hopes to devise protective strategies to limit oxygen toxicity when treating prematurely born babies, thereby reducing the number of children affected by BPD.

Kristen Feemster, MD, MPH, MSHP

Infectious Diseases - Kristen Feemster, MD, MPH, MSHP, Division of Infectious Diseases, focuses her research on understanding how environmental factors, social networks, and community systems affect the epidemiology, prevention, and treatment of pediatric infectious diseases. Using geographic information systems-based methods, Dr. Feemster is working to create models of disease transmission within communities to help create better strategies for disease mitigation and prevention. For example, she is looking at the potential for primary care networks to perform population-based infectious diseases surveillance in the communities they serve. The goal of this research is to develop regional models that predict the prevalence and incidence of infectious diseases and patterns of antibiotic utilization and resistance, information that can be used to better serve the health service needs in the community.

Dr. Feemster is also dedicated to research evaluating the impact of vaccine policy. This work includes a project in which she investigated clinician knowledge, attitudes, and intention to administer the human papillomavirus vaccine to 11 and 12 year old girls and evaluated the relationship between intended and actual vaccine administration, published in the *Journal of Adolescent Health*. She also worked with the Philadelphia Department of Public Health on assessing risk factors for late initiation of immunization among an urban birth cohort, published in *Public Health Reports*. Currently, she is leading a study to evaluate the impact of a mandatory seasonal influenza vaccination program for healthcare workers as a mechanism for improving vaccination and hospital-based infection rates. Dr. Feemster plans to continue building a body of work related to vaccine policy, particularly the uptake of new vaccines and the impact of vaccine mandates.

Evan Fieldston, MD, MBA, MSHP, FAAP

Hospital Operations - Evan Fieldston, MD, MBA, MSHP, FAAP, Division of General Pediatrics, combines methods from health services research, operations management, and implementation science to improve the care of children in all settings by optimizing the structure and processes of care. Dr. Fieldston's current research focuses on hospital operations, patient flow, and quality of care at children's hospitals. This work includes using a national dataset of 39 children's hospitals to understand hospitals' response to high occupancy and use of bed capacity, analyzing how well traditional measures of hospital utilization report dynamic demand and flow; directly observing patient flow in the pediatric intensive care unit; and developing a patient flow composite score for hospital operations and quality improvement work. One recent study to come out of this area of investigation was published in *Pediatrics*.

Dr. Fieldston's future goals include defining composite measures of workload and workforce at discrete intervals of time and linking them to quality of care outcomes, work for which he was awarded an inaugural Young Investigator's Research Award from the Society of Hospital Medicine in 2010. He also is doing work in behavioral economics, looking at use of incentives directed to parents for adherence in childhood asthma. He remains active in more general policy discussions of healthcare reform and child coverage. The ultimate goal of Dr. Fieldston's work is to improve the care of children in all settings by optimizing the structure and processes of care, increasing the likelihood that the right care is delivered at the right time, in the right place, by the right provider.

Mark R. Zonfrillo, MD, MSCE

Injury Prevention - Identifying risk factors for crash-related injuries from motor vehicle crashes, the leading cause of death and a leading cause of non-fatal injuries for youth, is essential for developing preventative measures. Operating within the Center for Injury Research and Prevention, Mark Zonfrillo, MD, MSCE, focuses on the association between motor vehicle crash-related injury and pediatric obesity, an increasingly common condition that has not been adequately explored as an injury risk factor in children. In a study conducted using data from children aged 3 to 8 years, and published in *Annals of Advances in Automotive Medicine*, Dr. Zonfrillo found that overweight children may have more crash-related injuries in the upper and lower extremities compared to children of normal weight. His future work will focus on prospective measurements of car seat and seat belt fit in overweight children, research that may have public health implications for the obesity epidemic, and engineering implications for motor vehicle and car seat design.

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Dr. Zonfrillo's research interests also include exploring and evaluating potential injury prevention interventions conducted in the emergency department. In a study in press at Academic Emergency Medicine, he found that while emergency medicine physicians value including pediatric car safety information in discharge instructions given to families following motor vehicle crashes, the physicians do not have adequate knowledge of pediatric vehicle safety nor do they regularly provide appropriate safety instructions to families. Dr. Zonfrillo plans to use these findings to launch further investigations focusing on effective, evidence-based methods of providing injury prevention information to patients and families in the emergency department. The research may include an evaluation of strategies such as assessing patient risk for future injuries, distributing computerized kiosks that contain educational information, and subsidizing safety devices as a supplement to education efforts.

Joanne N. Wood, MD, MSHP

Child Abuse & Neglect - Each year, more than 3 million reports of suspected child abuse and neglect are made to child protective service agencies in the United States. Joanne Wood, MD, MSHP, Child Abuse Pediatrics Fellowship Program director, focuses her research on addressing the many challenges of providing quality care to victims of child abuse and neglect and improving the quality of hospital-based care to this uniquely vulnerable population. In one such study, looking at the use of skeletal surveys to screen for additional injuries in infants with skull fractures, Dr. Wood found that this series of x-rays rarely identifies additional injuries. The results, published in *Pediatrics*, also indicated that the socioeconomic status of the family might have influenced the decision to perform an evaluation for physical abuse, findings that have changed clinical practice at Children's Hospital.

Based on these results, Dr. Wood addressed the potential impact of clinician biases on the decision to perform an evaluation for suspected child abuse by assessing the treatment of approximately 3,000 infants admitted to 39 pediatric hospitals with traumatic brain injuries not related to car accidents. She found that black families and families with governmental insurance were more likely to come under scrutiny for possible abuse than white families and families with private insurance. These results, also published in Pediatrics, highlight the need for standard guidelines that will minimize the impact of bias when determining which families are evaluated for abuse and neglect.

In her future research, Dr. Wood will use quantitative and qualitative methods to gain a better understanding of the factors impacting the quality of hospital-based child abuse care with the eventual goal of designing and testing interventions to improve care and decrease disparities. She also plans to work as the scientific director on a collaborative project with the City of Philadelphia Departments of Human Services and Behavioral Health to pilot a mental health intervention for children in foster care.

Ignacio E. Tapia, MD

Sleep Apnea - Ignacio Tapia, MD, Division of Pulmonary Medicine, focuses on the pathophysiology of obstructive sleep apnea syndrome (OSAS), a condition that causes the upper airway to close and breathing to stop. OSAS can lead to many severe complications such as cognitive impairment, hypertension, and heart failure. With funding from the American Heart Association, Dr. Tapia is currently conducting a clinical research study in children aged 6 to 12 years to investigate whether children with OSAS have a decreased perception of respiratory stimuli compared to healthy children. Dr. Tapia's research team is using objective measurements of the brain's response to respiratory stimuli in study participants and comparing the results in children with OSAS before and after adenotonsillectomy, the standard treatment for OSAS in children, in which the tonsils and adenoids are removed.

The study team is testing whether patients can discern that two closely placed objects touching the skin of the tongue and the palate are distinct points, a technique Dr. Tapia used in a recent study, published in *Sleep*, that indicates children with OSAS have impaired airway sensation. Using a non-invasive vibration device, he is also determining whether children can perceive vibration on the hard palate. To identify subject perception of resistance, subjects breathe through a mask that presents three different resistances to inspiration and rate the ease of breathing using a standardized scale. As subjects use the mask, Dr. Tapia measures respiratory-related evoked potentials elicited by the different resistances. Together, these evaluations will determine the degree of perception impairment before and 2 to 3 months after surgery, findings that could ultimately help identify children that are at risk for recurrence of OSAS after adenotonsillectomy.

Elizabeth Fox, MD

Cancer Therapy - Elizabeth Fox, MD, focuses her research on the development and pharmacology of anti-cancer drugs for children, such as enhancing the understanding of how molecularly targeted drugs produce their effect through interactions with cellular receptors, essential for optimal development of these agents. The molecular abnormalities in childhood cancers are often distinct from those in adult cancers, and research is needed to identify cancer therapies for children that are more effective and cause fewer toxic side effects than adult drugs used to treat children. Dr. Fox uses pharmacokinetics (what the body does to the drug), pharmacodynamics (how the drug alters the body), and pharmacokinetic-pharmacodynamic modeling to better understand the therapeutic and toxic effects of drugs and to establish ideal doses of cancer drugs for children in clinical trials.

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Dr. Fox, who heads the developmental therapeutics team within the Division of Oncology, recently completed a clinical trial of an oral drug that acts against a tumor's blood supply by inhibiting vascular endothelial growth factor receptor (VEGFR). Conducted at Children's Hospital and one other center, the investigator-initiated study enrolled 16 children and adolescents with recurrent solid tumors to establish a safe dose for children with cancer. By measuring the pharmacokinetics of the drug in children, Dr. Fox's team demonstrated that children and adults handle the drug in a similar way and established a safe dose for children. They also found that the level of VEGFR circulating in the blood decreased as the amount of drug increased and that 25 percent of children with recurrent solid tumors had a decrease in the size of their tumor during treatment. Results of this clinical trial have been published in the *Journal of Clinical Oncology*.

Endowed Chairs Critical Component in Advancing Ideas, Innovation

With a global reputation for advancing ideas and innovation in biomedical research, The Children's Hospital of Philadelphia Research Institute seeks avenues to ensure that the flow of discovery is not stifled by a lack of funding, which can be attributed to the fiercely competitive nature of the field or diminished research budgets within funding organizations.

Endowed chairs provide a source of continuous research or programmatic funding, allowing Children's Hospital and the Research Institute to confidently move forward with their missions of unrivaled patient care, innovative research, and education – even in times of economic uncertainty.

The bottom line: this generous form of support ensures that new ideas continue to be born, research moves forward, and better treatments and therapies are developed for sick children everywhere.

Through the generosity of a growing number of benefactors, for which the Institute is overwhelmingly thankful, Children's Hospital now has nearly 80 established endowed chairs, and several more in the planning stages. Five new endowed chairs were established at Children's Hospital in fiscal year 2010:

Stephen Ludwig Endowed Chair in Medical Education, awarded to Patricia J. Hicks, MD

Jeffrey Modell Endowed Chair in Pediatric Immunology Research, awarded to Jordan Orange, MD, PhD

Lucy Balian Rorke-Adams Endowed Chair in Neuropathology, appointment pending

Richard D. Wood Jr. and Jeanette A. Wood Endowed Chair in Pediatric Diagnostic Medicine, appointment pending

Louis and Amelia Canuso Family Endowed Chair for Clinical Research in Oncology, awarded to Frank M. Balis, MD

Mourning the Loss of Psychiatrist, Scientist Elizabeth Weller, MD

The field of child and adolescent psychiatry is critical for the emotional and behavioral health of children and teens who may suffer from myriad disorders, including depression and anxiety.

The field lost a distinguished practitioner and investigator in 2009 when Elizabeth Weller, MD, passed away after a lengthy battle with breast cancer.

A national leader in research on child and adolescent psychiatry, including mood and anxiety disorders, depression, and bereavement, Dr. Weller focused on the proper diagnosis and pharmacological treatment of depressive disorders and mania in children and adolescents.

As part of her research she helped to develop Children's Interview for Psychiatric Syndromes (ChIPS), a brief interview of succinct, simply worded questions used to screen children for a variety of psychiatric conditions, and the parent section of the interview, known as PChIPS.

Dr. Weller also served as the principal investigator of multiple clinical research studies examining the appropriate treatment of psychological conditions, such as assessing the safety and efficacy of medications in children and adolescents with bipolar disorder, comparing treatments for major depressive disorder, and evaluating treatments for atypical depression.

An extraordinarily productive and highly acclaimed child psychiatrist, Dr. Weller served with distinction as a professor of psychiatry and pediatrics at Children's Hospital. She was the first chair of the Hospital's Department of Child and Adolescent Psychiatry and the first woman to hold an endowed professorship in psychiatry.

Her work positioned her to lead by example as an exemplary teacher, mentor, and clinician beloved by her trainees as well as her patients and their families.

With much perseverance and appreciation for her care at the Abramson Cancer Center at the University of Pennsylvania, Dr. Weller prevailed over breast cancer for many years while continuing to attend to her research, academic activities, and clinical care, rarely missing a single day of work until the time of her death.

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A Window on Our Success

The greatest reward of pediatric research is helping to improve the care of children. A close second is recognition from the scientific community that the hard work, long hours, and dogged efforts are breaking through the barricades that would oppose transforming scientific discovery to medical innovation.

The Research Institute's continued luster is entirely dependent on our talented investigators and staff impressing the scientific community with their dedication, expertise, passion, intellect, and verve. Lucky for us, our investigators remain tireless in the pursuit of innovation.

The awards featured here represent the breadth and variety of honors bestowed upon CHOP Research investigators, and stir our excitement for the achievements that are yet to come.

Awards/Honors

Several investigators were appointed to the Society for Pediatric Research, including Diva DeLeon, MD, Division of Endocrinology; Aaron Donoghue, MD, Division of Emergency Medicine; James Kreindler, MD, Division of Pulmonary Medicine; Susmita Pati, MD, Division of General Pediatrics; Michael Sebert, MD, Division of Infectious Diseases; and Kelly Wade, MD, Division of Neonatology.

Harry Ischiropoulos, PhD, holder of the Gisela and Dennis Alter Endowed Chair in Pediatric Neonatology, was named a member of the American Pediatric Society, limited to those individuals who have distinguished themselves in leadership, teaching, research, and contributions at a national and international level.

Lawrence Brown, MD, Division of Neurology, was named president of the Child Neurology Foundation, a national outreach and philanthropic organization that funds the neurologic research of young investigators.

Albert Yan, MD, Division of General Pediatrics, is president-elect of the Society of Pediatric Dermatology, the only U.S. organization specifically dedicated to the field of pediatric dermatology.

The Association of Pediatric Program Directors, dedicated to advancing pediatric education to ensure the health and well-being of children, named Patricia Hicks, MD, the Stephen Ludwig Endowed Chair in Medical Education, as president-elect of the association.

Edwin M. Horwitz, MD, PhD, Division of Oncology, was elected president of the International Society for Cellular Therapy, a global association driving the translation of scientific research to deliver innovative cellular therapies to patients.

Diego Jaramillo, MD, MPH, Radiologist-in-chief, received the "A una obra" Award, the highest award given to a radiologist by The Colombian Radiological Association.

Amy Scholtz and AnneMarie Monachino of the Simulation Center, received an award for the Best Trainee Research Abstract at the 2010 Annual International Meeting on Simulation in Healthcare for their abstract titled "Central Venous Catheter Dress Rehearsal: Every Line Counts."

Andrei Thomas-Tikhonenko, PhD, was appointed chief of the Division of Cancer Pathobiology and was named associate editor of the *Journal of Clinical Investigation*. Dr. Thomas-Tikhonenko also received the Innovation Award from Alex's Lemonade Stand Foundation for the project "In-UTR Mutations in Neuroblastoma: Functional Consequences and Therapeutic Implications."

Adda Grimberg, MD, scientific director of the Diagnostic and Research Growth Center, was a co-author on a paper in *Hormone Research* titled "Long-Term Non-Surgical Therapy of Severe Persistent Congenital Hyperinsulinism With Glucagon," that received the 2008 European Society of Pediatric Endocrinology Best Publication Award for Novel Insights from Clinical Practice. Dr. Grimberg was also appointed co-chair of the Drugs and Therapeutics Committee of the Pediatric Endocrine Society.

A paper by Rita Valentino, PhD, Division of Research Anesthesiology, titled "Convergent Regulation of Locus Coeruleus Activity as an Adaptive Response to Stress" was one of the top ten cited articles from the *European Journal of Pharmacology* from 2008 to 2010.

Theo Zaoutis, MD, MSCE, associate chief of the Division of Infectious Diseases and associate director for the Center for Pediatric Clinical Effectiveness Research, received the Society for Healthcare Epidemiology Pediatric Investigator Award for the breadth and quality of his contributions to the field of pediatric infection prevention and control and healthcare epidemiology, and on the scientific merit of his abstract at the society's Annual Scientific Meeting.

Pamela Weiss, MD, MSCE, Division of Rheumatology, received a Career Development Bridge Funding Award from the American College of Rheumatology Research and Education Foundation and the Arthritis Foundation, designed to help foster investigators in the early stages of their career as they prepare National Institutes of Health K08/K23 application resubmissions.

The March of Dimes Foundation awarded Fraz Ahmed Ismat, MD, Division of Cardiology, the Basil O'Connor Starter Scholar Research Award for his research titled "MicroRNA Function in Cardiac Neural Crest and its Role in Cardiac Outflow Tract Development."

Naomi Balamuth, MD, Division of Oncology, received the Hyundai Hope on Wheels Scholar Award, designed to support the further training and research of childhood cancer specialists.

The American Society for Blood and Marrow Transplantation awarded Alix Seif, MD, MPH, Division of Oncology, with the Robert A. Good New Investigator Award, for his project titled "Chemotherapeutic Strategies to Induce Graft-Versus-Tumor Activity in Pediatric Acute Lymphoblastic Leukemia." He also received the Canuso Foundation Innovation Award for his project titled "Novel Chemotherapeutic Strategies to Induce Durable Immune-Mediated Control of Pediatric Acute Lymphoblastic Leukemia."

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Robert Campbell, MD, Division of Orthopaedics, was the 2009 recipient of the Scoliosis Research Society's Walter P. Blount Humanitarian Award, which honors those who have provided outstanding service for those with spinal deformities.

John Maris, MD, chief of the Division of Oncology, received the William Osler Patient Oriented Research Award, an Award of Excellence from the University of Pennsylvania School of Medicine, in recognition of his reputation as an outstanding teacher who effectively fuses basic science and clinical medicine.

Debra Bangasser, PhD, Division of Stress Neurobiology, received a Poster Award and a Travel Award at the Society for Behavioral Neuroendocrinology 2010 Meeting and a Young Investigator Award at the 2009 Gordon Research Conference on Catecholamines.

The Multiple Hereditary Exostoses Research Foundation honored John P. Dormans, MD, chief of the Division of Orthopaedics, with the Humanitarian Scientific Achievement Award for a lifetime of "dedication and service to children, and efforts that have been felt around the world." Dr. Dormans was also elected to serve as president of the Pediatric Orthopedic Society of North America for 2009-2010.

David Sherry, MD, Division of Rheumatology, was given the James Cassidy Award from the American Academy of Pediatrics. This award recognizes an individual who has distinguished himself through his service to the field of pediatric rheumatology.

Carsten Bonnemann, MD, Division of Neurology, received the Derek Denny-Brown Neurological Scholar Award from the American Neurological Association, given to a newly elected member who has achieved significant stature in neurological research and who promises to continue making major contributes to the field of neurology.

The Federation of Pediatric Organizations presented Stephen Ludwig, MD, associate physician-in-chief for Medical Education, with the Joseph W. St. Geme Jr. Leadership Award, which recognizes an individual who is a leader in the field of pediatrics, a role model, and one who has contributed broadly to the field.

Rodney Finalle, MD, Samir Shah, MD, MSCE, and the Global Health Team were given the Burtis Burr Breese Award from the Pediatric Infectious Diseases Society. This award celebrates contributions to pediatric teaching and clinical practice.

Edward M. Behrens, MD, Division of Rheumatology, was given the Robert Austrian Award for Outstanding Basic Science Research by Junior Faculty from the University of Pennsylvania School of Medicine.

Gil Binenbaum, MD, MSCE, Division of Ophthalmology, received the 2010 Young Investigator Faculty Award from the Eastern Society for Pediatric Research.

Paul Offit, MD, chief of the Division of Infectious Diseases, received the William Osler Patient Oriented Research Award, a University of Pennsylvania School of Medicine Award of Excellence that recognizes outstanding achievements for research in which the investigator directly interacts with human subjects.

Craig Bassing, PhD, Division of Cell Pathology, was selected for the Michael S. Brown New Investigator Research Award, a University of Pennsylvania School of Medicine Award of Excellence that recognizes emerging faculty investigators engaged in innovative discoveries. He was also selected as a Leukemia and Lymphoma Society Scholar.

Soma Jyonouchi, MD, Division of Allergy and Immunology, received a Fellowship Award from the Clinical Immunology Society and the Talecris Biotherapeutics Center for Science and Education.

Jordan Orange, MD, PhD, holder of the Jeffrey Modell Endowed Chair in Pediatric Immunology Research, was elected into the American Society for Clinical Investigation, an honor society of physicians who have accomplished outstanding achievements relatively early in their careers, and was awarded the Judson Daland Prize from the American Philosophical Society, which recognizes outstanding achievement in patient-oriented research.

Flaura K. Winston, MD, PhD, Center for Injury Research and Prevention founder and co-scientific director, received the Excellence in Science Award from the Injury Control and Emergency Health Services section of the American Public Health Association.

Katherine High, MD, HHMI, received the Investigator Recognition Award from the International Society on Thrombosis and Haemostasis for her accomplishments, internationally regarded as exemplary models of excellence in research and teaching. Dr. High also received the Audrey E. Evans Award of Excellence from the Philadelphia Ronald McDonald House, and an Outstanding Achievement Award from the American Society of Gene and Cell Therapy.

Barbara Medoff-Cooper, PhD, the Ruth M. Colket Professor of Pediatric Nursing and director of the Biobehavioral Research Center, was selected to be a Robert Wood Johnson Senior Nurse Faculty Mentor.

Lakshmi Srinivasan, MD, Division of Neonatology, was awarded a two-year fellowship by the Institute for Translational Medicine and Therapeutics at the University of Pennsylvania. The fellowship provides salary support for pursuing a master's degree in translational research at Penn.

Andrew Chu, MD, a fellow in the Division of Gastroenterology, Hepatology, and Nutrition, was presented with a Childhood Liver Disease Research and Education Network training grant and the Alexander M. White, III Postdoctoral Research Fellowship Award from the American Liver Foundation.

Rudy Fuentes, a doctoral student in the lab of Mortimer Poncz, MD, was granted the Mary Rodes Gibson Memorial Award in Hemostasis and Thrombosis, established to recognize the trainee who is the first author and presenter of the highest-scoring abstract submitted in the field of hemostasis and thrombosis for the American Society of Hematology annual meeting.

Kenneth R. Ginsburg, MD, MSEd, an adolescent medicine specialist and a member of the Young Driver Research Initiative team within the Center for Injury Research and Prevention was

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named associate medical editor for healthychildren.org, the American Academy of Pediatrics Web site for parents.

Tara Hayden, MHSA, a core director with the Philadelphia Collaborative Violence Prevention Center at the Center for Injury Research and Prevention and co-founder of the Philadelphia Area Research Community Coalitions was honored with the University of Pennsylvania 2010 Dr. Martin Luther King Jr. Community Involvement Award.

Lela S. Jacobsohn, PhD, a behavioral scientist and principal investigator with the Young Driver Research Initiative, received the 2009 Young Alumni Award of Merit from the University of Pennsylvania. The award recognizes leaders in the Penn community for outstanding service to the university.

Kristy Arbogast, PhD, director of the Engineering Core within the Center for Injury Research and Prevention was elected to the Association for the Advancement of Automotive Medicine board of directors. She also received two best paper awards, the first from the Association for the Advancement of Automotive Medicine for a paper in *Annals of Advances in Automotive Medicine* and the second from the *Stapp Car Crash Journal* for a paper published by the journal.

For his outstanding contributions to the field of pediatric dermatology, Paul Honig, MD, received the "Alvin Jacobs Award" from the dermatology section of the American Academy of Pediatrics.

Evan Fieldston, MD, MBA, MSHP, FAAP, Division of General Pediatrics, received the Society of Hospital Medicine's Young Investigator's Award, a 2-year award with a $25,000 grant per year designed to bolster academic pursuits for young hospitalists.

Jerilynn Radcliffe, PhD, ABPP, director of the Behavioral Neuroscience Core within the Clinical Translational Research Center, was named a fellow of the American Psychological Association, an honor bestowed for unusual and outstanding contributions or performance in the field of psychology.

The CHOP Distinguished Research Trainee Award provides institution-wide recognition for exceptional current and past Children's Hospital trainees, and creates an avenue for mentors to show appreciation for their researchers in training. Carrie Daymont, MD, was selected to receive the award in the Physician Fellow category and Sharon Diskin, PhD, was selected as the Postdoctoral Fellow awardee.

The annual CHOP Mentor Award recognizes faculty who have demonstrated extraordinary dedication to fostering the professional development of other members of the Children's Hospital of Philadelphia faculty. This year's awards were given to Louis M. Bell, MD, chief, Division of General Pediatrics; Dennis R. Durbin, MD, MSCE, Division of Emergency Medicine; and Marc Yudkoff, MD, chief, Division of Child Development, Rehabilitation, and Metabolic Disease.

The Ethel Brown Foerderer Fund for Excellence grants are awarded annually by CHOP Research. Project awards to move ongoing research into new areas were given to Yair Argon, PhD; Jessica Guite, PhD; and Mitchell Weiss, MD, PhD. New investigator grants were given to Edward Behrens, MD; Antonella Cianferoni, MD, PhD; Diva De Leon, MD; Paul Gadue, PhD; Qing Lin, PhD; and Douglas Marsteller, PhD, to support preliminary data efforts necessary for external grant applications. An innovation award, to support investigations that are high risk but have the potential for high impact, was given to Wayne Hancock, PhD.

Peter de Blank, MD, a fellow in the Division of Oncology, and Michelle Denburg, MD, a fellow in the Division of Nephrology received Pilot Grant Awards from the Center for Pediatric Clinical Effectiveness at CHOP Research. The awards provide one year of support to promote and support clinical effectiveness pilot research studies that will attract external support for large-scale studies.

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The 2010 Research Annual Report was produced by the Department of Research Communications.

Links of Interest

The Children's Hospital of Philadelphia Research Institute Web Site
http://www.research.chop.edu

The Children's Hospital of Philadelphia Web Site
http://www.chop.edu

The Children's Hospital of Philadelphia Foundation Web Site
http://giving.chop.edu/site/PageServer

The CHOP Research Institute Press Releases
http://www.research.chop.edu/publications/press/

***Bench to Bedside*, CHOP Research's Monthly News Publication**
http://www.research.chop.edu/publications/bench_to_bedside/

***Discovery to Innovation*, CHOP Research's Quarterly News Source**
http://www.research.chop.edu/discovery_to_innovation/

Social Media Pages

The Chop Research Institute's Facebook Page:
http://www.facebook.com/pages/The-Childrens-Hospital-of-Philadelphia-Research-Institute

The Chop Research Institute's Twitter Page:
http://twitter.com/CHOP_Research

The Children's Hospital of Philadelphia's YouTube Page:
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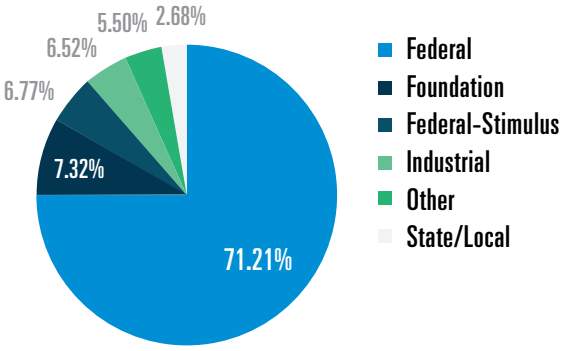
SOURCES OF GRANTS & CONTRACTS



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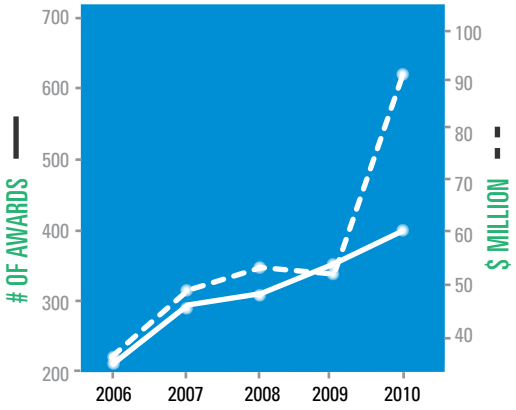

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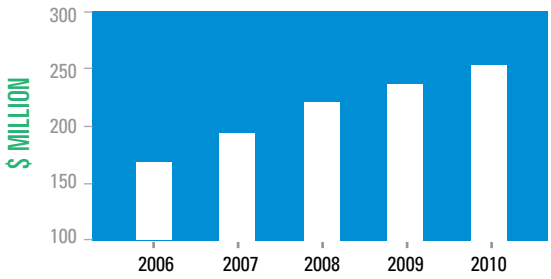

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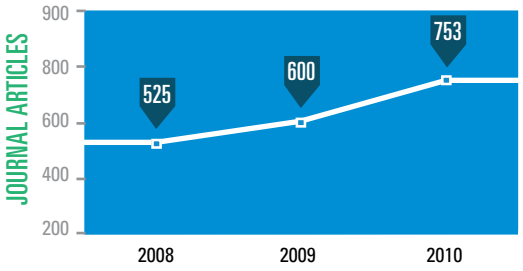

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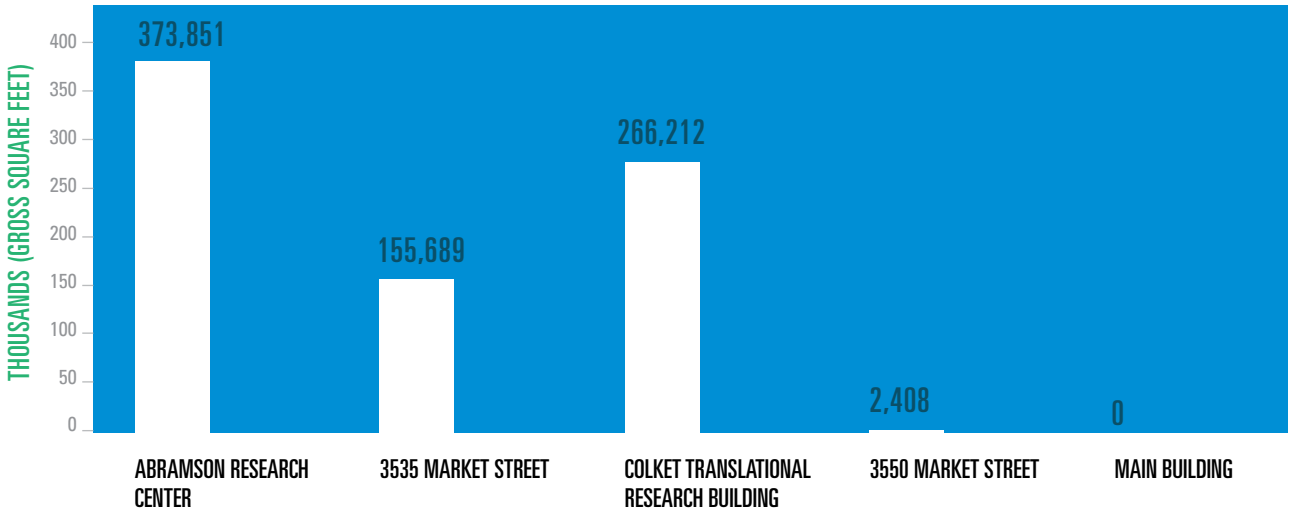

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