

Bench to Bedside



RESEARCH AT THE CHILDREN'S HOSPITAL OF PHILADELPHIA

August 2012

Children's Hospital Joins Genetic Research Network

On December 10, 1962, in a speech given during the Nobel banquet, DNA pioneer James Watson said, "I feel that it is very important ... to remember that science does not stand by itself, but is the creation of very human people." By working in a "humane spirit," Dr. Watson continued, "we shall help insure that our science continues and that our civilization will prevail."

Nearly fifty years after Dr. Watson delivered his remarks, The Children's Hospital of Philadelphia Research Institute has joined a network of hospitals and research bodies working in such a spirit, combining their energies and expertise to translate genetic data into improved patient care.

The **Center for Applied Genomics** (CAG) was recently awarded roughly \$2.5 million over three years to mine electronic medical record data for future clinical use as part of the ongoing Electronic Medical Records and Genomics (eMERGE) Network. Director of CAG **Hakon Hakonarson, M.D., Ph.D.**, will act as the principle investigator of the project.

Funded and organized by the National Human Genome Research Institute (NHGRI), the **eMERGE initiative** is a consortium of U.S. medical institutions brought together to "develop, disseminate, and apply approaches to research that combine DNA biorepositories with electronic medical record (EMR) systems, for large-scale, high-throughput genetic research," according to NHGRI. Phase I of the consortium, which was first launched in 2007, ran through 2011.

The goal of the eMERGE network "is to connect genomic information to high quality data in electronic medical records during the clinical care of patients. This will help us identify the genetic contributions to disease," said NHGRI Director Eric D. Green, M.D., Ph.D. "We can then equip health care workers everywhere with the information and tools that they need to apply genomic knowledge to patient care."

Now in its second phase, in addition to including an expanded number of institutions, a key goal of eMERGE Phase II is to explore ways to best incorporate genetic information into EMR

data so it can be used in a clinical setting. CHOP is one of only three pediatric sites selected to take part in eMERGE Phase II, and one of only ten sites included overall. The eMERGE network is coordinated out of Vanderbilt University in Nashville, Tenn.

CAG inclusion in eMERGE is significant, as it currently has the largest pediatric biorepository — comprising over 40,000 children — and genome-wide association study (GWAS) genotyping facility in the world. Moreover, CAG's biorepository includes a large minority population, and important detail because only modest numbers of African American patients have been conducted in GWAS to date. Approximately 38 percent of the subjects in CAG's biorepository are African American, 6 percent Hispanic, and 4 percent are Asian.

Dr. Hakonarson and his team plan to use these patients' EMRs to mine "disease phenotypes and environmental exposure data in over 40 phenotypes" in order to establish a database for future clinical use. They will work to enable future sharing of genetic and genomic data with patients and, following that, establish guidelines for CAG's biorepository and databases. In so doing Dr. Hakonarson hopes to generate informed consent procedures that will foster clinical use of genomic data in concert with other eMERGE members.

CAG also plans to use this data to determine pharmacogenetic response profiles, working to determine biomarkers to inform clinical care. While the initial eMERGE funding will largely support disease susceptibility studies, Dr. Hakonarson hopes to extend his group's pharmacogenetic research through additional grants.

In addition to being selected to join eMERGE Phase II, CAG has taken on the role of pediatric leader in the network. The consortium is currently up and running, with members holding weekly teleconferences to discuss findings and strategies. Overall, being a part of the eMERGE network will "elevate the important information that genomic information delivers," Dr. Hakonarson said.

“Inconsistent and Unreliable”: Study Notes Heat Stroke Prevention Devices’ Faults

A recent study of products designed to prevent children from being forgotten in closed, parked vehicles — a scenario that can lead to heatstroke — found the devices to be “inconsistent and unreliable.” The study, which was released as the **hottest July in U.S. history** came to a close, raises questions about the effectiveness of available products to prevent heatstroke in children.

Sponsored by the National Highway Traffic Safety Administration (NHTSA), the study was led by Director of Engineering at the **Center for Injury Research and Prevention (CIRP)** **Kristy Arbogast, Ph.D.** After identifying a number of heat stroke prevention technologies, Dr. Arbogast and her team narrowed their list down to three devices, which they subjected to a series of tests.

According to a study performed by the NHTSA, heat stroke is the most common form of non traffic-related fatality suffered by children 14 and younger. Additionally, research by San Francisco State University’s Jan Null found that between 1998 and 2009 an estimated 494 children died as a result of being left in hot vehicles. Approximately half of these children were left inadvertently, the CIRP report notes.

“Leaving a child in a vehicle can happen to even the most vigilant parents when they are distracted and off their normal routine,” Dr. Arbogast noted.

Heat stroke — roughly defined as a body temperature of approximately 104° — occurs when the body cannot dissipate the heat it absorbs and produces when exposed to high temperatures, and can arise even in seemingly moderate temperatures. For example, on an 80° day the temperature inside of a closed, parked car can reach fatal levels in ten minutes, according to NHTSA.

The devices Dr. Arbogast and her team selected for testing were the Suddenly Safe Pressure Pad, the ChildMinder Smart Clip System, and the ChildMinder Smart Pad, all of which are available commercially on the market and are designed to prevent children from being left in locked cars by sensing the presence of a child in a child restraint. Before testing the devices with volunteers, the devices were put through a variety of “misuse scenarios” — such as determining whether cell phone

signals interfered with their operation — and accidents, like having apple juice spilled on them. Then, for each device, a typical commute was simulated using volunteers.

Dr. Arbogast and her team found that none of the devices were reliable across these various evaluations. The devices “often required adjusting of the position of the child within the child restraint,” and issues with signal interferences and an inability to operate “in the presence of liquids” were observed, according to the report. Moreover, in order to function correctly the devices require a number of active steps on the part of the caregiver, and the devices would not help in scenarios where the driver or parent intentionally leaves the child in the vehicle (such as to run an errand), the report says.

“The devices required considerable effort from the parent to ensure smooth operation and often that operation was not consistent,” Dr. Arbogast noted, adding “during the simulated commute with actual human child volunteers, some of the devices often turned on or off or beeped during the drive.”

Unfortunately, “at this time there is not a completely reliable engineering solution that can function as a stand-alone preventative measure to eliminate a child’s risk of stroke in a vehicle,” Dr. Arbogast noted. “As a result, education aimed at parents and caregivers and the implementation of behavior routines to prevent this from happening is critically important,” she concluded.

“Everything we know about child heat stroke in motor vehicles is that this can happen to anyone from any walk of life — and the majority of these cases are accidental tragedies that can strike even the most loving and conscientious parents,” said NHTSA Administrator David L. Strickland. “While many of these products are well intended, we cannot recommend parents and caregivers rely on technology to prevent these events from occurring.”

To learn more about the study and heat stroke prevention tips, see http://www.research.chop.edu/programs/injury/our_research/heat_stroke.php.

Share Your Story!

The success stories from CHOP Research are incredible. They have the power to connect investigators who can combine unique approaches for enhanced success, inspire donors to contribute the resources necessary to take a project to its next step, and provide hope for patients and families struggling with childhood disease. Sharing your story is essential so that we can spread the word about the amazing, groundbreaking work accomplished every day at CHOP Research.

We want to know your story, your news, your success. Many steps in the research process are newsworthy. Some of the things we are interested in include:

- trends in scientific research, and the ways we are taking a lead
- new grant awards
- forming a new study
- publishing a research paper
- honors and awards
- accepting a position of leadership
- completing a successful mentoring experience
- presentation of research results at national conferences
- new personnel joining your team

The Research Institute benefits from a spirit of collaboration that extends beyond the workbench. We encourage you to share not only your news, but also the news of your CHOP Research colleagues.

Please share your news with us by contacting Jennifer Long, director of Research Communications, at longj@email.chop.edu.

By Upholding Obamacare, Supreme Court Preserves Research Body

In a decision with wide-ranging consequences for the healthcare industry, politics, and the American public, in late June the U.S. Supreme Court ruled 5-4 to uphold most of the 2010 Patient Protection and Affordable Care Act. Among the decision's many repercussions was the ensured survival of an organization created by the Act to support comparative effectiveness research.

At issue before the Supreme Court was whether certain aspects of the **Affordable Care Act** (ACA) — also known as “Obamacare” by both its detractors and proponents — were legal under the Constitution. A variety of parties, including 26 states, challenged the law, arguing that Congress had overstepped its authority in drafting the legislation.

A key point of contention was the constitutionality of the so-called “individual mandate,” and whether without the revenue the mandate will create any parts of the law could survive. What is popularly called the “individual mandate” is in fact known as a “shared responsibility payment” in the Act. Under the law, any American who can afford to purchase health insurance but chooses not to will be subject to a penalty, to be paid with their tax return.

Indeed, it was the tax aspect of the penalty that led to Chief Justice John Roberts's **decision** to side with the four liberal justices in deciding to uphold the individual mandate. Though Roberts did not accept the government's argument that the penalty is authorized under Congress's power to regulate interstate commerce, he did agree that if it is viewed as a tax that Congress was in its power to impose the penalty.

As expected, politicians' reactions to the verdict were sharply divided. President Obama for his part celebrated the Supreme Court's decision, saying that the ruling “reaffirmed a fundamental principle that here in America — in the wealthiest nation on Earth — no illness or accident should lead to any family's financial ruin.”

Impact on Research

Though the ACA is largely concerned with how Americans receive insurance coverage, and how health services are paid for, the law also included a number of research-specific components, one of which was the creation of a new research body, the **Patient-Centered Outcomes Research Institute** (PCORI).

The PCORI, a nonprofit corporation, was established to fund and carry out comparative effectiveness research, in which therapies and treatment strategies are compared to provide clinicians with the evidence needed to provide the highest quality care. The PCORI recently announced its first group of award recipients, including **Katherine Bevens, Ph.D.**, a psychologist at The Children's Hospital of Philadelphia Research Institute.

Dr. Bevens was awarded more than \$650,000 for a project titled the “Development of Methods for Identifying Child and Parent Health Outcomes.” The goal of Dr. Bevens's project is to develop methods of incorporating the views of children into research that affects treatment decisions, and by so doing to work to standardize methods of taking patient perspectives account in comparative effectiveness research.

Dr. Bevens and her team plan to develop and test tools to help clinicians and researchers identify patient priorities. One of these tools will be a computer program that, by presenting a series of pairs of health outcomes to children or their caregivers, will generate a list of those outcomes patients value most.

“We are very proud to join PCORI in enhancing the patient-centeredness of the clinical research enterprise. Our work is one component of the broader movement toward empowering patients to make informed decisions about healthcare that best meets their personalized needs,” Dr. Bevens said.

Shalom! Injury Expert Flaura Winston Shares Expertise in Israel

Flaura Winston, M.D., Ph.D., is a very busy woman. In addition to her responsibilities as the director of the **Center for Injury Research and Prevention** (CIRP), Dr. Winston is a researcher, pediatrician, and public health advocate. For example, she recently testified before a House committee on **pediatric brain injury research**, making the case for continued support for injury prevention and treatment research.

So what better way for her to unwind than a whirlwind tour of Israel? Dr. Winston recently spent a week and a half in Israel, hopping from Tel Aviv to Jerusalem to Haifa, conferring with safety organizations, visiting hospitals, and meeting with government officials.

Dr. Winston was invited to Israel by **Beterem Safe Kids Israel** to attend a conference on child accident trauma. Located just outside Tel Aviv, Beterem works to “promote child safety and create a safer environment for children in Israel,” by partnering with public authorities and other partners to prevent child injury and reduce child injury and mortality rates, according to the organization's website. Dr. Winston also had a number of meetings with the **Or Yarok Association for Safer Driving in Israel**, which strives to minimize the number of injuries caused by traffic accidents.

In Jerusalem, prior to delivering a lecture on trauma-informed care at the **ALYN Hospital pediatric and adolescent rehabilitation center**, Dr. Winston held meetings with two government bodies, the Ministry of Health and the National Road Safety Authority, at the latter giving a talk on child passenger and teen driver safety. Later in the northern port city of Haifa she attended the Shmulik Katz Professional Conference on Child Trauma, where she delivered another two lectures, including one on creative evidence-based interventions in child safety.

Last, but certainly not least, she was featured in an article in the English-language daily newspaper **The Jerusalem Post**. In a wide-ranging interview touching on her life and accomplishments, Dr. Winston, who holds degrees in bioengineering and medicine, reflected on how her background as both an engineer and pediatrician has affected her work.

“My brain works like an engineer's because I think in terms of flow charts, but my interaction with people is more that of a pediatrician's. I love being with people, and I care the most about behavioral change so that they adopt a safety culture,” Dr. Winston said.

Donna McDonald-McGinn Honored for Chromosome Deletion Syndrome Work

Donna McDonald-McGinn, M.S., C.G.C., Associate Director of Clinical Genetics and Program Director of the “22q and You” Center at The Children’s Hospital of Philadelphia, received the Angelo DiGeorge Medal of Honor during the recent 8th Biennial International 22q11.2 Deletion Syndrome Conference. Ms. McDonald-McGinn, who began her career at CHOP in 1985, is only the second person to receive this highly esteemed honor.

The Angelo DiGeorge Medal recognizes outstanding contributions to understanding and/or treatment of chromosome 22q.11.2 deletion syndrome, a relatively common multisystem genetic disorder. The International 22q11.2 Deletion Syndrome Consortium established the award in 2010 to commemorate the life and work of the late Dr. DiGeorge, a pediatrician at St. Christopher’s Hospital for Children in Philadelphia who described aspects of the syndrome nearly 50 years ago.

While presenting the award to Ms. McDonald-McGinn, Dr. Peter Scambler of Great Ormond Street Hospital for Children in London praised her “singular breadth of achievement and dedication.” In particular, he singled out her recent work co-authoring an important scientific article that presents best practice recommendations for patients with this syndrome.

Chromosome 22q.11.2 deletion syndrome is a congenital disorder that occurs when a portion of the DNA on chromosome 22 is missing. It occurs in about 1 into 2,000 to 1 in 4,000 births, making it nearly as common as Down syndrome. The loss of genetic material has multiple effects, which may include abnormalities in the immune system, the heart, the endocrine system, facial features and cognitive abilities.

Over the years, researchers have found that deletions on this section of chromosome 22 are an underlying cause of various clinical diagnoses, known by such names as DiGeorge syndrome, velocardiofacial syndrome, and conotruncal anomaly face syndrome, among others.

The Children’s Hospital of Philadelphia has a long history of studying chromosome 22q11.2 deletion syndrome. Elaine Zackai, M.D., the medical director of the “22q and You” Center, recalls that she saw a child with DiGeorge syndrome in 1982, and realizing that the patient had more than the usual findings, suggested doing a chromosomal analysis. Her colleague, Beverly Emanuel, Ph.D., now chief of Human Genetics at Children’s Hospital, discovered the deletion in chromosome 22, and ultimately developed a diagnostic test.

Shortly after Children’s Hospital developed this laboratory test in 1992, Ms. McDonald-McGinn was instrumental in launching the Hospital’s “22q and You Center,” which draws patients from throughout the world. In addition to publishing more than 80 articles on this deletion syndrome, she has served as a tireless advocate for children and families, and has spent countless hours working on support and educational events related to this condition.

Donna McDonald-McGinn “has unique qualities: being very smart and savvy, having the ability to bring the right people together, and being the glue that holds them together ... she is innovative, ambitious, never stops until the job is done, and then goes the extra mile looking toward the future,” Dr. Zackai noted.

New Legislation Could Spur Pediatric Drug Development

In July, President Obama signed the [Food and Drug Administration Safety and Innovation Act](#) into law. Much of the law is focused on various fees, regulatory improvements, supply chain rules, and legislation addressing drug shortages, but also buried among the Act’s many pages of legalese is a pearl of hope for pediatric patients and their families.

Section 908 of the Act — originally a separate bill known as the Creating Hope Act of 2011 — is concerned with the “Rare Pediatric Disease Priority Review Voucher Program.” In short, the law creates a powerful incentive for drug companies to develop drugs to fight pediatric diseases: the ability to obtain a relatively speedy “priority” review of new treatments for rare childhood diseases. Companies that qualify for the review will receive action on their treatments within six months, much faster than that of standard reviews, which can take a year or more.

Patients with rare diseases are often woefully underserved, because the paucity of patients with any given disease makes it challenging for institutions and drug companies to recoup research investments. This problem is compounded for children with rare diseases, as fewer drugs are developed with children specifically in mind.

For example, a quick scan of [drugs approved by the FDA in 2012](#) shows that only three new drugs specifically tailored to children have been approved so far this year, and that two of the drugs treat common ailments (in this case, rhinitis and lice). The hope then, with this new legislation in place, is that pharmaceutical companies will have more incentive to develop pediatric treatments.

While the signing of the Act “marks an important moment for innovators across industry, research and clinical care settings, its most important beneficiaries are the patients and families that will be helped by the next generation of affordable medical products this bill will help to foster,” Secretary of Health and Human Services Kathleen Sebelius said.

In related news, the Children’s Hospital of Philadelphia Research Institute recently launched a venture with Beijing-based genomics leader BGI to [sequence 1,000 rare childhood diseases](#). The project’s aim is to accelerate the discovery of genetic variants underlying those rare diseases, by so doing laying the foundation for future treatments.

New Federal Conflict of Interest Regulations Going into Effect

On August 24, 2012, new federal regulations on financial conflicts of interest (“FCOI”) in PHS-funded research went into effect. The new, substantially revised regulations contain detailed requirements for the disclosure, review, and management of researchers’ conflicts and increase the obligations of both investigators and the institution with regard to potential conflicts of interests in research. The new regulations apply to all PHS-funded grants and contracts with a Notice of Award (“NOA”) issued on and after August 24, 2012 (including non-competing continuations).

To prepare for implementation of the new regulations:

- CHOP’s Conflicts of Interest Policy has been revised.
- CHOP’s electronic disclosure system (eCOI) will be expanded to include a research transaction disclosure form.
- All Investigators will be required to complete training on the new regulations and CHOP’s new policy

The newly revised CHOP COI Policy, with certain exceptions, applies the same requirements to all research, without regard to the source of funding.

What does this mean for you?

Disclosures: In addition to completing your annual disclosure in eCOI, if you are an Investigator who will have responsibility for the design, conduct, or reporting of any research submitted through eSPA or eIRB, you will be required to complete a research-specific supplement to your annual disclosure. Typically this means the Principal Investigator, Key Personnel and Other Significant Contributors will disclose. This electronic process

replaces the current paper forms. This new functionality within eCOI will be launched on August 23.

Training: All Investigators will be required to complete training on the new regulations and CHOP policy and retrain every four years. CHOP is using the Collaborative Institutional Training Initiative (CITI) for online training. The training is comprised of three modules taking approximately forty-five minutes to complete. User guides for accessing the training modules are attached. All Investigators on the research project are required to complete this training no later than August 24, 2012. This will ensure CHOP is able to accept the award and Investigators are able to use the funding. If the training requirements are not met, funds from any budget segment starting on or after August 24, 2012 will not be available for expenditure, and an alternate funding source must be used. For new awards, activity numbers will not be established.

For more information, you may visit the Conflict of Interest intranet page found [here](#), or contact the Office of Compliance and Privacy at 267-426-6044 or COI@email.chop.edu.

COI training module: <https://www.citiprogram.org>

For first time CITI users, visit the User guide at <https://intranet.research.chop.edu/download/attachments/1736718/New+User+CITI++Guide.pdf>

For existing CITI users, the User guide is available at <https://intranet.research.chop.edu/download/attachments/1736718/Registered+User+CITI+Guide.pdf>

Discover CHOP Research Video Now Available

The Office of Responsible Research Training is pleased to announce Discover The Children’s Hospital of Philadelphia Research Institute (Discover the CHOP Research Institute) an 8-minute highly visual, Web-based video designed to promote research at CHOP, recruit investigators and showcase the Institute to potential research donors.

Discover the CHOP Research Institute is an updated and abbreviated version of “Discover Stokes” originally launched in 2007.

All members of the CHOP community are encouraged to take a few moments to view this inspiring video at <http://www.research.chop.edu/discover/>.

Questions about the video can be directed to researchtraining@email.chop.edu.

HAVE NEWS?

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

Read this and previous versions of *Bench to Bedside*
online at <http://www.research.chop.edu/publications/>.

 The Children’s Hospital of Philadelphia®

RESEARCH INSTITUTE

34th Street and Civic Center Boulevard, Philadelphia, PA 19104-4399
1-800 TRY CHOP www.chop.edu

Produced by The Children’s Hospital of Philadelphia Research Institute.
© 2012 by The Children’s Hospital of Philadelphia, All Rights Reserved.