

# 2012 RESEARCH ANNUAL REPORT

## Cornerstone Where Science & Medicine Converge



THE CORNERSTONE OF PERSONALIZED MEDICINE



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# THE CORNERSTONE OF PERSONALIZED MEDICINE

## Personalized medicine: it's all about you.

The idea of “personalized” medicine isn’t just about a one-on-one encounter with a doctor, the use of sophisticated mobile applications, or heightened access to healthcare providers, medical records, and services. Personalized medicine also extends into the depths of who each of us are at our essence — to our individual genetic makeup.

Why does this matter? Because now, more than ever before, rapid technological advances and scientific breakthroughs mean we know more about how genes may point to a predisposition for developing certain diseases. By understanding the cause of a disease, rather than focusing solely on its symptoms, we have far greater opportunities to try to delay the onset of a disease or prevent it altogether.



Understanding our genetic makeup also sheds light on why a medicine may work well in one person but be ineffective in someone else with the same condition. Armed with this information, doctors can tailor treatments to those that carry the greatest chance of success based on a patient’s genetic predisposition.

A relatively new field of study, personalized medicine rocketed onto the scene after the completion of the [Human Genome Project](#) in 2003, the ambitious multi-billion-dollar federal initiative that analyzed 3 billion chemical base pairs involved in DNA and provided the genetic makeup of humans.

“On its surface, the concept of personalized medicine may seem complicated and perhaps a bit futuristic, but it’s far more science than science fiction,” says [Philip R. Johnson, MD](#), chief scientific officer at the CHOP Research Institute. “It’s here now, and it is expanding what scientists understand about disease and changing the ways we care for patients.”

And, as in many areas of investigation, research conducted within the [Centers of Emphasis](#) at [The Children’s Hospital of Philadelphia Research Institute](#) serves as the cornerstone of this new foundation in personalized healthcare.

# Building a Knowledge Base

The hunt for genes associated with various diseases at the CHOP Research Institute often starts with the [Center for Applied Genomics](#) (CAG). Using state-of-the-art technology and techniques, the CAG team tirelessly searches for the genes underlying diseases to prevent and treat pediatric illnesses.

The progress CAG has made in the mere six years since it was formed is nothing short of astounding. The Center has one of the world's largest programs for genotyping, the technical term for detecting gene variants and linking them to diseases. And CAG's efforts are not only focused on common pediatric diseases like diabetes, autism, ADHD, and cancer, but numerous rare ones as well.



**"In a very real sense, we are on the cusp of a new era where the combination of biology and technology is about to transform our understanding of pediatric disease," says CAG director [Hakon Hakonarson, MD, PhD](#).**

In addition, CAG operates the world's largest pediatric biorepository, collecting and organizing more than 150,000 specimens and providing a centralized and efficient resource for investigators across the Research Institute conducting their own studies.

During FY2012, the Center for Applied Genomics made significant advances in understanding the genetic underpinnings of ADHD, autism, and obesity, among others, and launched a new initiative aimed at gaining a better understanding of the genetic underpinnings of rare diseases.

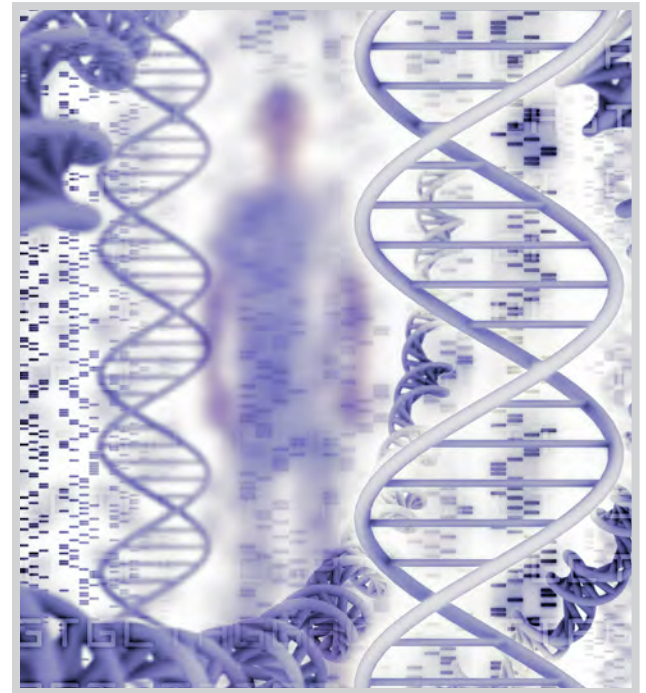


# Reading the Blueprints of Common Diseases

Although the Center for Applied Genomics has numerous active genomics studies underway, in the last year the Center made groundbreaking discoveries on some of the most common diseases and conditions affecting children, most notably attention-deficit/hyperactivity disorder (ADHD) and obesity.

The CAG team, as well as that of the [Center for Biomedical Informatics](#), collaborated with child psychiatrist [Josephine Elia, MD](#), on the study of the genetic influences of ADHD, a common but complex neuropsychiatric disorder of unknown etiology. The focus of the study centered on copy number variations, or CNVs, which are segments of chromosomes of variable size where DNA has been deleted, duplicated, or rearranged.

The team found alterations in specific genes, called GRM genes, involved in important brain signaling. These genes come into play in up to 20 percent of children with ADHD. This new discovery made by CAG investigators may lead to new drugs and therapies that target those pathways, possibly offering new treatment options to more than a million children in the U.S. alone who have those gene variants.



Specifically, Children's Hospital investigators are eyeing the redevelopment of a medication previously used for another condition that targets the GRM network, providing a much-needed alternative treatment approach for that subset of children with the ADHD gene variants who have not responded well to existing treatments. This innovative, genomics-based "test and treat" approach may represent the first personalized therapeutic for a neuropsychiatric disorder.

As prevalent as ADHD has become, perhaps equally prevalent are the number of childhood obesity cases in the United States and across the globe. Obesity is one of the major health issues affecting modern societies, and has grown to astronomical levels in the last decade among adults and children alike.

Although environmental factors like food choices and sedentary habits are key players in the condition, there is far more to obesity than that.

In FY12 CAG investigators led by [Struan F.A. Grant, PhD](#), associate director of the Center for Applied Genomics, conducted the largest genome-wide study to date on childhood obesity. What they found was at least two new gene variants that increase the risk of the condition.

The approach taken by Dr. Grant and his colleagues diverged from previous studies that focused on gene variants associated with extreme obesity in adults and children. Despite possessing the largest collection of DNA from children with common obesity, the investigators broadened their study and formed an international consortium to combine the results from similar datasets from around the world.

The team identified two novel loci — one on chromosome 13 and the other on chromosome 17 — implicated in obesity, and found evidence that suggests at least two other gene variants are at play.

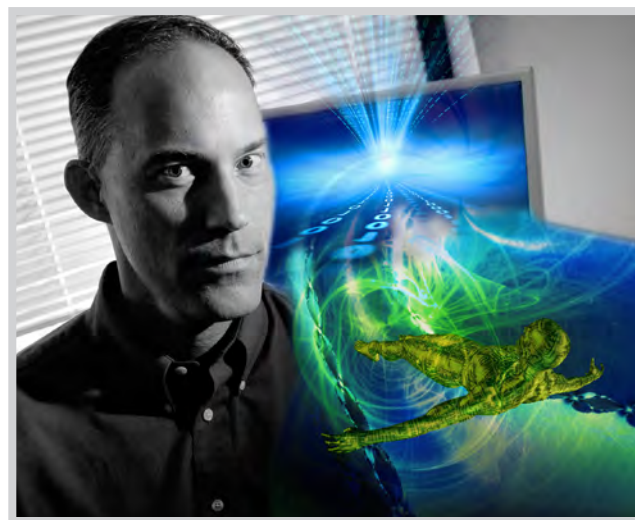
“This work opens up new avenues to explore the genetics of common childhood obesity,” says Dr. Grant, who added that the findings may one day lead to the development treatments and preventive interventions based on a children’s individual genomes.

# Fortifying the Data Structure

Every study produces mounds of data to be sifted through, organized, and made sense of before conclusions can be drawn, implementations made, and results ultimately applied to clinical care.

Having the infrastructure and the knowledge base to take genomic information from the lab and apply it to clinical and diagnostic settings requires more than sophistication and expertise. It also requires an enterprise-level approach, one that is provided by the [Center for Biomedical Informatics](#) (CBMi).

Led by [Peter White, PhD](#), CBMi develops innovative solutions that address the informatics needs of the Research Institute — and beyond. It provides the aptitude and infrastructure critical to maximizing the value of the data and other information relevant to research and clinical activities at Children's Hospital.



Put more simply, CBMi's expertise in medicine, biology, statistics, mathematics, linguistics, and computer science empowers it to help investigators, clinicians, and families alike best use the ever-evolving and expanding pediatric health information.

CBMi is also uniquely positioned to integrate the Hospital's genomics capabilities into daily clinical practice. The Center explores how to merge genomic, clinical, and other data into existing systems — like the electronic health record — that can be powerful tools for healthcare providers. Indeed, the Center has a new director of Genomic Medicine, [Patrick Warren, PhD](#), who helps meet the increasing needs of personalized genomics at CHOP by working with researchers, clinicians, regulatory groups, and informaticians to incorporate genome-based discoveries into the electronic health record through clinically governed decision support systems.

But the Center's efforts don't stop there. CBMi's work includes zeroing in on the most effective ways of presenting the results of genomics studies to clinicians, patients, and families; providing the structure and support for genetic counselors to use creative informatics solutions; and taking a close look at the ethical implications of [making genomic data available](#) in a patient's electronic health record.

“CHOP’s recent high volume of breakthroughs in genomics research is a direct results of its thoughtful approach to translational science,” says Dr. White. “CBMi will further develop the infrastructure and knowledge needed to fully support clinical and diagnostic genomic medicine practices throughout the Hospital.”

In FY12, the Center continued its collaboration with the Department of Pathology and Laboratory Medicine to develop genomic sequencing-based diagnostics tests for a variety of conditions. In April, the Hospital’s first whole genome sequencing-based diagnostic test was introduced for Noonan syndrome, a congenital disease linked to a number of symptoms, including developmental delays, short stature, distinctive facial and body features, and cardiac issues.

CBMi is also heading a key project on the sequencing, analysis, and interpretation of data on the recently awarded \$2.2 million [Clinical Sequencing Exploratory Research Project](#). One unique tool already being put to use, called Varify, gives healthcare providers and researchers a quick overview at suspected genetic variants for a sample.

“Overall, this project will build a framework for systematically assessing the gene sequence data we collect, to integrate the data with medical care,” Dr. White says. “We envision Children’s Hospital as a ‘working lab’ of sorts to combine genomic analysis with our clinicians’ observations and diagnostic expertise to support physicians and families in making healthcare decisions.”

# Framing the Issues Underlying Rare Diseases

In FY2012, the Center for Applied Genomics teamed up with Beijing, China-based BGI, the world's largest genomics organization, to launch the 1,000 Rare Diseases Project. The project aims to accelerate the discovery of genetic variants underlying rare diseases — often life-threatening or chronically debilitating ailments.

Despite the thousands of rare diseases in the world, patients with these diseases are an exceptionally underserved population. Although affecting approximately one in 12 newborns, the number of patients with a specific rare disease is usually small; therefore, these patients often lack the social and medical support available to others with more common conditions.



On top of that, the relatively small number of patients with a particular rare disease unfortunately also means that it's difficult for research organizations to justify investing limited research dollars to understand and treat a disease that affects so few.

CHOP and BGI are tackling this problem by using next-generation sequencing technologies to analyze DNA samples from patients and families who have donated samples to the CAG biorepository.

"The most accurate and efficient way to achieve this goal is to sequence genomes of affected children, as well as their first-degree relatives," says Dr. Hakonarson, who adds that the project will ultimately provide a solid genetic foundation for future clinical diagnosis and treatment for those with rare diseases, and in some instances, may inform therapies for more common complex diseases.



# Interpreting the Genetic ‘Plan’

With more and more DNA sequence data generated every day, revealing new versions of genes and other genetic variants, a host of questions has arisen about what to do with the information. How much is clinically relevant? How should it be integrated into practice? And how should this information be shared with patients?

And that’s just on the healthcare side. What about patients and their families? Would they want to know about their child’s genetic predisposition to a disease? Supposing parents decided to have their child’s genome sequenced to determine a predisposition — would they make different decisions today based on what might happen tomorrow?

An innovative project at Children’s Hospital seeks to look beyond the massive data surge to consider the ethical issues accompanying knowledge that comes from the sequencing of an individual’s genome.

Children’s Hospital is one of six U.S. centers, and the only one focused exclusively on pediatrics, to receive a [Clinical Sequencing Exploratory Research Project](#) award from the [National Human Genome Institute](#). The \$2.2 million four-year award was made to the husband and wife team of [Ian D. Krantz, MD](#), and [Nancy B. Spinner, PhD](#).

In addition to examining the ethical issues associated with clinical sequencing, the consortium will propose guidelines on sharing, interpreting, and using genetic information. The [Center for Biomedical Informatics](#) leads the critical informatics component of this ambitious project. The consortium’s work will then help physicians, healthcare professionals, and genetic counselors best interpret the data for patients and their families.



“Currently, when gene analysis helps us arrive at a diagnosis of a child’s disorder, we can counsel a family, providing information about what to expect and what options may be available for therapy and medical intervention,” says Dr. Krantz, who notes that genome-wide sequencing can also uncover “incidental findings” — gene variants that are not related to a current condition but may have a bearing on a patient’s future health.

However, only a handful of the thousands of gene variants in a person’s genome will be clinically significant or actionable, giving physicians greater knowledge to suggest medical interventions, if warranted.

“By the end of this decade, we anticipate that genomic sequencing will be readily available for the diagnosis of pediatric disorders,” Dr. Krantz says. “Our goal is to help make the information-sharing process systematic, thoughtful, and sensitive to the needs and desires of patients and families.”

# The Next Level: Direct Patient Care

Cancer. It's a small word, but one that sure bears a hefty punch.

Only a few decades ago, cancer in children was usually fatal. Thankfully, that's not the case anymore, and there is tremendous reason for hope. Advances in research and treatment approaches have led to a far greater understanding of the myriad issues surrounding cancer, and cure rates have reached an all-time high.

But a cancer diagnosis continues to instill fear. Parents are rightfully concerned about both the short- and long-term negative affects of chemotherapy or other treatments their children may need to undergo — and there are no guarantees that a standard treatment will work.

And then there are discoveries that take cancer care and treatment to a whole new level, providing even greater hope for patients and their families.

In FY12, Children's Hospital investigator and oncologist [Yaël P. Mossé, MD](#), made headlines around the world with news that a drug originally developed for use in adults with lung cancer showed amazing results in early trials in children with two aggressive forms of cancer — anaplastic large-cell lymphoma (ALCL) and neuroblastoma.

The drug, called crizotinib (brand name Xalkori®), was approved by the [Food and Drug Administration](#) in 2011 to treat late-stage non-small cell lung cancers in patients who express a gene called anaplastic lymphoma kinase (ALK). Just three years earlier, Dr. Mossé and her team in the [Center for Childhood Cancer Research](#) discovered that mutations in the ALK gene were implicated in 10 to 15 percent of the cases of neuroblastoma, the most common solid cancer of early childhood.

Once crizotinib hit the market, Dr. Mossé was able to expedite her phase 1 clinical trial, bypassing the extensive early development stage that is typical for most new drugs. The results were astounding, and highly encouraging.



Dr. Mossé gave crizotinib to eight children with ALCL whose cancer was not responding to traditional chemotherapy. Within days of receiving crizotinib, an oral medication, seven of the patients found that their fever and chills went away and their pain had significantly lessened or disappeared altogether.

But even more impressive were the subsequent imaging scans that showed no trace of cancer in the patients.

While further investigations are needed to determine the effectiveness and appropriate dose of crizotinib, Dr. Mossé 's study underscores the tremendous promise of personalized medicine, even for the sickest of patients with among the most complex and aggressive diseases.

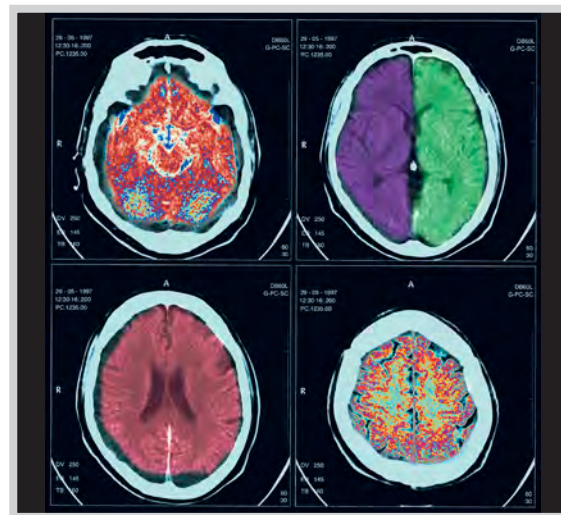
“We are entering a new era of cancer therapy, in which we use knowledge of basic biology to design very specific drugs that target cancer cells with few side effects on healthy tissue,” Dr. Mossé says. “In addition, as we concentrate on targets in molecular pathways, we move away from an exclusive focus on one form of cancer to customizing treatments according to biological activity.”

# TRAILBLAZERS

## Infant Brain Differences Linked to Autism

Rather than appearing suddenly in young children, autism develops over time, according to a recent study by the Infant Brain Imaging Network, a nationally funded research network with four primary sites, including the [Center for Autism Research](#) at [The Children's Hospital of Philadelphia](#). The investigators found significant differences in brain development starting at age 6 months in high-risk infants who later develop autism. The finding is important because it brings scientists one step closer to developing a biomarker to assist with very early diagnoses for autism spectrum disorders.

The investigators studied 92 infants considered to be at high risk for autism spectrum disorder (ASD) because they all have older siblings with autism. Each infant underwent diffusion tensor imaging — a type of magnetic resonance imaging — at 6 months and behavioral assessments at 24 months. Most of the children also had additional brain imaging scans at either or both 12 and 24 months.



At 24 months, 28 infants (30 percent) met criteria for ASDs while 64 infants (70 percent) did not. The two groups differed in white matter fiber tract development — pathways that connect brain regions — as measured by fractional anisotropy (FA). FA measures white matter organization and development, based on the movement of water molecules through brain tissue.

This [study](#) examined 15 separate fiber tracts, and found significant differences in FA growth trajectories in 12 of the 15 tracts between infants who did develop autism versus infants who did not. Infants who later developed autism had elevated FA at six months but then experienced slower development over time. By 24 months of age, infants with autism had lower FA values than infants without autism.

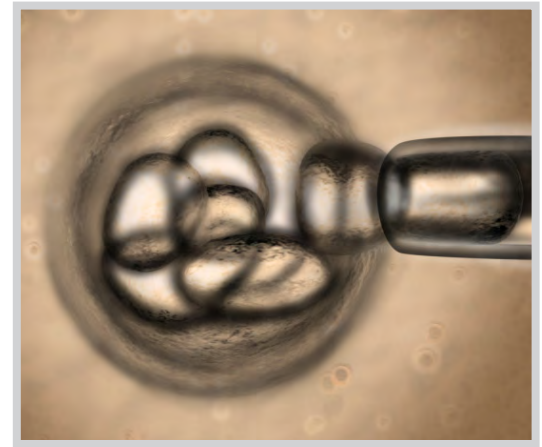
Intensive early intervention has been shown to improve outcomes in children with developmental delays and autism. The research therefore raises the possibility that healthcare givers may be able to intervene even before a child is 6 months old, to blunt or prevent the development of some autism symptoms.



# New Stem Cells Provide Safe Study Source

CHOP researchers have generated a new type of human stem cell that can develop into numerous types of specialized cells, including functioning pancreatic beta cells that produce insulin. Called endodermal progenitor (EP) cells, the new cells show two important advantages over embryonic stem cells and induced pluripotent stem cells: they do not form tumors when transplanted into animals, and they can form functional pancreatic beta cells in the laboratory.

“Our cell line offers a powerful new tool for modeling how many human diseases develop,” said study leader [Paul J. Gadue, PhD](#), a stem cell biologist at Children’s Hospital. In addition to producing beta cells, the researchers also directed EP cells to develop into liver cells and intestinal cells — both of which normally develop from the endoderm tissue layer early in human development.



The researchers manipulated two types of human stem cells — embryonic stem cells (ESCs) and induced pluripotent stem cells (iPSCs) — to become EP cells. Because both stem cell populations proliferate in great numbers and potentially generate all types of tissue, they offer enormous promise for scientists to precisely control cell development, both for the study of basic biology and for future cell-based treatments.

[In the current study](#), the researchers used signaling molecules called cytokines to steer ESCs and iPSCs into becoming EP cells, committed to developing into endoderm, one of the three tissue layers found in early human development. The EP cells have nearly unlimited potential for growth in the laboratory. Both in cell cultures and when transplanted into animals, the team showed that EP cells can differentiate into multiple cell types, representing those found in the liver, pancreas, and intestine. Importantly, undifferentiated EP cells did not form teratomas in the team’s transplantation studies.

However, Dr. Gadue stressed that these early results are only the first steps in researching EP cells. Further work may focus on taking cells from individual patients with genetic forms of diabetes or liver disease to derive EP cell lines. And although applying this science to cell therapy is years away from practical clinical use, EP cells may offer a powerful starting point for developing tissue replacement treatments.

# Gene Therapy for Blindness Shows Success

Gene therapy for congenital blindness has taken another step forward, as researchers recently improved vision in three adult patients previously treated in one eye. After receiving the same treatment in their other eye, the patients' ability to see in dim light increased, and two were able to navigate obstacles in low-light situations.

Neither the first treatment nor the readministered treatment triggered an immune reaction that cancelled the benefits of the inserted genes, as has occurred in human trials of gene therapy for other diseases. The [current research](#) targeted Leber congenital amaurosis (LCA), a retinal disease that progresses to total blindness by adulthood.



"Patients have told us how their lives have changed since receiving gene therapy," says study co-leader Jean Bennett, MD, PhD, F.M. Kirby professor of Ophthalmology at the University of Pennsylvania. "They are able to walk around at night, go shopping for groceries and recognize people's faces — all things they couldn't do before. At the same time, we were able to objectively measure improvements in light sensitivity, side vision and other visual functions."

Other objective results came from brain signals seen in neuroimaging. When a dimly flickering checkerboard pattern flashed in front of a patient's recently treated eye, an area in the brain responsible for vision lit up during functional magnetic resonance imaging (fMRI). "This finding is telling us that the brain is responding to the eye's sensitivity to dim light," said radiology researcher and study co-leader Manzar Ashtari, PhD, of Children's Hospital.

Furthermore, Dr. Bennett adds, the research holds promise for using a similar gene therapy approach for other retinal diseases. Dr. Ashtari said that fMRI could play a future role in helping to predict patients more likely to benefit from gene therapy for retinal disease.

# Green Tea Could Treat Metabolic Disease

Green tea has been the subject of numerous research studies in the last decade in an effort to determine whether the tea can ward off diseases like cancer or heart disease. A CHOP endocrinologist is now exploring whether green tea may be used to treat a rare childhood disease.

[Charles Stanley, MD](#), is an internationally prominent expert on forms of congenital [hyperinsulinism](#) (HI), rare inherited disorders in which children produce abnormal levels of insulin. He also discovered a syndrome in which HI is combined with hyperammonemia (HA), an abnormal level of blood ammonia.

In HI/HA, the mutation that he identified prevents an enzyme called GDH from functioning normally, leading to excessive levels of insulin, as well as childhood epilepsy, seizures and learning disabilities. Current drug treatment controls insulin levels, but not the neurological problems. The drug also has side effects, such as excessive hair growth.



Based on a decade-long scientific collaboration, Dr. Stanley co-authored a recent study showing that a compound found in green tea controls this enzyme defect in animals, raising the possibility of a new treatment for HI/HA in children. The study, which appeared in the [Journal of Biological Chemistry](#), showed that the compound controlled blood sugar levels in the animals.

“Our research doesn’t mean that people should automatically expect green tea to treat the rare disease HI/HA,” says Dr. Stanley. “However, with further research, we may be able to modify this green tea compound to derive a drug that can be tested in children with HI/HA. It’s possible that such a derivative may control blood sugar levels in people, as successfully as in mice, with fewer side effects than existing drugs. An even more exciting prospect is that this may lead to a drug that is more effective than existing drugs in treating neurological problems in the disease.”

# Newborn Period May Be Crucial to Preventing Diabetes

Children's Hospital researchers who tested newborn animals with an existing human drug used in adults with diabetes report that this drug, when given very early in life, prevents diabetes from developing in adult animals. If this finding can be repeated in humans, it may become a way to prevent at-risk infants from developing type 2 diabetes.

"We uncovered a novel mechanism to prevent the later development of diabetes in this animal study," says senior author [Rebecca A. Simmons, MD](#), a Children's Hospital neonatologist. "This may indicate that there is an important developmental window, a period of time in which we can intervene to permanently protect the body's insulin-producing cells."



Dr. Simmons and lead author Sara E. Pinney, MD, a pediatric endocrinologist at Children's Hospital, published the study in the October issue of [Diabetologia](#). The research may be relevant to children with intrauterine growth retardation (IUGR), a common complication during the mother's pregnancy. Simmons's previous research showed that IUGR, which is associated with decreased availability of nutrients and hormones to the developing fetus, permanently alters gene expression and impairs the function of insulin-producing cells in the pancreas. These defects have been shown to cause type 2 diabetes to develop in adulthood.

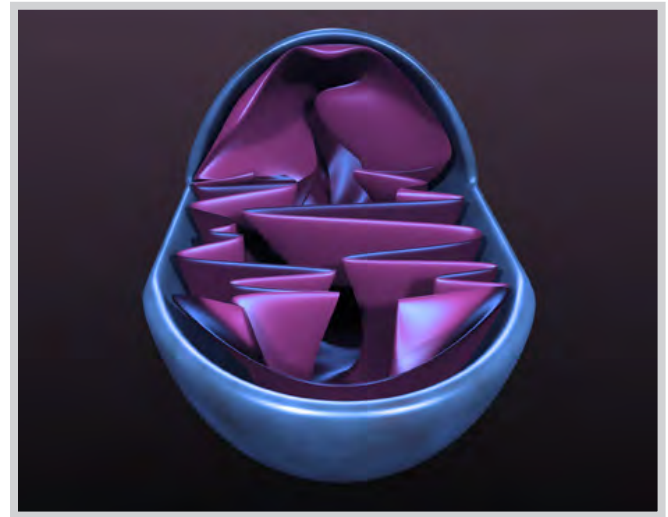
The study team used exendin-4 (Ex-4), a drug recently approved for use in adults with type 2 diabetes — a condition in which a patient produces insufficient insulin, or is unable to process insulin normally. In their study, Drs. Simmons and Pinney used rats with an induced form of IUGR. They found that after being given to newborn rats, Ex-4 had epigenetic effects — modifying gene function without changing the underlying DNA sequences. Ex-4 increased the expression of a gene called Pdx1 that is necessary for beta cells to function properly. Beta cells produce insulin in the pancreas of mammals, including humans.

"In our study, giving exendin-4 during the newborn period had permanent beneficial effects on beta cells," says Dr. Pinney. "This could be important for people, in whom abnormal changes in infancy may irreversibly alter beta cells and lead to adult-onset diabetes."

# Study Improves Understanding of Mitochondria

A new study by Children's Hospital researchers answers a long-standing question about how mitochondrial DNA figures in the production of cellular energy. The study, which was led by Neal Sondheimer, MD, PhD, improves our understanding of how mitochondria work, and could eventually lead to new ways of treating mitochondrial diseases.

The mitochondrion is a key supplier of the energy needed for the multiple functions of our cells. These organelles play a pivotal role in human health, because when the mitochondrial power plants of our cells become damaged the energy output for the body's cells and tissues progressively declines. Mitochondria contain their own DNA, called mitochondrial DNA (mtDNA). The purpose of Dr. Sondheimer's study was to determine how mtDNA is used to create proteins used in the generation of cellular energy.



In order to make new proteins, mtDNA must be converted, or transcribed, into mitochondrial RNA (mRNA). But exactly how mtDNA does this has been a source of some controversy. While some investigators suggested the existence of a second heavy strand promoter — a specialized segment of DNA required for RNA synthesis — some researchers doubted the second promoter's existence because they couldn't get it to work in the lab.

In addition to determining how to make the promoter, known as HSP2, work, Dr. Sondheimer and his team identified several of its key features. The most important and "unexpected" feature of HSP2 is that a protein that normally activates mitochondrial promoters, transcription factor A (TFAM), acts to block transcription at HSP2. The study team's finding "suggests that the cell may manipulate TFAM levels to change the genes that are expressed by the mitochondrion," Dr. Sondheimer said.

Because determining the inner workings of the mitochondria could provide a major new approach to understanding and developing therapies for myriad rare and common diseases, the study's findings could have significant repercussions.



# Virus Mimics Cell Signals to Drive Infection

New research reveals how an invading virus hijacks a cell's workings by imitating a signaling marker to defeat the body's defenses. By manipulating cell signals, the virus destroys a defensive protein designed to inhibit it. This finding may represent a broader targeting strategy used by other viruses, and could lay the groundwork for developing more effective treatments for infectious diseases.

"Learning details of how cells respond to viruses helps us to understand key cellular machinery better," said CHOP investigator and study leader [Matthew D. Weitzman, PhD](#).



Biologists have long known that viruses hijack cellular processes to replicate themselves, and that host cells have evolved defense systems to resist viral invasion. To replicate, viruses must deliver their own DNA into a cell's nucleus, so a viral infection entails a conflict between two genomes — the DNA of the host cell versus the foreign DNA of the virus. This study focused on herpes simplex virus type-1 (HSV-1), a common human virus that results in recurrent infections alternating with inactive periods. Like other viruses, HSV-1 is known to manipulate cellular processes in order to infect cells, but the specific mechanisms by which it acts on the DNA repair pathway were previously unknown.

Dr. Weitzman's study team was studying a viral protein called ICPo that overcomes host defenses by targeting cellular proteins for destruction. They found that ICPo exploits phosphorylation, a chemical mark that is often used in cells to promote interactions between proteins, especially as part of the cellular signaling response to DNA damage. In HSV-1 infection, the phosphorylation signal on ICPo attracts a cellular DNA damage response protein, RNF8, which binds to the false signaling marker and is then degraded. Because RNF8 normally inhibits viral replication, its destruction leaves the cell vulnerable to HSV-1 infection, as the virus takes over the cell's machinery.

The investigators also found that ICPo exploits the same phosphorylation signal to bind to other cellular proteins in addition to RNF8, a hint that it may play a broader role in defeating antiviral defenses and manipulating cellular machinery. Dr. Weitzman plans to continue to investigate HSV-1 infection in neurons and in animal models, eventually extending his research into other viruses, which may act on different pathways than HSV-1 does.

# Asthma Measures Do Not Reduce Hospital Visits

Asthma remains the major cause of preventable hospitalizations for children in the U.S. A recent study in the [\*Journal of the American Medical Association\*](#) is the first to look at the association of asthma care quality measures during hospitalization and subsequent asthma-related readmissions or emergency care.

The three Children's Asthma Care (CAC) core measures are monitored by the Joint Commission and are meant to evaluate whether patients aged 2 to 17 years with an asthma exacerbation received relievers and systemic corticosteroids during their stay, and whether they were discharged with a complete plan of care for at-home management of asthma. [Evan Fieldston, MD, MBA, MSHP](#), a pediatrician and health services researcher at [PolicyLab](#), was one of several investigators to collaborate on this multi-center study.

The study included data from 30 freestanding children's hospitals in the United States. Researchers found that, while compliance for the three CAC core measures increased over the 2-year study period, improved compliance was not associated with declines in returns to the emergency department or hospital readmission in the 7, 30, and 90 days that followed an initial hospitalization for asthma.



While home management plans of care may be an important component of treatment of asthma, the authors conclude that they may not be appropriate to classify as “accountability measures” for hospitals given that hospital-based physicians cannot monitor what happens to a family once they leave the hospital and that so much of what happens to a patient with asthma is influenced by exposures beyond the walls of the hospital.

Although post-discharge education and follow up is an important aspect of care to measure, the lack of an association between this specific measure and readmission highlights an opportunity for further investigation and refinement. The research team recommended that the asthma home management plan of care be re-evaluated as an accountability measure used by the Joint Commission, with the understanding that the key is to ensure that evidence-based practices are part of the plan families follow at home and that the plan is communicated effectively to enhance adherence.

# Genome Editing Corrects Hemophilia in Animals

Using an innovative gene therapy technique called genome editing that hones in on the precise location of mutated DNA, scientists have treated the blood clotting disorder hemophilia in mice. This is the first time that genome editing, which precisely targets and repairs a genetic defect, has been done in a living animal and achieved clinically meaningful results.

As such, it represents an important step forward in the decades-long scientific progression of gene therapy — developing treatments by correcting a disease-causing DNA sequence.

In this new study, published in the journal [\*Nature\*](#), researchers used two versions of a genetically engineered virus called adeno-associated virus, or AAV — one carrying enzymes that cut DNA in an exact spot and one carrying a replacement gene to be copied into the DNA sequence. All of this occurred in the liver cells of living mice.

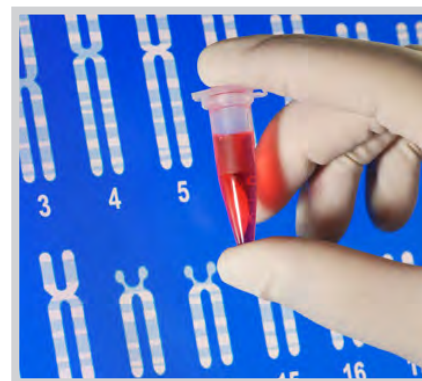


“Our research raises the possibility that genome editing can correct a genetic defect at a clinically meaningful level after *in vivo* delivery of the zinc finger nucleases,” said the study leader, [Katherine A. High, MD](#), a hematologist and gene therapy expert at Children’s Hospital. Dr. High, a [Howard Hughes Medical Institute](#) Investigator, directs the [Center for Cellular and Molecular Therapeutics](#), and has investigated gene therapy for hemophilia for more than a decade.

# Chromatin Loop Manipulation May Offer Treatments

By exploring how proteins interact with DNA sequences to regulate gene activity, CHOP researchers have shed light on biological processes that could be manipulated to provide new disease treatments. In a cell's nucleus, elements in DNA called promoters and enhancers communicate with each other while carrying out gene activity, and as these elements come into physical contact, the intervening DNA sequences bend into loops made of chromatin fiber — the substance of chromosomes.

"Many researchers ... have shown that chromatin looping is widespread during gene expression," said study leader [Gerd A. Blobel, MD, PhD](#), of the Division of Hematology. "However, many details remain uncertain — even whether chromatin loops are a cause or effect of gene transcription."



The researchers focused on gene transcription — the process by which DNA is converted into RNA to make new proteins — studying a portion of DNA called the beta-globin locus that expresses part of the hemoglobin molecule. While they understood the mechanics of how chromatin loops form, the investigators did not know all the proteins that were necessary to generate chromatin loops, nor how those proteins interacted with other proteins during gene transcription.

The team sought to identify a looping factor, a protein that triggers chromatin looping. "We had a strong candidate for a looping factor — a molecule called Ldb1," noted first author Wulan Deng. In the current study, Dr. Blobel's team used a genetically-engineered DNA binding protein called a zinc finger (ZF) protein, which was designed to latch onto a chosen gene location. The researchers attached Ldb1 to a ZF, ultimately causing a chromatin loop to form between the enhancer and promoter, and allowing high-level gene transcription to occur.

In addition to showing that Ldb1 plays a key role in gene expression, the "results suggest that chromatin looping is a cause, not an effect, of gene transcription. We will further study whether and how we can use forced chromatin looping to manipulate gene expression for scientific or therapeutic purposes," Dr. Blobel said.

Though the findings have no immediate clinical impact, the work could lead to a number of future applications, such as treating sickle cell anemia. And more broadly, forced chromatin looping might enable researchers to turn off the expression of specific genes known to drive particular diseases, Dr. Blobel added.

# Genetic Mutations Found to Impair Childhood Growth

CHOP investigators studying rare genetic disorders have gained insights into biological structures that regulate chromosomes when cells divide. The researchers found mutations that disrupt the cohesion complex, a group of proteins forming a bracelet encircling chromosome pairs, cause a recently recognized class of diseases called cohesinopathies.

The cohesin complex is associated with Cornelia deLange syndrome (CdLS), a genetic disease affecting an estimated 1 in 10,000 children. The disease has a range of severity, but classically includes mental retardation, impaired growth, heart defects, and distinctive facial features. Children's Hospital researchers were the first to discover gene mutations that cause CdLS, and the current study identified another gene, *RAD21*, that when mutated causes mild cognitive and physical impairments.



After performing an analysis of children with typical CdLS and overlapping features of the disease, the researchers found that none of the children had mutations in the three genes already known to cause CdLS. They then identified a boy with a deletion in a section of chromosome 8 that contains the *RAD21* gene, which was known to express a cohesin protein but not previously associated with CdLS. As an infant, the boy had been diagnosed with facial features resembling CdLS, and subsequently experienced growth retardation, but had normal cognitive development.

The researchers then focused on additional children with *RAD21* deletions or mutations within the gene, and found a similar pattern — physical features, such as short stature and distinctive facial features, but with only minor cognitive delays. “These findings suggest that children who are very mildly affected may go undiagnosed,” noted study leader Matthew A. Deardorff, MD, PhD, a specialist in pediatric genetics at Children's Hospital.

While the team's studies investigating the molecular mechanisms involved in cohesin disorders were illuminating, the research does not currently explain the full sequence of molecular events, and further studies will investigate knowledge gaps in the process. But because the cost of whole-genome sequencing is rapidly dropping, researchers may eventually discover additional genes involved in cohesinopathies, offering further clues to how these diseases function in human development.



## \$2.5 Million Gift Supports Groundbreaking Autism Research

Christina Weiss Lurie and Jeffrey Lurie, Philadelphia Eagles owners and co-founders of the Lurie Family Foundation, made a \$2.5 million gift to CHOP's [Center for Autism Research](#) (CAR) in 2011. The gift supports genetic and brain imaging research to enable earlier diagnoses and more effective treatments for autism spectrum disorders (ASDs) that will help families of children with ASDs.

The gift supports two distinct lines of research. The majority will fund CAR investigators examining genetic samples from 1,000 individuals with an ASD, to look for new genetic variants that might be related to an ASD. As part of this one-of-a-kind study, families will have the option of receiving individualized genetic test results and the opportunity to discuss the results with a genetic counselor.



This information may help families as they consider future treatments, interventions, and family planning decisions.

The remainder of the gift will support research using MEG technology (magnetoencephalography) at the Lurie Family Foundation's [MEG Imaging Center](#) at CHOP. This study will follow school-aged children over time as they develop, and will measure the brain's activity in real time in order to better understand brain development and differences in the way the brain processes signals in children with ASD.

"We are especially excited about the possibility of using genetic information to better understand which treatments are most effective for each child and to develop better treatments in the future," says CAR director [Robert Schultz, PhD](#). "This requires developing a better foundation of knowledge about genes, brain functions, specific symptoms, and treatment outcomes. We hope that this kind of gift will enable us not only to determine who is at greatest risk for an ASD, but also to be able to begin to develop personalized interventions based on more precise understanding of the different causes."

# Grant Awarded to Examine Personalized Genetic Data

After a decade of work and at an expense of nearly \$3 billion, the sequencing of the entire human genome was completed in 2003. Technological advances since then mean that an individual's genome can now be sequenced in only a few months, for about \$4,000.

Knowing just what to do with this knowledge has not kept pace with the gusher of genetic data. People can now have their own genome analyzed, which can offer clues to their current and future risks of genetic diseases. But what will individuals do with this flood of information? Is some of it information that they prefer not to know? And how could knowledge of a child's possible future risks affect parents' decisions now?



These are just a few of the issues being explored in a grant from the [National Human Genome Research Institute](#), the federal agency that sponsored the [Human Genome Project](#). The Children's Hospital of Philadelphia is one of five U.S. centers, and the only one focusing on pediatrics, to receive a new four-year [Clinical Sequencing Exploratory Research Project](#) award. Children's Hospital will receive \$2.2 million per year for four years.

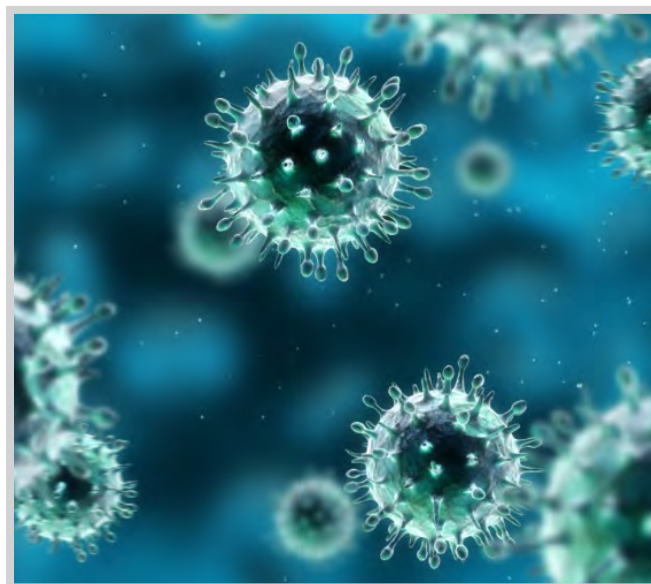
Clinical geneticist Ian D. Krantz, MD, is the principal investigator of the project along with [Nancy B. Spinner, PhD](#), director of the Clinical Cytogenomics Laboratory at Children's Hospital.

"By the end of this decade, we anticipate that genomic sequencing will be ready to be offered for the diagnosis of pediatric disorders," says Dr. Krantz. "Our goal in this research is to help make that information-sharing process systematic, thoughtful and sensitive to the needs and desires of patients and families," adds Dr. Krantz.

# Grand Challenges Explorations to Fund HIV Research

Children's Hospital recently announced that it will receive funding through [Grand Challenges Explorations](#), an initiative created by the [Bill & Melinda Gates Foundation](#), to fund a new HIV study. [Terri Finkel, MD, PhD](#), chief of Rheumatology and Professor of Pediatrics at the Perelman School of Medicine at the University of Pennsylvania, will pursue an innovative global health research project, titled "Use of a BET Antagonist to Control and Cure HIV Infection."

Dr. Finkel and her research team will study the potential of drugs called synthetic BET (bromodomain extra terminal) family protein antagonists to control HIV infection and latency. Current HIV drugs reduce the disease-causing virus to undetectable levels, but the virus goes into a dormant state called latency, from which it can make a resurgence if a patient stops taking medication. Previous studies by Dr. Finkel and other scientists have suggested that BET antagonists may flush HIV out of its hiding places where it can be destroyed by other antiretroviral drugs.



Dr. Finkel's chief collaborator in this project is [Gerd A. Blobel, MD, PhD](#), holder of the Frank E. Weise III Endowed Chair in Pediatric Hematology at Children's Hospital, who has focused on the biological activities of BET family proteins. In the first part of the project, Drs. Finkel and Blobel will investigate the effectiveness of BET antagonists against HIV in cell cultures. If these results are encouraging, the project will progress to clinical trials in patients with HIV.

Grand Challenges Explorations is a \$100 million initiative funded by the Bill & Melinda Gates Foundation. Launched in 2008, Grand Challenge Explorations grants have already been awarded to nearly 500 researchers from more than 40 countries.

# TECHNOLOGY

## Cellie: It's Much More Than a Toy

Pop quiz: what looks like a stuffed gray and red tube sock, is soft and huggable, has a zipper for a mouth, and can help comfort children with cancer?

### It's Cellie!

To be more specific, it's the [Cellie Cancer Coping Kit](#), a tool designed by Children's Hospital of Philadelphia researchers to help children and their families manage the physical and emotional challenges associated with cancer treatment. In addition to Cellie, the namesake plush toy — or critter, as some of the researchers who work with Cellie call it — the kit also includes a pack of "cancer coping cards" and a booklet for caregivers.



Cellie was co-invented by [Meghan Marsac, PhD](#), a behavioral researcher and director of training at the [Center for Injury Research and Prevention](#) (CIRP), and Anne Vinsel, MFA, a Salt Lake City, Utah-based artist and photographer. Dr. Marsac originally came up with the idea for the Cellie Coping Kit while working with pediatric cancer patients and finding that there was a need for additional resources to help children deal with stress related to cancer and its treatment.

CIRP staff who have worked with Dr. Marsac on the Cellie Cancer Coping Kit include [Nancy Kassam-Adams, PhD](#), associate director of behavioral research at CIRP, and Aimee Hildenbrand, a first-year doctoral candidate in clinical psychology at Drexel University and a clinical research assistant at CIRP. In addition to having taken part in [CIRP's Research Experience for Undergraduates program](#), Hildenbrand has aided Dr. Marsac in her Cellie research for the past two years. Additional key Cellie team members include CHOP psychologists [Melissa Alderfer, PhD](#), and [Lamia Barakat, PhD](#).

Cellie is currently offered at no cost to cancer patients and their families receiving care at CHOP, with the goal of offering a kit to every newly diagnosed patient at CHOP. The Cellie Team plans to make Cellie available to children with cancer receiving treatment at other cancer centers as well. Currently, 1000 Cellie kits have been manufactured and will be distributed to patients in the coming years, said Dr. Marsac.

At its straight, zippered mouth the toy is approximately nine inches wide, and is roughly 14 inches tall. Cellie's body is the gray often found in thermal socks, and its "limbs" are tipped in the same bright red that rings its mouth. In addition to being gender neutral, the critter was deliberately designed to be emotionally neutral, according to Hildenbrand, hence its straight mouth and heavy pink eyelids.

The Kit's caregiver book contains information designed to help parents and caregivers help their child cope with cancer and tips for using the Cellie Kit. Meanwhile, the "cancer coping cards" — which are designed for children — present coping strategies for a range of topics, from treatment side effects, to dealing with needle sticks, to stress reduction techniques. For example, one card reads, "I get sick (throw up, headache) on the way to the doctor's," and includes coping tips such as:

- > Make a plan with your mom or dad the day before you go to the doctor.
- > Pick foods to eat in the morning that do not bother your stomach.
- > Tell your doctor and ask him/her for ideas to help you to stop getting sick.

Both the booklet and cards are color-coded by topic — yellow for "communication," purple for "school and friends," and so on — and each card features pictures of Cellie, or several Cellies, engaging in some of the suggested coping strategies: playing videogames, listening to music, squeezing a stress ball, and drawing, to name a few.

Dr. Marsac and her team recently published a study in *Supportive Care in Cancer* on the Kit's effectiveness, finding that the kit "is an engaging, helpful, and easy-to-use coping tool for families facing pediatric cancer treatment." The research team recruited a number of current Children's Hospital patients and their caregivers to assess the feasibility and acceptability of the Kit, and found that, overall, the tool has been well received by patients.



"I would use him wherever I go. I would bring Cellie with me to the hospital ... he (would be) my buddy ...and help me out," one child who participated in the study noted. "I sleep with Cellie. I keep her with me when I'm getting the needle in. Cellie's the bomb ... it helps me a lot," another child said.

Parents who took part in the study also had positive things to say about the Cellie kit, pointing out that it helped them talk about cancer with their children. The Kit "made us more comfortable talking about," cancer with their son, one parent said, adding that before receiving Cellie "there were a lot of things we probably wouldn't talk about."

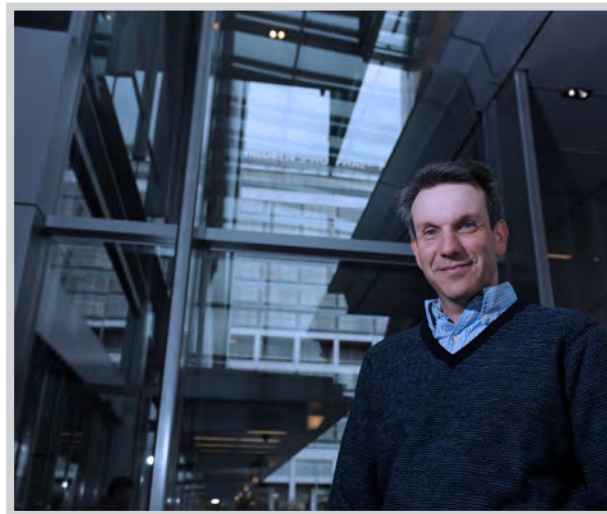
Additional studies to evaluate adapting the Kit for other pediatric populations— such as [sickle cell disease](#) — are currently underway. The CIRP team is considering which illnesses, or injuries, would be appropriate to target, but they would "likely be the kind of thing where there's some ongoing stressors," noted Dr. Kassam-Adams.

Cellie is "creative and wonderful and really speaks to kids' needs," but what has been really impressive about the project has been the introduction of "rigor to the development" of the Kit, said Dr. Kassam-Adams.

# Making Families “Active Partners” in Care

Let’s face it: we live in the future. At no point in human history has so much information been so accessible to so many people, and gone are the days when specialized information was only available to those privileged few who had the resources to attain it. The rise of the personal computer, then the internet, and then smartphones that (in addition to functioning as phones) can browse the internet from anywhere, means that more people than ever have access to more information than they could ever need.

It also means that patients and families, not to mention researchers, have access to more detailed health information than ever before. [Alexander G. Fiks, MD, MSCE](#), co-medical director of The Children’s Hospital of Philadelphia’s Pediatric Research Consortium and a PolicyLab faculty member, works to best make sense of, and use, the wealth of health information available clinicians, researchers, and families.



Dr. Fiks initially joined Children’s Hospital as resident in 1997, shortly after his receiving his MD from Harvard in 1997. In 2003 he was awarded an MSCE from the University of Pennsylvania, and in 2006 was appointed Assistant Professor of Pediatrics at CHOP. He is currently co-principal investigator of an American Academy of Pediatrics electronic health record-based project, “Comparative Effectiveness Research Through Collaborative Electronic Reporting.”

The project, also known as CER<sup>2</sup>, is a partnership between Children’s Hospital and networks based in Boston and Cleveland. CER<sup>2</sup> investigators plan to use from approximately 800,000 pediatric patients to conduct long-term comparative effectiveness research on the side effects of medication in children.

In addition to his role in CER<sup>2</sup>, Dr. Fiks has been focused on developing and testing shared decision making (SDM) tools to help families make informed, engaged care choices. SDM is a method of making treatment decisions wherein doctors and families make choices together by actively communicating and contributing their knowledge and preferences, respectively, to the decision-making process.

An approach to healthcare that is being used increasingly in adults, SDM “has been shown to lead to more successful treatment outcomes for patients and increased satisfaction among physicians,” said Dr. Fiks. He was recently the lead author of a study published in *Academic Pediatrics* that evaluated a questionnaire used to help parents of pediatric patients make improved attention deficit-hyperactivity disorder (ADHD) treatment decisions using SDM.

## SDM Asthma Portal

Dr. Fiks has also been working with [Robert Grundmeier, MD](#), director of clinical informatics at the Center for Biomedical Informatics (CBMi), on the development of an interactive SDM “portal” that patients can use at home. [Dean Karavite, MS](#), lead computer interaction specialist and an expert in human computer interaction at CBMi, has been overseeing the design and testing of the portal.

The portal, known as the “Shared Decision Making Portal for Pediatric Chronic Illness,” works with Children’s Hospital’s new [MyChart](#) patient site, which is currently being rolled out to the entire CHOP network and was originally developed by Dr. Grundmeier. By providing access to portions of medical records remotely, MyChart allows families to request appointments, view test results, and access health summaries and growth charts. In effect, MyChart replaces the telephone, Karavite said.

Drs. Fiks and Grundmeier’s portal is a modification of MyChart that greatly expands MyChart’s capabilities. While the pilot version of the portal is focused solely on asthma, Dr. Fiks and his team hope to eventually introduce versions geared toward other diseases, such as ADHD.

The portal contains a number of features that families can interact with. For example, the portal allows parents to fill out monthly symptom and care surveys, which can help free up time in the examination room. The system will send families regular reminders to fill out these care surveys, and through the portal doctors will be able to see detailed timelines of how their patients are progressing.

The portal also contains an extensive library of educational materials about asthma, including videos, materials geared toward children, and literature on symptom triggers such as cigarette smoke and dustmites. There is also a version of the portal for doctors that they can use to view detailed records, fill out assessments, and “assign” educational materials for patients to view.

“Research shows that patients adhere much better to the treatment options that they are comfortable with and that are the most practical for them,” Dr. Fiks said, pointing out that “choosing a treatment that doesn’t “fit” can lead to unsuccessful results.” Overall, projects like the new portal, that use the wealth of information available to doctors and patients, make families “active partners in care,” he noted.

## Stats

53

Invention Disclosures  
Received

7

Licenses and Options  
Agreements

52

International Patent  
Applications Filed

42

New U.S.  
Patents Filed

6

U.S. Patents  
Issued

10

International Patent  
Applications Issued

# List of Patents

## **U.S. Patent Number 7,972,796**

**Josep Dalmau, MD, PhD, David Lynch, MD, and Myrna R. Rosenfeld, MD**

Diagnosis of autoimmune encephalitic conditions is difficult. This patent covers methods of diagnosing or determining the cause of autoimmune encephalitis or certain epilepsies by testing for the presence of antibodies against the NR1 subunit of the NMDA receptor. One cause of autoimmune encephalitis is paraneoplastic syndrome that can be manifested by several types of malignant tumors.

## **U.S. Patent Number 7,994,147**

**Terri H. Finkel, MD, PhD and Jiyi Yin, PhD**

This patent involves a method of decreasing the number of HIV-1-infected cells through administration of an inhibitor of the HIV-Associated Life Preserver (HALP) protein. In this case, the inhibitors are anti-sense RNA molecules.

## **U.S. Patent Number 7,998,734**

**Katherine A. High, MD, HHMI, and Roland W. Herzog, PhD**

This is part of the patent family that protects the CHOP intellectual property surrounding use of adeno-associated virus vectors plus Factor IX to treat hemophilia.

## **U.S. Patent Number D646339**

**Meghan L. Marsac, PhD, and Anne Marie Vinsel**

This is a design patent that protects one of the versions of the doll that is part of the Cellie Cancer Coping Kit.

## **U.S. Patent Number 8,063,022**

**Katherine A. High, MD, HHMI, Paul A. Fields, Roland Herzog, PhD, and Valder R. Arruda, MD, PhD**

This patent is part of the patent family that provides methods of preventing formation of inhibitory antibodies in mammals undergoing gene therapy by administration of immunosuppressant drugs at the time of the administration of the therapeutic vector.

## **U.S. Patent Number 8,071,293**

**Katherine A. High, MD, HHMI, Fayaz R. Khazi, PhD, Kirk Chu, Luca Monaldini, PhD, MBA, Mustafa Yazicioglu, PhD, and Samuel Murphy**

Testing the levels of PRRG4 and PRRG2 molecules can detect predisposition to colon cancer and provide insights as to tumor presence and stage. Levels can also be used in tumors of the lung, liver, breast, pancreas, etc. This is a blood-based test and may be a reasonable substitute for current methods of detecting colon cancers.



# INVESTMENT

## New Facilities Underscore Commitment to Excellence

By providing investigators with cutting-edge technology and centralized resources, the two new core facilities established this fiscal year at The Children's Hospital of Philadelphia Research Institute underscore the Institute's longstanding commitment to medical innovation, and reinforce its reputation as one of the world's leading pediatric research institutions.

The new facilities are the DNA-sequencing facility BGI@CHOP, a groundbreaking collaboration with Beijing-based genomics institute BGI; and a biorepository, a library of samples and data. Through its more than a dozen "core" facilities, the Research Institute provides investigators with instrumentation and technical skill to service research programs.



"With the establishment of the BGI@CHOP and biorepository cores, investigators at CHOP will be empowered to conduct genomic research using state-of-the-art technologies on the full range of pediatric diseases that afflict our patients," noted [Tom Curran, PhD, FRS](#), deputy scientific director at CHOP Research. "This research will pave the way to provide personalized medicine for all children," Dr. Curran added.

BGI is a world leader in high-throughput sequencing (HTS), a next-generation method of DNA sequencing that reduces sequencing time and costs, and can produce multiple sequences simultaneously. In the near future, using technology like HTS, an entire human genome will be able to be sequenced in under a day, for less than \$1000. As part of the BGI@CHOP partnership, BGI has provided the Research Institute with a number of HTS sequencers. By focusing its efforts on larger scale genome and exome sequencing projects, the BGI@CHOP core complements the nucleic acid sequencing services provided by the already well-established Nucleic Acid and Protein core.

“BGI@CHOP combines the capabilities and experience of BGI, the world’s largest genomics institute, with our extensive biobanking efforts at CHOP and expertise in clinical phenotyping. The partnership will accelerate the discovery of genes underpinning both rare and common pediatric diseases using next-generation sequencing, and will allow researchers to harness the power of large, detailed data sets,” said [Hakon Hakonarson, MD, PhD](#), director of the [Center for Applied Genomics](#) and faculty advisor of BGI@CHOP.

Calling the establishment BGI@CHOP an “ideal collaboration,” [Philip Johnson, MD](#), chief scientific officer at Children’s Hospital, said the partnership with BGI is an “important first step” in changing the way we treat pediatric diseases.

The biorepository core, meanwhile, collects and organizes biospecimens from investigators across the Research Institute. The biorepository helps to anticipate investigators’ requests, avoid specimen duplication, preserve materials, and provides broad access to data and materials.

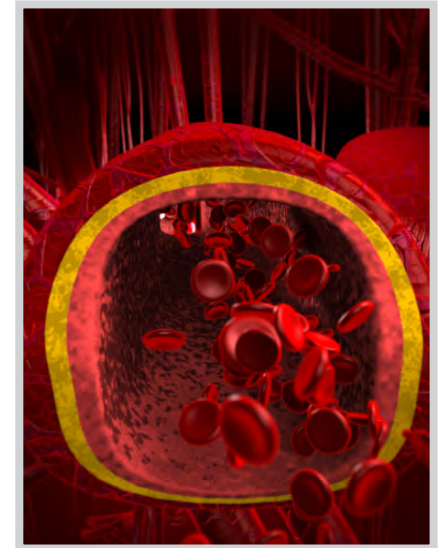
With a capacity for approximately 5 million samples, the biorepository is designed to house all of the biospecimens available at Children’s Hospital. While DNA samples may eventually make up the bulk of the biorepository’s holdings, with the addition of other freezers in the near future it will also be able to store fluids, RNA, tissue samples, and other biospecimens.

# Fortifying the Data Structure

Over the past decade, [Robert J. Levy, MD](#), the William J. Rashkind Endowed Chair in Pediatric Cardiology, and his team have investigated a new approach to stent-based therapy that uses magnetically guided nanoparticles to deliver drugs to diseased blood vessels.

The technology led to the Hospital's first startup company, called [Vascular Magnetism Inc.](#) (VMI), which was founded in 2010. And last year, [Devon Park Bioventures](#), of Wayne, Pa., invested \$7 million in the company to advance development of an innovative drug delivery system to treat peripheral artery disease, or PAD.

The drug delivery system at the heart of the company's work is called vascular magnetic intervention. The system combines biodegradable, magnetic drug-loaded particles with a magnetic targeting catheter and a device that creates a uniform magnetic field. The system, which Levy has tested in animals, guides the particles to the walls of arteries narrowed by PAD. At the disease site, the particles remain in place, slowly biodegrading and releasing the drug paclitaxel, which prevents re-obstruction of the artery.



Vascular magnetic intervention could fill an important unmet need in treating PAD, in which blocked arteries, primarily in the legs, exact a heavy toll in some 30 million older adults in North America and Europe. Diabetes patients and smokers are particularly affected by this painful, debilitating condition, which is responsible for the majority of amputations performed in this country.

Drug-eluting stents, currently used in heart disease, are less effective in PAD. Magnetic intervention could deliver more effective doses of drugs than the standard drug-eluting stents, and could be used to re-administer drugs as needed, Dr. Levy said.

As a new platform technology, vascular magnetic intervention could also be adapted to delivering other agents, such as therapeutic genes or cells, and has potential utility in treating heart conditions in children, Dr. Levy added. In the near future, Vascular Magnetism will complete preclinical development of its technology, and plans to conduct its first clinical trial in 2014, in adult patients.

# The Human Genome — Yep, There's an App for That!

It's been nearly a decade since scientists completed the [Human Genome Project](#) — a scientific marvel that, in its essence, provided the blueprint for the genetic make-up of humans. It was quite an accomplishment, given the 3 billion chemical base pairs that make up the human genome and the tens of thousands of genes in our DNA.

Now the results of the Human Genome Project are at your fingertips — literally.

With the iPad® application [Genome Wowser](#), investigators can quickly and efficiently navigate the vast information on the human genome. Developed by the [Center for Biomedical Informatics](#) (CBMi) at Children's Hospital, Genome Wowser provides for the convenient, intuitive, and highly mobile exploration of genomic information.

Anyone with an iPad® can download the free app from the iTunes App Store<sup>SM</sup> online. From there it's simple to traverse the entire human genome — just like planning a travel route on Google Maps.



A common use for the tool is to enter the name of a gene in Wowser's search box. The app finds the gene on one of the 23 human chromosomes, displaying an interactive image of its precise location among the genome's 3 billion base pairs.

Another valuable feature of the app are from investigators about the known or suspected biological functions, identified mutations and variants of each gene. Users can find information about neighboring genes or about epigenetics — how a gene's functions are modified when chemicals attach or separate from exposed sections of DNA. Touching the screen (by pinching and spreading one's fingers) allows a user to zoom in or out of the chromosome region.

Genome Wowser's name plays on the name of the data source that it emulates — the venerable UCSC Genome Browser, a website established in 2000 at the University of California Santa Cruz that serves as a popular worldwide data repository and genome exploration tool for human genome data. This information is constantly being updated as scientists uncover new gene data.

“With this app, researchers can now access genomic data from anywhere with minimal effort, and they can immediately explore the genome visually by using the intuitive screen touches and gestures that have made the iPad® platform so powerful,” says CBMi director [Peter White, PhD](#).

Genome Wowser supports viewing and querying multiple types of genomic data, so users can select the information that interests them and view the data concurrently in a stacked display for a selected region. In addition to text-based and graphical search options, the app provides zooming capabilities for its genome graphics, and drag-and-swipe navigation to move seamlessly across a chromosome.

Perhaps most importantly, Genome Wowser allows convenient portability of genomic data.

“With this app, I can hear about an interesting disease gene at a seminar and see its genomic and functional contexts in a few screen touches, including epigenetic and variation profiles, neighboring genes, and other critical associations you can’t determine from a simple web search,” says Dr. White. “Then, I can walk over to a colleague and share it with them, all in a few seconds.”

Since its launch, Genome Wowser has been consistently ranked as a top 10 “What’s Hot” medical app on iTunes, downloaded more than 7,000 times and updated more than 25,000 times from researchers in 79 countries. A second version of the app, released in August 2012, includes access to the genome sequences of more than three dozen non-human species, including dogs, cats, mice, chimpanzees, elephants, and 11 species of fruit fly, plus further improvements in the touch interface.

Genome Wowser, which now has its own [Facebook page](#), has been featured in numerous media outlets, including [Popular Science](#), [Forbes](#), and even on [MTV](#). It was also cited in a recent book by Eric Topol, MD, titled, “The Creative Destruction of Medicine: How the Digital Revolution Will Create Better Health Care.”



# New Program Exposes Students to Research

Advancing research at Children's Hospital doesn't just revolve around recruiting world-class investigators and providing the best possible facilities and resources to foster collaboration and accelerate discoveries.

Such discoveries — aimed at improving the health and well-being of children and contributing to the collective scientific knowledge — are always the end goal. But CHOP Research has never lost sight of the importance of not only the needs of those with established research programs, but also those who will soon be stepping into the research ranks to serve as the next generation of investigators.

CHOP Research has long been committed to finding, training, and mentoring the best and brightest students who have a passion for biomedical research, and whose future discoveries may alter the landscape of available therapies and treatments for children.



As part of this commitment, the Institute launched a new, highly competitive program in June 2012 aimed at giving undergraduate students valuable experience in biomedical science, and introducing the Institute as a premier setting to train and work.

[The CHOP Research Institute Summer Scholars Program](#) (CRISSP) aims to foster student interest in biomedical research as a career. While other institutions offer summer programs for undergraduates, CHOP's program is unique because of its pediatric research focus.

Applicants reviewed the profiles of faculty members participating in CRISSP and identified those whose research programs were best aligned with their interests. Fifteen undergraduate students from numerous institutions — including Princeton University, Swarthmore College, the University of Pennsylvania, Villanova University, and Franklin & Marshall College, among others — were ultimately selected from nearly 300 applicants to form the pilot CRISSP scholars group.

Each CRISSP scholar was paired with a faculty “host” for the duration of the 10-week program and completed an independent research project that they presented at the end of the summer. The projects among the students varied from specialized techniques in laboratories to learning how best to interact with patients and families in a clinic. All of the students reported enhanced research skills as a result of taking part in the program.

“Not only have I become comfortable with such techniques as plasmid transformation, tissue culture work, transfection, and Western immunoblotting, but I feel confident that I will be able to apply these skills to my own research in the future,” said Joana Petrescu of Villanova University, whose mentor was [Matt Weitzman, PhD](#).

And investigators who served as mentors heralded the success of the program.

“Our goal as faculty was to give an opportunity to bright and serious students to learn and carry out biomedical research but in fact, I believe we gave as much as we received from the CRISSP scholars,” says [Maurizio Pacifici, PhD](#). “What each was able to accomplish in 10 weeks is truly impressive, and their passion and long-term commitment are beyond doubt. The program is indeed inspiring the next generation of researchers.”

Fifteen students will again be selected as 2013 CRISSP scholars, with plans for expanding the program in 2014.

# Researcher's Gene Chip Proves Helpful Data Source

A DNA chip created by a Children's Hospital scientist has been used as an important research tool for geneticists analyzing genes that play a role in heart disease — as well as other complex, common metabolic diseases.

[Brendan Keating, PhD](#), of the [Center for Applied Genomics](#), conceived and developed the cardiovascular gene array to collect signals from gene variants that raise the risk of coronary artery disease (CAD) and heart attacks — myocardial infarctions (MI).



The DNA chip, also called an array, contains millions of micron-sized beads holding specific DNA probes for genetic variants of interest. When a test sample, such as DNA to be analyzed, is brought into contact with the chip, the sites at which test DNA binds to matching probes in the chip lets investigators identify specific DNA sequences occurring in the test sample.

An international consortium of scientists, led by [British Heart Foundation](#) researchers recently used Dr. Keating's chip to help discover five new gene variants associated with susceptibility to coronary heart disease. When added to existing heart-related genes, the findings may contribute eventually to helping identify individuals at high risk of developing CAD — the most common cause of premature death and disability worldwide.

At the time of the array design in 2006 there were few robust signals known for CAD and MI, and there was much controversy about the strength of some of the findings already published.

"This low-cost array allowed many research groups to pool appropriately collected CAD and MI cases and controls, and to meta-analyze these datasets together," says Dr. Keating, a co-author of the study by the international consortium. "This study reinforces the value of large-scale collaboration of international groups in the cardiovascular community to discover new genes that may become useful targets for therapy."

Dr. Keating's cardiovascular gene chip has also been used for other studies nearing completion by large consortiums, including those investigating type 2 diabetes, stroke, lipids and body mass index.

# LEADING THE WAY

## Researcher Honored for Mitochondrial Work

“Mitochondria” may sound vaguely familiar to anyone who learned about cell functions and structures in high school biology. These specialized subcellular structures play a crucial role, by extracting energy from food. Simply put, mitochondria are the tiny “power plants” within the cytoplasm of animal and plant cells.

Mitochondrial function plays essential roles across the human lifespan, in both rare and common childhood diseases, in adult-onset metabolic and degenerative diseases, and in cancer and aging. What high school students don’t learn is that [Douglas C. Wallace, PhD](#), director of the Center for Mitochondrial and Epigenomic Medicine at Children’s Hospital, is widely considered the founder of mitochondrial genetics in humans. Dr. Wallace has conducted ground-breaking research into the mysteries of mitochondria and its role in the development of disease.



The [Gruber Foundation](#) honored Wallace with the 2012 Genetics Prize on Nov. 9 at the annual meeting of the [American Society of Human Genetics](#) in San Francisco. The prestigious international award — a \$500,000 prize — recognizes Dr. Wallace’s pioneering scientific investigations of the wide-ranging role of mitochondria in the development of disease and as markers of human evolution. Based at Yale University, the Gruber Foundation’s Genetics Prize annually honors leading scientists for groundbreaking contributions to genetics research.

Dr. Wallace joined Children’s Hospital in 2010 to launch the Center for Mitochondrial and Epigenomic Medicine. The Center researches mitochondrial dysfunction in many clinical problems, and also focuses on preclinical studies relevant to developing therapies for mitochondrial diseases, for which few effective clinical treatments currently exist.

Dr. Wallace and his colleagues also have linked mutations in mitochondrial DNA to a broad range of human diseases, including types of blindness, deafness, metabolic disorders such as diabetes, neuropsychiatric conditions, and age-related diseases such as heart disease and cancer.

“The Children’s Hospital of Philadelphia Research Institute is privileged to number Douglas Wallace among our research leaders,” says Philip R. Johnson, MD, the Hospital’s chief scientific officer. “His commitment to the field of mitochondrial genetics and his pioneering nature embody the mission of research at CHOP, and his research and leadership are shaping the way we approach therapies for genetic disorders previously considered beyond treatment.”

Dr. Wallace first gained prominence in the scientific community in the 1970s as the leader of a research team at Stanford University that defined the genetics of mitochondrial DNA. This DNA, which resides within each mitochondrion, is distinct from nuclear DNA found inside chromosomes. Dr. Wallace’s group discovered that human mitochondrial DNA is inherited exclusively from the mother.

Building on his maternal inheritance discovery, Dr. Wallace identified the first inherited mitochondrial DNA disease, Leber’s hereditary optic neuropathy, which causes sudden blindness. He subsequently linked mitochondrial DNA mutations to a wide range of other clinical symptoms, including deafness, neuropsychiatric disorders, cardiac and muscle problems, and metabolic diseases such as diabetes. Significantly, Dr. Wallace also showed that mitochondrial DNA mutations accumulate in human tissue with age, and therefore play a role in age-related diseases, such as heart disease, cancer, and dementia.

Today, Dr. Wallace and his team are studying the potential role mitochondrial DNA plays in common diseases including autism, epilepsy, heart disease, diabetes and obesity, forms of blindness, Alzheimer and Parkinson disease, cancer, and aging.

Dr. Wallace holds the Michael and Charles Barnett Endowed Chair in Pediatric Mitochondrial Medicine at Children’s Hospital and also is a professor of Pathology and Laboratory Medicine in the [Perelman School of Medicine at the University of Pennsylvania](#). He is a member of the [National Academy of Sciences](#), the nation’s premier organization of leading researchers, as well as the Academy’s [Institute of Medicine](#), and is also a member of the [American Academy of Arts and Sciences](#).



# Cancer Expert Joins Elite Honorary Society

An expert in childhood brain cancer at CHOP is in the elite company of Secretary of State Hillary Clinton, musician Paul McCartney, playwright Neil Simon, musician and conductor Andre Previn, and actor-filmmakers Clint Eastwood and Mel Brooks as part of the 2012 class of the [American Academy of Arts and Sciences](#).

The Academy, one of the nation's most prestigious honorary societies as well as a leading center for independent policy research, elected [Tom Curran, PhD, FRS](#), to join the select and highly diverse group.

The 2012 class was inducted on Oct. 6, at the Academy's headquarters in Cambridge, Mass. Dr. Curran joins a select group of scholars, scientists, writers, artists, civic, corporate and philanthropic leaders that includes winners of the [National Medal of Science](#), the [Lasker Award](#), the Fields Medal, Pulitzer Prize awardees, and winners of MacArthur Fellowships, Oscar, Emmy, Grammy and Tony Awards, and Kennedy Center honors. Fellow scientific inductees to the 220-member class include cancer researcher Brian Druker and astronomer Debra Ann Fischer.



Dr. Curran's research targets the molecular biology of the brain's growth and development to find new treatments for childhood brain tumors. He has been awarded grants from the [National Cancer Institute](#) and the [National Institute of Neurological Disorders and Stroke](#), as well as from private foundations.

He currently is the deputy scientific director of The Children's Hospital of Philadelphia Research Institute and is a professor of Pathology and Laboratory Medicine and professor of Cell and Developmental Biology at the [Perelman School of Medicine at the University of Pennsylvania](#).

Born in Scotland, Dr. Curran earned his PhD from University College London. He was the founding chairman of the Department of Developmental Biology at St. Jude's Research Hospital before joining Children's Hospital in 2006. Dr. Curran is an elected member of the [Royal Society](#) in the United Kingdom, as well as the [Institute of Medicine](#) in the U.S. He is a former president of the [American Association of Cancer Research](#).

Founded in 1780 by John Adams, John Hancock, and other scholar-patriots, the Academy elects leading "thinkers and doers" from each generation. Past members have included George Washington, Benjamin Franklin, Daniel Webster, Ralph Waldo Emerson, Albert Einstein, and Winston Churchill.

The current membership includes more than 250 Nobel laureates and more than 60 Pulitzer Prize winners.

# Injury Investigator Testifies Before Congress

Traumatic brain injury (TBI) is the leading cause of injury-related death in children, resulting in more than 6,000 deaths and hospitalizing 60,000 children and adolescents each year. Every day, more than 125 children die or are hospitalized with TBIs that, sadly, are caused by largely preventable events, such as car crashes and sports accidents.

The cost to families and society is enormous. On average, the annual cost of children dying from a TBI is \$29 billion and \$53 billion for those who are hospitalized, according to [Flaura K. Winston, MD, PhD](#), director of the [Center for Injury Research and Prevention](#) (CIRP) at Children's Hospital, who recently presented findings to a Congressional committee.



Dr. Winston, along with several other TBI experts, testified March 19 before the [House Energy and Commerce Committee's Subcommittee on Health](#) on the state of TBI prevention, treatment, recovery, related research, and federal efforts to address TBI. Dr. Winston, whose pioneering research has focused on preventing child occupant and teen driver deaths and injuries in motor vehicle crashes, pointed out that the average medical cost for children hospitalized with TBI is \$40,000. "That's a lot of helmets," she said.

But despite advances in preventing and treating traumatic brain injury, "We're just beginning to understand the biomechanics of brains," continued Dr. Winston. While many pediatric brain injuries are preventable, the science behind treating those injuries that do occur is limited, because most research has focused on adults. "Children are not small adults," she emphasized.

In fact, recent developments have led researchers to question the traditional belief that children are more resilient than adults. Dr. Winston pointed out that researchers have seen a connection between an increase in disabilities and mild TBI in teenagers.

Noting that the “brain is the organ that is least able to heal,” Dr. Winston stressed the need for continued research to prevent and treat pediatric brain injuries. “New and improved child-focused strategies will only emerge from investments in basic and translational biomechanical, behavioral, and medical research to inform new safety products and their testing,” she said.

Federal funding has been “crucial” to brain injury research, said Dr. Winston. She called on the [National Institutes of Health](#) and other agencies to continue to invest in TBI research. “We need to build up our scientific foundation,” she said.

# Vaccine Advocate Elected to Institute of Medicine

An outspoken advocate of the science, safety, and value of childhood vaccinations, who has fought misconceptions and controversies associated with such vaccinations, has been elected to the [Institute of Medicine](#) (IOM) at the [National Academy of Sciences](#). Election to the IOM recognizes individuals who have demonstrated outstanding professional achievement and commitment to service.

[Paul Offit, MD](#), a leading researcher in the fields of virology and immunology for three decades, is the director of the [Vaccine Education Center](#) and chief of Infectious Diseases at Children's Hospital. The Vaccine Education Center was launched in October 2000 to provide accurate, comprehensive, and up-to-date information about vaccines and the diseases they prevent to parents and healthcare professionals. In addition, Dr. Offit holds the Maurice R. Hilleman Endowed Chair in Vaccinology and is a Professor of Pediatrics at the University of Pennsylvania's [Perelman School of Medicine](#).



The IOM announced the names of 65 new members and five foreign associates on October 17, 2011. Established in 1970 by the Academy of Natural Sciences, the IOM honors professional achievements in the health sciences and serves as a national resource for independent analysis and recommendations on issues related to medicine, biomedical sciences, and health.

A pediatrician specializing in infectious diseases, Dr. Offit dedicated 25 years to the development of [RotaTeq](#), one of two vaccines currently used to fight rotavirus, a disease that is the leading cause of severe, dehydrating diarrhea in infants and young children. RotaTeq is recommended for universal use in infants by the [Centers for Disease Control and Prevention](#) and has the capacity to save as many as 2,000 lives per day.

He is one of the most public faces of the scientific consensus that vaccines have no association with autism. Through his advocacy, Dr. Offit has successfully helped to educate parents about the health benefits of vaccinating their children.



Dr. Offit is the co-editor of the foremost vaccine text, *Vaccines*, and he has published more than 130 papers in medical and scientific journals. Dr. Offit is also the author or co-author of several books including: *Breaking the Antibiotic Habit: A Parent's Guide to Coughs, Colds, Ear Infections, and Sore Throats* (Wiley, 1999); *Autism's False Prophets* (Columbia University Press, 2008); *Deadly Choices: How the Anti-Vaccine Movement Threatens Us All* (Basic Books, 2011); and *Vaccines and Your Child: Separating Fact from Fiction* (Columbia University Press, 2011).

Dr. Offit is the eighth physician or researcher from Children's Hospital to be elected to the IOM. After receiving his bachelor of science degree from Tufts University, he earned a medical degree from the University of Maryland School of Medicine. Dr. Offit completed his residency at the Children's Hospital of Pittsburgh and his fellowship in Infectious Diseases at The Children's Hospital of Philadelphia.

# Retired Rotavirus Vaccine Co-Developer Passes

H Fred Clark, DVM, PhD, a retired research professor of Pediatrics at Children's Hospital and the [Perelman School of Medicine at the University of Pennsylvania](#), died on April 28. Dr. Clark, who helped develop a vaccine that has saved the lives of hundreds of thousands of children around the world, died of complications from heart and Parkinson's diseases after a protracted illness. He was 72.

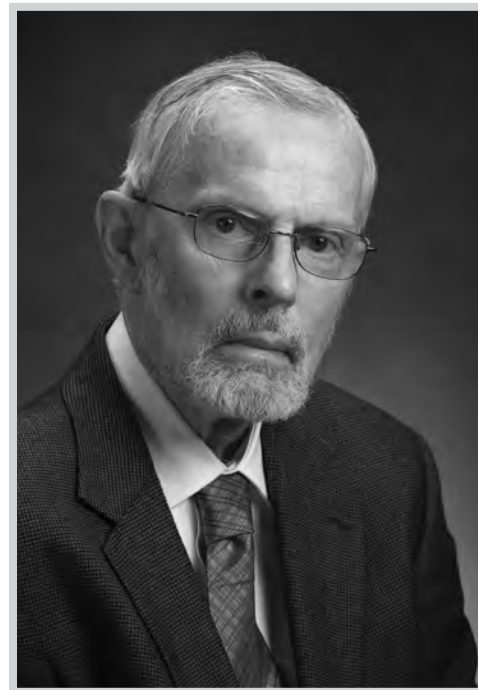
The Children's Hospital of Philadelphia recognized Dr. Clark in 2006 with its highest honor, the Gold Medal, which is awarded to those who have had a profound impact on children's health in the United States and internationally. The medal saluted Dr. Clark's achievements as a co-inventor of the rotavirus vaccine, RotaTeq, along with fellow honorees Dr. Stanley Plotkin and [Dr. Paul Offit](#). Rotavirus gastroenteritis is a common childhood illness that is the largest infectious-disease killer of infants and young children worldwide.

Dr. Clark earned a degree in veterinary medicine from Cornell University and a PhD in microbiology and immunology from the University of Buffalo. He studied and published extensively on both human and animal diseases, including rabies, tuberculosis, and hepatitis B, before joining Children's Hospital in 1979, and concentrating on rotavirus research. Dr. Clark was also an adjunct professor at the [Wistar Institute](#).

In addition to his research, Dr. Clark was a committed social activist. In the 1970s, he joined the Philadelphia chapter of Common Cause to advocate for a fair police complaint procedure, according to his wife, Karen. In the 1980s, Dr. Clark turned to peace activism to help prevent the proliferation of nuclear weapons.

Dr. Clark also devoted his time to providing care and support to Haitians who suffered from poverty and injustice. As members of the First United Methodist Church of Germantown, the Clarks participated in a program to help those in need in Fondwa, Haiti.

Dr. Clark is survived by his wife and their children.



# CHOP Cancer Expert Featured at Annual Meeting

Neuroblastoma, a cancer of the peripheral nervous system, accounts for 7 percent of all childhood cancers, but because it frequently appears in an aggressive form, it causes approximately 12 percent of all childhood cancer deaths. In high-risk forms of neuroblastoma, the cancer tends to return after initial treatment, usually with deadly results.

The [American Association for Cancer Research](#) (AACR) highlighted this form of childhood cancer in one of a series of videos it presented at its 2012 annual meeting. [John Maris, MD](#), director of the [Center for Childhood Cancer Research](#) at CHOP, [was featured in the video](#) describing how cancer research helped save the life of a young neuroblastoma survivor. Dr. Maris is the first pediatric expert to be included in the AACR's annual meeting videos.



The AACR annual meeting highlights the best and latest findings in all major areas of cancer research. Founded in 1907, the AACR is the oldest and largest scientific organization in the world focused on every aspect of high-quality, innovative cancer research. The AACR's mission is to prevent and cure cancer through research, education, communication, and collaboration. More than 16,000 attendees participated in the 2012 annual meeting held March 31 to April 4.

Children's Hospital has been using immunotherapy as part of standard treatment for children with high-risk neuroblastoma since 2009. Children from around the world have received this treatment at the Hospital, which has a long-established research and clinical program in neuroblastoma.

In 2010 Dr. Maris achieved what he called "a home run" in neuroblastoma research when he co-authored a study that examined the effects of immunotherapy — biologic agents that stimulate the body's immune system — on neuroblastoma. The study showed that patients receiving immunotherapy experienced a 20 percent improvement in two-year survival rates.

“That is about as much of a home run as you can expect in a large, randomized Phase III clinical trial, and something that overnight changed the way that we approach the disease, and has led to the implementation of immunotherapy as now as a standard way to treat neuroblastoma to improve survival by preventing relapse,” explained Dr. Maris.

The Center for Childhood Cancer Research was established in 2007 and, under Dr. Maris’s leadership, has quickly become a highly integrated basic, translational and clinical research environment dedicated to eradicating the pain and suffering caused by cancer in children.

# ADHD Expert Thomas Power Takes on New Roles

CHOP veteran child psychologist [Thomas Power, PhD](#), recently received a new appointment, as associate chief of Academic Affairs and chief psychologist in the Department of Child and Adolescent Psychiatry and Behavioral Science.

Dr. Power, who has been with CHOP since 1984, was instrumental in founding the Hospital's attention-deficit hyperactivity disorder (ADHD) program. [The Center for Management of ADHD](#) is now the region's largest and most comprehensive center for diagnosing and treating learning and attention problems in children. A progression of appointments and accolades for Dr. Power followed, including his being appointed the director of the ADHD Center in 1999, and receiving a CHOP Mentor Award in 2009.

In addition to investigating the assessment and treatment of children with ADHD, Dr. Power has been very involved in prevention research in urban schools and other primary care settings, and has led a number of projects evaluating family-school interventions for children with ADHD. He is currently an associate editor of the journal *School Mental Health*, and serves as the president of the Society for the Study of School Psychology.



In his new role in the Department of Child and Adolescent Psychiatry and Behavioral Science, Dr. Power will provide leadership for the development of academic programs for the department, while acting as a mentor for faculty and professional development. In his role as chief psychologist he will provide oversight for psychology training programs and for the professional practice of psychologists at Children's Hospital.

# President's Scholars Provide Vital Research Support

Financial support for research does not come solely through grants to investigators or funds budgeted by Children's Hospital. Philanthropy is a critical element that allows Hospital investigators to explore new and novel ways to improve the health and well-being of children everywhere.

For nearly 25 years, the Endowed Chair Program at Children's Hospital has provided valuable support to our physician-scientists who are pursuing innovative research ideas. Endowed chairs are named for an honoree and ensure that financial support for the chairholder's work will continue in perpetuity.



The Endowed Chair Program at Children's Hospital has expanded since its inception in 1988, and now includes more than 100 chairs. Eight new endowed chairs were established in FY12, among them three new President's Scholars chairs that were established from an anonymous \$12 million gift.

The President's Scholars Program represents a new initiative at Children's Hospital, one that aims to attract and retain the best and brightest scientific talent in pediatric medicine. President's Scholar chairs provide a high level of endowed annual support for the chairholder's work and help CHOP recruit and retain the very best minds in pediatric medicine.

The anonymous donor of the new President's Scholar chairs chose to name them in honor of several CHOP pioneers, including two of the Hospital's founding physicians — R.A.F. Penrose and T. Hewson Bache. Penrose specialized in diseases of women and children and served as Acting Assistant Surgeon in the Union Army during the Civil War. Later, he was instrumental in founding the American Gynecological Society. Bache, a great-great-grandson of Benjamin Franklin, served as an attending physician, manager and treasurer of Children's Hospital.

Stewart A. Anderson, MD, will be the first to hold the R.A.F. Penrose Endowed Chair in Pediatrics. Dr. Anderson studies the development and functioning of specific neurons implicated in a number of illnesses, including epilepsy and schizophrenia. He also provides care for patients with schizophrenia.



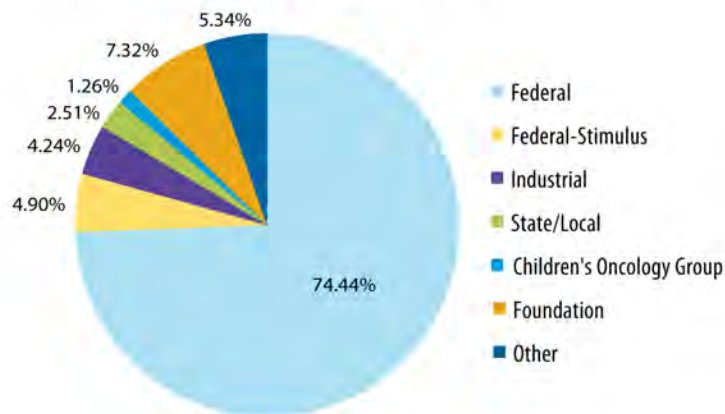
Robert W. Doms, MD, PhD, the Hospital's new Pathologist-in-Chief, will be the inaugural holder of the T. Hewson Bache Endowed Chair in Pediatrics. Dr. Doms is a nationally recognized HIV/AIDS researcher who has contributed to significant discoveries in the way the AIDS virus enters cells, as well as how the disease develops.

"To my way of thinking, success is directly tied to people and talent," said Chief Scientific Officer Philip R. Johnson, MD  
"This program will give CHOP a leg up in our drive to attract the best people, who will in turn fulfill our quest to turn scientific discovery into medical innovation."

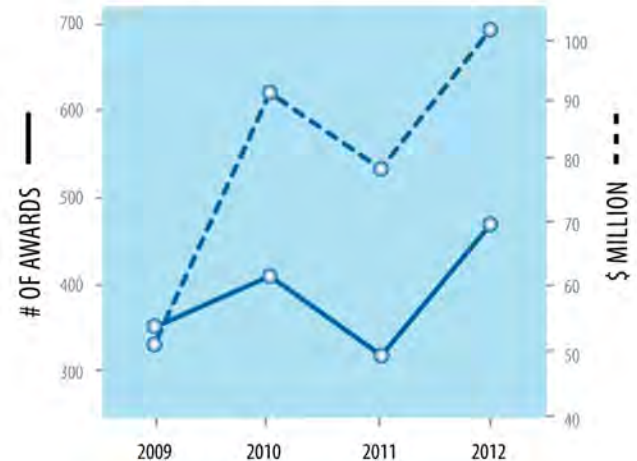
# FACTS & FIGURES

## By the Numbers

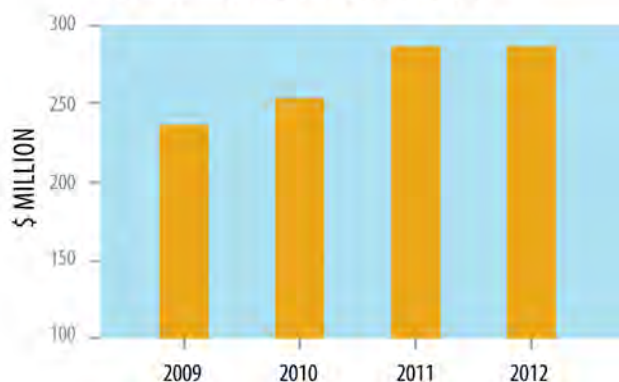
SOURCES OF  
GRANTS & CONTRACTS



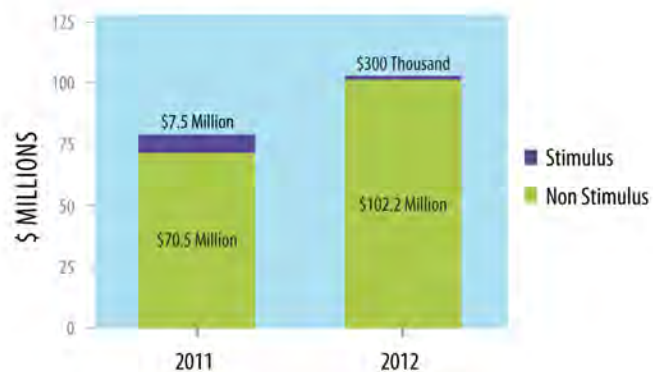
NEW AWARDS  
GRANTS/CONTRACTS



## TOTAL RESEARCH OPERATING EXPENSES



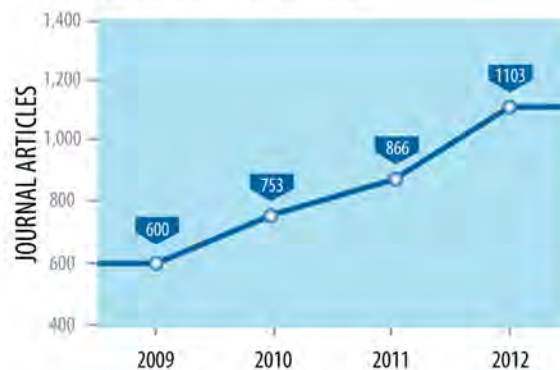
## NUMBER OF GRANTS STIMULUS/NON STIMULUS



## TOTAL RESEARCH SPACE



## PUBLICATIONS



# Who's Who

## *CHOP Research Institute Leadership*

Philip R. Johnson, MD  
Chief Scientific Officer  
Director, The Children's Hospital of  
Philadelphia Research Institute

Tom Curran, PhD, FRS  
Deputy Scientific Director

Mary Leonard, MD, MSCE  
Director, Office of Clinical and Translational Research

Mary Tomlinson  
Deputy Administrative Director  
Vice President, Research Administration

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Jeffrey Golden, MD  
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Tom Curran, PhD, FRS  
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Meg Jones

Jeffrey Kahn, Esq  
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Mary Tomlinson  
Bryan Wolf, MD, PhD

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Paul Offit, MD  
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Mortimer Poncz, MD  
Sue Souder  
Matthew N. VanKouwenberg  
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Robert McNair, Esq  
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Timothy Roberts, PhD  
Lisa Speicher, PhD  
J. Fraser Wright, PhD

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Nancy Spinner, PhD  
Lisa Speicher, PhD  
David Stokes, PhD  
Matthew Weitzman, PhD

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Wendy Williams, PhD, Vice Chair  
Melissa Alderfer, PhD  
Aditya Belwadi, PhD  
Kelly Dougherty, PhD  
Mary Field, PhD  
Michael Hogarty, MD  
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Gail Slap, MD  
Diana Stanescu, MD  
Natalie Steinel  
David Taylor, PhD  
Mary Anne Timmins  
Rita Valentino, PhD  
David Weber, MD  
Susan Weiss, PhD

## **Centers of Emphasis**

### **Center for Applied Genomics**

Director: Hakon Hakonarson, MD, PhD

### **Center for Autism Research**

Director: Robert Schultz, PhD

### **Center for Biomedical Informatics**

Director: Peter White, PhD

### **Center for Cellular and Molecular Therapeutics**

Director: Katherine High, MD, HHMI

### **Center for Childhood Cancer Research**

Director: John Maris, MD

### **Center for Developmental Biology**

Acting Director: Bryan Wolf, MD, PhD

### **Center for Injury Research and Prevention**

Directors: Flaura Winston, MD, PhD and  
Dennis Durbin, MD, MSCE

## **Center for Mitochondrial and Epigenomic Medicine**

Director: Douglas Wallace, PhD

### **Center for Pediatric Clinical Effectiveness**

Director: Ron Keren, MD, MPH

### **PolicyLab**

Director: David Rubin, MD, MSCE

## **Research Affinity Groups**

### **Fetal Biology and Therapy**

Group Leader: Alan Flake, MD

### **Genes, Genomes, and Pediatric Disease**

Group Leaders: John Maris, MD, and Nancy Spinner, PhD

### **Health and Behavior**

Group Leaders: Anne Kazak, PhD, and Joel Fein, MD, MPH

### **Metabolism, Nutrition, and Physical Development**

Group Leader: Babette Zemel, PhD

### **Mitochondria**

Group Leaders: Marni Falk, MD, and Neal Sondheimer, MD, PhD

### **Neuroscience**

Group Leader: Michael Robinson, PhD

### **Normal and Malignant Hematopoiesis**

Group Leader: Carolyn Felix, MD

### **Proteins**

Group Leader: Yair Argon, PhD

### **Vaccine and Immunotherapies**

Group Leader: Terri Finkel, MD, PhD

## **Endowed Chairs**

Leonard and Madlyn Abramson Endowed Chair in Pediatrics

Alan R. Cohen, MD

Leonard and Madlyn Abramson Endowed Chair in Pediatric Urology

Douglas A. Canning, MD

Frederick H. Allen Chair in Child Psychiatry  
Pending Appointment

Gisela and Dennis Alter Endowed Chair in Pediatric Neonatology  
Haralambos Ischiropoulos, PhD

David Lawrence Altschuler Endowed Chair in Genomics and  
Computational Biology  
Peter S. White, PhD

Mary D. Ames Endowed Chair in Child Advocacy  
Pending Appointment

Richard M. Armstrong Jr. Endowed Chair in Pediatric Orthopaedic  
Surgery John P. Dormans, MD

T. Hewson Bache Endowed Chair in Pediatrics  
Pending Appointment

Lester Baker Endowed Chair in Pediatric Diabetes  
Michael A. Levine, MD

Michael and Charles Barnett Endowed Chair in Pediatric Mitochondrial  
Medicine and Metabolic Diseases  
Douglas Wallace, PhD

James Battaglia Endowed Chair in Pediatric Pain Management  
Gordon Barr, PhD

William H. Bennett Professor of Pediatrics at the University of  
Pennsylvania Perelman School of Medicine  
Katherine High, MD

Fred and Suzanne Biesecker Endowed Chair in Pediatric Liver Disease  
David A. Piccoli, MD

Irma and Norman Braman Endowed Chair for Research in GI  
Motility Disorders  
Pending Appointment

Evelyn Willing Bromley Endowed Chair in Clinical Laboratories  
and Pathology  
Michael Bennett, PhD

Evelyn Willing Bromley Endowed Chair in Pathology and  
Clinical Laboratories  
Nancy B. Spinner, PhD, FACMG

Catherine D. Brown Endowed Chair in Pediatric Epilepsy  
Dennis Dlugos, MD

Patricia Borns Endowed Chair in Radiology Education – *NEW*  
Pending Appointment

Buck Family Endowed Chair in Hematology Research  
Monica Bessler, MD, PhD

Daniel B. Burke Endowed Chair for Diabetes Research  
Pending Appointment

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

Henry S. Cecil, MD Endowed Chair in Rehabilitative Medicine at  
Children's Seashore  
House Susan E. Levy, MD

Children's Hospital of Philadelphia Endowed Chair in Critical  
Care Medicine  
Vinay Nadkarni, MD

Children's Hospital of Philadelphia Endowed Chair in Pediatric  
Anesthesiology – *NEW*  
Pending Appointment

Children's Hospital of Philadelphia Endowed Chair in  
Pediatric Hematology  
Mortimer Poncz, MD

Children's Hospital of Philadelphia Endowed Chair in  
Pediatric Neurology  
Robert R. Clancy, MD

Children's Hospital of Philadelphia Endowed Chair in  
Pediatric Neuroradiology  
Robert Zimmerman, MD

Children's Hospital of Philadelphia Endowed Chair in  
Pediatric Neurosurgery  
Pending Appointment

Children's Hospital of Philadelphia Endowed Chair in  
Pediatric Orthopaedic Surgery – *NEW*  
Pending Appointment



Children's Hospital of Philadelphia Endowed Chair in Pediatric Otolaryngology and Pediatric Airway Disorders – *NEW*  
Pending Appointment

Children's Hospital of Philadelphia Endowed Chair in Pediatric Otolaryngology  
Ken Kazahaya, MD

Children's Hospital of Philadelphia Endowed Chair in the Prevention of Child Abuse and Neglect  
Cindy Christian, MD

Ruth M. and Tristram C. Colket Jr. Endowed Chair in Pediatric Surgery  
Alan W. Flake, MD

Ruth M. Colket Endowed Chair in Pediatric Nursing  
Barbara Medoff-Cooper, PhD, RN, FAAN

Colman Family Endowed Chair in Pediatric Inflammatory Bowel Disease  
Robert N. Baldassano, MD

David Cornfeld Endowed Chair in Pediatrics  
Richard Rutstein, MD

Jean Cortner Endowed Chair in Pediatric Gastroenterology  
Virginia A. Stallings, MD

Nicholas Crognale Endowed Chair in Pediatric Emergency Medicine  
Kathy M. Shaw, MD

Giulio D'Angio Endowed Chair in Neuroblastoma Research  
John Maris, MD

John J. Downes, MD Endowed Chair in Pediatric Anesthesiology and Critical Care Medicine  
William J. Greeley, MD, MBA

Mary Downs Endowed Chair in Pediatric Craniofacial Treatment and Research  
Pending Appointment

John W. Duckett, Jr. Endowed Chair in Pediatric Urology  
Stephen A. Zderic, MD

Audrey E. Evans Endowed Chair in Pediatric Oncology  
Garrett M. Brodeur, MD

Kenneth E. Fellows Endowed Chair in Radiology Quality and Patient Safety  
James S. Meyer, MD

Friends of Brian Endowed Chair in Pediatric Plastic and Reconstructive Surgery  
Pending Appointment

William T. Grant Endowed Chair in Child Development and Rehabilitation, University/CHOP Chair  
Marc Yudkoff, MD

Jane Fishman Grinberg Endowed Chair in Stem Cell Research  
Mitch Weiss, MD

Steven D. Handler Endowed Chair in Medical Ethics  
Christopher Feudtner, MD, PhD, MPH

Robert and Dolores Harrington Endowed Chair in Pediatric Cardiology  
Jack Rychik, MD

George Leib Harrison Endowed Chair in Fetal Therapy  
Mark Paul Johnson, MD

Werner and Gertrude Henle Endowed Chair  
Phyllis Dennery, MD

Maurice R. Hilleman Endowed Chair in Vaccinology  
Paul Offit, MD

Joseph Lee Hollander Endowed Chair in Pediatric Rheumatology, University/CHOP Chair  
Pending Appointment

John Westgate Hope Endowed Chair in Radiology Faculty Development – *NEW*  
Kassa Darge, MD, PhD

Orton P. Jackson Endowed Chair in Adolescent Medicine  
Carol Ford, MD

John H. and Hortense Cassell Jensen Endowed Chair in Pediatric Development and Teaching  
Stephen Ludwig, MD

Joshua Kahan Endowed Chair in Pediatric Leukemia  
Carolyn Felix, MD

C. Everett Koop Endowed Chair in Pediatric Surgery  
N. Scott Adzick, MD

Laffey-Connolly Endowed Chair in Pediatric Nephrology  
Susan Furth, MD

Dr. Bong S. Lee Endowed Chair in Pediatric Orthopaedics  
Maurizio Pacifici, PhD

Mabel E. Leslie Endowed Chair in Pediatric Ophthalmology  
Monte Mills, MD

Grace R. Loeb Endowed Chair in Neurosciences  
Brenda Banwell, MD

Stephen Ludwig Endowed Chair in Medical Education  
Lisa Zaoutis, MD

Suzi and Scott Lustgarten Endowed Chair for Clinical Care of  
GI Motility Disorders  
Pending Appointment

Jeffrey Modell Endowed Chair in Pediatric Immunology Research  
Pending Appointment

Robert Gerard Morse Endowed Chair in Pediatric Pulmonary Medicine  
Julian Allen, MD

Thomas Moshang Endowed Chair in Endocrinology  
Pending Appointment

E. Mortimer Newlin Endowed Chair in Pediatric Otolaryngology and  
Human Communication  
Ralph Wetmore, MD

Edmond F. Notebaert Endowed Chair in Pediatric Research  
Phillip R. Johnson, Jr. MD

Yetta Deitch Novotny Endowed Chair in Pediatric Oncology  
Beverly J. Lange, MD

Oberkircher Family Endowed Chair in Pediatric Radiology  
Timothy Roberts, PhD

Patrick S. Pasquariello Jr. Endowed Chair in General Pediatrics  
Louis M. Bell, MD

R.A.F. Penrose Endowed Chair in Pediatrics  
Pending Appointment

Stanley Plotkin Endowed Chair in Pediatric Infectious Diseases  
Jeffrey M. Bergelson, MD

William Potsic Endowed Chair in Pediatric Otolaryngology and  
Childhood Communication  
Pending Appointment

Peter Randall Endowed Chair in Plastic and Reconstructive Surgery  
Scott P. Bartlett, MD

Russell C. Raphaely Endowed Chair in Critical Care Medicine  
Robert A. Berg, MD

William J. Rashkind Endowed Chair in Pediatric Cardiology  
Robert J. Levy, MD

Regional Autism Center Endowed Chair  
Robert T. Schultz, PhD

Mildred L. Roeckle Endowed Chair at The Children's Hospital of  
Philadelphia  
Andrei Thomas-Tikhonenko, PhD

Lucy Balian Rorke-Adams Endowed Chair in Neuropathology  
Pending Appointment

Richard and Sheila Sanford Endowed Chair in Pediatric Oncology  
Rochelle Bagatell, MD

Hubert J.P. and Anne Faulkner Schoemaker Endowed Chair in  
Pediatric Neuro-oncology  
Peter C. Phillips, MD

Elias Schwartz, MD Endowed Chair in Hematology  
Kim Smith-Whitley, MD

Letitia B. and Alice Scott Endowed Chair in Human Genetics and  
Molecular Biology  
Elaine H. Zackai, MD

William Wikoff Smith Endowed Chair in Pediatric Genomic Research  
Bryan Wolf, MD, PhD

Howard M. Snyder III Endowed Chair in Pediatric Urology  
Pending Appointment

Daniel M. Tabas Endowed Chair in Pediatric Cardiothoracic Surgery  
J. William Gaynor, MD

Evelyn Rome Tabas Endowed Chair in Pediatric Cardiology  
Victoria L. Vetter, MD

Josephine J. and John M. Templeton Jr. Endowed Chair in  
Pediatric Trauma  
Michael L. Nance, MD, FAAP, FACS

Josephine J. Templeton Endowed Chair in Pediatric Anesthesiology  
Clinical Education  
Susan C. Nicolson, MD

Jennifer Terker Endowed Chair in Pediatric Cardiology  
Robert E. Shaddy, MD

Charles E.H. Upham Endowed Chair in Pediatric Medicine,  
University/CHOP Chair  
Beverly S. Emanuel, PhD

William L. Van Alen Endowed Chair in Pediatric Radiology  
Diego Jaramillo, MD

Frank R. Wallace Endowed Chair in Infectious Diseases  
Kathleen Sullivan, MD, PhD

Alice Langdon Warner Endowed Chair in Pediatric Cardiothoracic  
Surgery Thomas L. Spray, MD

Wawa Endowed Chair in International Adoption  
Susan Friedman, MD

Frank E. Weise III Endowed Chair in Pediatric Hematology  
Gerd Blobel, MD, PhD

Mai and Harry F. West Endowed Chair in Pediatric Research  
Thomas Curran, PhD

Evelyn and George Willing Endowed Chair in Pathology Research  
Janis Burkhardt, PhD

Arthur Vincent Meigs Endowed Chair in Pediatrics – *NEW*  
Pending Appointment

John M. Keating Endowed Chair in Pediatrics – *NEW*  
Pending Appointment

Louis Starr Endowed Chair in Pediatrics – *NEW*  
Pending Appointment

### ***Administrative Units***

**Clinical Trials Office**  
Lisa Speicher, PhD, Director

**Clinical and Translational Research**  
Mary Leonard, MD, Director

**Clinical Trials Financial Management**  
Mitch Appleson, Director

**Core Facilities Administration**  
Lisa MacDowell, Administrative Director

**Faculty Development**  
Virginia Stallings, MD, Director  
Mary Blitzer Field, Assistant Director

**Postdoctoral Affairs**  
Wendy Williams, PhD, Director  
Jodi Leckrone, Assistant Director

**Research Communications**  
Jennifer Long, Director

**Research Compliance and Regulatory Affairs**  
Deborah Barnard, Director  
Marsha Wallace, Assistant Director

**Research Finance**  
Steve Wiley, Director  
Luz Arrison, Assistant Director  
Bethann Kurek, Assistant Director

**Research Human Resources**  
Alexandra Jorgensen, Director

**Research Information Systems**  
Peter Witzleb, Director  
Robert Del Campo, Assistant Director

**Research Resources**

Howard Eck, Director

**Research Safety**

Raymond Colliton, Director

Denise Melvin, Assistant Director

**Responsible Research Training**

Wendy Williams, PhD, Director

Jodi Leckrone, Assistant Director

**Sponsored Projects and Research Business Management**

Sara Dubberly, Director

Brigid Czyszczin, Assistant Director

Robert Denight, Assistant Director

**Supply Chain**

Kim Gossin, Manager

**Technology Transfer**

Ellen Purpus, PhD, Director

Greg Baker, PhD, Associate Director

Debbie Schmidt, Associate Director

# Credits

Steven M. Altschuler, MD  
Chief Executive Officer

Madeline Bell  
President

Philip R. Johnson, MD  
Chief Scientific Officer  
Director, The Children's Hospital of  
Philadelphia Research Institute

Mary Tomlinson  
Deputy Administrative Director  
Vice President, Research Administration

Jennifer Long  
Director, Research Communications

Kevin O'Rourke  
Medical/Science Writer

Angela Knott  
Art Director

Melissa LaVigne  
Graphic Designer

Juliet Kilcoyne  
Production and Creative Services Coordinator

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Photographer

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# Links of Interest

[The Children's Hospital of Philadelphia Research Institute Website](#)

[The Children's Hospital of Philadelphia Website](#)

[The CHOP Research Institute Press Releases](#)

[\*Bench to Bedside\*, CHOP Research's Monthly News Publication](#)

[\*Discovery to Innovation\*, CHOP Research's Quarterly News Source](#)



[CHOP Research's Facebook Page](#)



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[The Children's Hospital of Philadelphia YouTube Channel](#)

[The Children's Hospital of Philadelphia Foundation Web Site](#)