Research Horizons

A PUBLICATION OF THE CINCINNATI CHILDREN'S RESEARCH FOUNDATION
FALL 2013

Biomedical Informatics

Medicine's Next Evolution

Cincinnati Children's®

From the Director

Dear Colleagues,

I recently announced my decision to relinquish my positions as Chair of Pediatrics, Director of the Cincinnati Children's Research Foundation (CCRF), and Chief Medical Officer for Cincinnati Children's Hospital Medical Center.

I look forward to continuing and, actually, having more time to pursue clinical and research activities as a member of the cardiology and Heart Institute faculty. I will also continue my involvement in overseeing completion of our new Clinical Research Tower, which will open in 2015.

I leave these roles confident that the Research Foundation is stronger than ever. Even with poorly-considered federal cuts, our external research funding this past year topped $173 million. We continue as a top three NIH-funded pediatric research institution. Our faculty publishes extensively in leading journals, holds leadership positions in their professional societies, and is highly sought after to present at national and international conferences.

I am especially proud of the faculty we have brought to CCRF during my nearly seven years here. In that time, we recruited 17 division directors among the 330 new faculty. Among them are many of the nation's most accomplished scientists as well as many promising young investigators, rising stars in their disciplines who will undoubtedly be at the forefront of tomorrow's seminal discoveries. Together, we have trained and educated hundreds of students, residents and fellows who will become future leaders in pediatrics and science.

We have created entirely new areas of research, including the Division of Reproductive Sciences and the Center for the Prevention of Prematurity, led respectively by S.K. Dey and Louis Muglia. We further enhanced the Center for Technology Commercialization, which helps our scientists turn promising discoveries into transformative treatments.

We formed Institutes in Perinatal, Heart, and Cancer and Blood Diseases, where close collaborations have broken down the usual barriers between basic research and clinical experts, resulting in breakthrough findings.

We have forged strong training, research and clinical partnerships around the globe – in Europe, Israel, India, Africa, and China.

The Clinical Sciences Building, now under construction, will focus on patient-oriented research and is testament to our continued growth and discoveries that will improve outcomes and health for children worldwide.

I am honored to have been part of these accomplishments, and I remain enthusiastic about what the future holds for Cincinnati Children's. These outcomes are the hard and smart work of the CCRF faculty and staff. My pride and joy have been to foster and assist the abundant spirit of intellectual curiosity, outstanding creativity, dedication to superlative care, and untiring pursuit of excellence that fuels this work. It has been a joy and privilege to serve Cincinnati Children's and the CCRF. Thank you all for making this the world's best children's hospital and research institute.

The medical center is now conducting a search for the new CCRF Director. I am confident that this individual will lead us to achieve even greater discoveries, enhanced learning, and better care. But I will still be around to bug and "encourage" all of you to do so, as well.

Peace,

Research Horizons

FALL 2013

Craig Erickson, MD, **Psychiatry,** received a three-year grant of $1 million from the John Merck Fund to study "Acamprosate in Fragile X Syndrome."

David Franz, MD, **Neurology,** received $1.1 million from Novartis Pharmaceuticals for a five-year efficacy and safety study of everolimus in patients with tuberous sclerosis complex (TSC) who have refractory partial-onset seizures.

Xi Jason Jiang, PhD, **Infectious Diseases,** was awarded a five-year, $910,007 grant by the US Department of Agriculture to study "Universal Flu Vaccine by a Norovirus P Particle Platform" with the University of Cincinnati.

Tatiana Kalin, MD, PhD, **Neonatology and Pulmonary Biology,** will use a four-year grant of $870,000 from the American Cancer Society to study "Transcriptional regulation of cancer progression and metastasis by FoxM1."

Raphael Kopan, PhD, will study "Assessing the Therapeutic Window for Future Anti-Notch Dimerization Agents" with a $1.6 million, five-year grant from the National Cancer Institute.

Punam Malik, MD, **Experimental Hematology,** received a $1.8 million grant over five years from the National Heart, Lung and Blood Institute to develop a "Cincinnati Center of Excellence in Hemoglobinopathies Research."

Keith Marsolo, PhD, **Anderson Center for Health Systems Excellence,** will develop a "CMS Partnership for Patients Initiative" with the help of a three-year, $3.3 million grant from the Department of Health and Human Services.

Louis Muglia, MD, PhD, will use $1 million to pursue research into prematurity over the next five years as part of the March of Dimes Prematurity Research Collaborative.

Avani Modi, PhD, **Adherence Psychology,** received a five-year, $3.6 million grant from the National Institute for Child Health and Human Development to study "Supporting Treatment Adherence Regimens in Pediatric Epilepsy."

Jeffrey Whitsett, MD, **Neonatology and Pulmonary Biology,** will use $2.6 million awarded by the National Heart, Lung and Blood Institute over five years to pursue "Transcriptional Programming of Asthma-Related Pathology."

Gurjit (Neeru) Khurana Hershey, MD, PhD, **Director, Division of Asthma Research,** has been accepted into the Association of Medical School Pediatric Department Chairs' (AMSPDC) Pediatric Leadership Development Program cohort for 2014-15. The year-long fellowship program, which begins in February 2014, is designed to help develop the next generation of pediatric chairs in North America.

Erna Olafson, PhD, PsyD, **Mayerson Center for Safe and Healthy Children,** was recognized by the American Professional Society on the Abuse of Children (APSAC) for outstanding service and commitment within the field of child maltreatment during the Society's Annual Colloquium this past June.

Research Horizons

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Pediatric Leaders Appeal for Continued Funding

On July 15, 2013, leaders of pediatric research institutions across the country sent a letter to members of Congress, asking that they restore National Institutes of Health (NIH) funding for pediatric research. The Director of our Research Foundation, Arnold Strauss, MD, was among them. Following is an excerpted version of the letter.

Dear Members of the U.S. Congress and U.S. Senate:

We write in opposition to sequestration and to strongly urge restoration of funding cut by it. ...As you work on the FY 2014 budget, seek restoration to FY 2012 pre-sequestration levels. NIH-funded pediatric researchers are working every day to find cures for children with devastating illnesses such as cancer, to develop interventions that promote health and longevity for children with lifelong chronic illnesses such as cystic fibrosis, and to find the scientific keys to preventing conditions that appear on the rise and worry us all, such as autism.

Children make up 30% of the US population, yet pediatric research represents only 6% of NIH directed dollars. If you are the parent, grandparent, teacher or friend of a child with … any one of the hundreds of pediatric diseases or illnesses currently under investigation and funded by the NIH, the day-to-day urgency of this research is high... It is often truly a matter of your child's life or death.

Largely due to the disproportionately low amount of funding for pediatric research, a significant amount of what pediatricians are required to practice is based on information derived only from studies in adults. It is a hazardous reality that medications ranging from pediatric antibiotics to anti-depressants are in fact frequently just adult drugs dosed-down for children.

The sequestration cutbacks threaten to reduce children's access to currently available clinical trials, and stalled advancements in pediatric research threaten delays in the development of new treatments and therapies to cure diseases in children and youth. Recent and emerging discoveries related to early predictors of childhood disease and risk for adult onset of certain diseases would go underutilized because funding for critical research to validate and translate for clinical use would be cut.

NIH cuts under sequestration are indiscriminate and arbitrary. Scientific research can't be switched on and off on a dime and continue to yield results. It requires predictable and sustained support that isn't possible when drastic, across-the-board cuts like sequestration are imposed… In-progress research will be disrupted, delaying the achievement of new medical breakthroughs.

Pediatric research is the path toward preventing chronic adult disease. Please restore NIH funding cuts that will delay discovery of urgently needed cures to childhood diseases.

Targeting Immune System Enzyme Kills Myelodysplastic Cells

Scientists at Cincinnati Children's have successfully targeted a malfunctioning immune system enzyme and killed diseased cells from patients with myelodysplastic syndromes (MDS), a group of blood disorders in which the bone marrow does not produce sufficient healthy blood cells.

Researchers reported July 8 in ***Cancer Cell*** that the immune system enzyme IRAK1 (Interleukin Receptor Associated Kinase-1) is over-expressed and hyper-activated in about 25 percent of MDS cells. The researchers tested the effect of blocking IRAK1 using a small-molecule inhibitor developed initially as a treatment for autoimmune disease and chronic inflammation.

"Not only does our research implicate errant immune system signaling in MDS cells, it strongly indicates that inhibiting the function of this hijacked immune pathway may become an effective treatment option for MDS," says Daniel Starczynowski, PhD, Division of Experimental Hematology and Cancer Biology, who led the study.

Both genetic and pharmacologic inhibition of IRAK1 slowed the progression of human MDS cells and in mouse models of the disease. Inhibiting IRAK1 had no effect on normal human blood cells, showing it selectively targets MDS cells.

MDS is a group of syndromes in which a person's blood stem cells do not mature into healthy red or white blood cells. Instead, they die off in the bone marrow or blood, leaving an insufficient number of healthy cells in the body. This can cause infections, anemia, bleeding disorders or acute myeloid leukemia (AML).

The disorders affect children but are more common in people over the age of 60. So far, the only cure for MDS is bone marrow transplant.

Starczynowski cautions that successful laboratory tests do not necessarily translate into effective treatments. And because IRAK1 is currently thought to be over-expressed in a subset of MDS patients, any drugs targeting the enzyme would in theory benefit only that group. Nevertheless, he is optimistic and his team will continue their studies.

"There is an urgent need to develop new targeted therapies that can eliminate MDS-initiating clone cells and provide a durable therapeutic response."

Image from a study published July 8 in *Cancer Cell* shows myelodysplastic cells accumulating in the bone marrow of a mouse model of myelodysplastic syndromes (MDS). MDS can cause infections, anemia, bleeding disorders or acute myeloid leukemia.

Taking the Pressure Off:
Team effort cuts incidence of pressure ulcers in half

When a study revealed that more than 10 percent of children in our intensive care units experienced pressure ulcers, Cincinnati Children's took action.

The hospital formed a quality improvement (QI) collaborative leadership team and implemented a QI "bundle" of solutions. The goal, and the result, was to reduce pressure ulcers among children hospitalized in the pediatric intensive care units by 50 percent within one year. The study, led by Marty Visscher, PhD (*below right),* Director of the Skin Sciences Program, was published July 23 in *Pediatrics*.

The team found that the causes of pressure ulcers in children are different than in adults. Although most pressure ulcers in adults occur due to pressure on bony parts of the body, pressure ulcers in children occur largely because of ill-fitting medical devices that are not designed for children, but must be adapted to them.

Those devices include facemasks used for mechanical ventilation, tracheostomy tubes, endotracheal tubes and orthopedic casts. Use of these devices is higher in critically ill patients, causing increased infection, pain and prolonged hospitalization.

Successful interventions included thorough staff training, daily head-to-toe skin assessments, teaching parents about skin care and identifying "skin champions" on each unit, nurses with a particular interest in skin and wound care who serve as resources to staff on the unit.

The study was co-authored by Sundeep Keswani, MD (*below left*), Director of the Pediatric Advanced Wound and Skin Service, which provides wound treatment throughout the medical center and conducts research on skin and wound healing.

Lactation Problems Could Link to Insulin Levels

Insulin could be the reason why many mothers have difficulty making enough milk to breastfeed, says a study by scientists at Cincinnati Children's and the University of California - Davis.

Published in July in *PLOS ONE* online, the study describes how the human mammary gland becomes sensitive to insulin during lactation and how specific genes are switched on in the gland during lactation.

The researchers used RNA sequencing to reveal a detailed blueprint for making milk in the human mammary gland, according to Laurie Nommsen-Rivers, PhD, a scientist in the Division of Neonatology and Pulmonary Biology at Cincinnati Children's and corresponding author of the study. Lead author was Danielle Lemay, PhD, of the University of California – Davis Research Center.

In earlier research, Nommsen-Rivers had shown that producing breast milk is more difficult for mothers who have markers of poor glucose metabolism – being overweight, of an advanced maternal age, or having a large birthweight baby. This suggested a role for insulin in the mammary gland. The new findings show how the mammary gland becomes sensitive to insulin during lactation.

"This new study shows a dramatic switching-on of the insulin receptor and its downstream signals during the breast's transition to a biofactory that manufactures massive amounts of proteins, fats and carbohydrates for nourishing the newborn baby," says Nommsen-Rivers.

"Considering that 20 percent of women between 20 and 44 are pre-diabetic, it's conceivable that up to 20 percent of new mothers in the United States are at risk for low milk supply due to insulin dysregulation."

Capturing mammary gland RNA in samples of human breast milk, the researchers created a library of genes expressed in the mammary gland based on RNA-sequencing technology. They discovered an orchestrated switching-on and -off of various genes as the mammary gland transitioned from secreting immunity-boosting colostrum to the copious production of milk in mature lactation.

Specifically, the PTPRF gene, known to suppress intracellular signals that are usually triggered by insulin binding to its receptor on the cell surface, may serve as a biomarker linking insulin resistance with insufficient milk supply. These results lay the foundation for future research focused on the physiological contributors to mothers' difficulties with milk supply.

The scientists plan a phase I/II clinical trial with a drug used to control blood sugar in type 2 diabetes to determine whether it improves insulin action in the mammary gland and increases milk supply.

Innovation Fund Picks Promising Projects

Six research projects that show promise for commercial development have been selected to share $500,000 from the Innovation Fund at Cincinnati Children's and $100,000 from the Greater Cincinnati Foundation.

The fund – now in its second year – provides early-stage bridge funding to further develop discoveries into medically and commercially viable products ready for outside investment.

"The Innovation Fund allows the medical center to select promising projects developed by its researchers and accelerate their bench-to-bedside transition and entry to the patient care market," says Niki Robinson, PhD, Assistant Vice President of the Center for Technology Commercialization (CTC). "This funding provides crucial financial support at a critical time to projects that otherwise might not continue their development."

THE FUNDED PROJECTS

Ted Denson, MD, Gastroenterology
A diagnostic technology that distinguishes between Crohn's disease and ulcerative colitis.

Punam Malik, MD, Experimental Hematology and Cancer Biology
An improved γ-globin gene developed for a prospective Phase I/II clinical trial of gene therapy for sickle cell disease.

Charles Dumoulin, PhD, Radiology
Neonatal MRI scanner for premature babies too fragile to transport beyond the NICU.

William Hardie, MD, Pulmonary Medicine
A prospective oral therapy that would target a specific molecule (P70S6K) to reverse pulmonary fibrosis.

Senthil Sadhasivam, MD, MPH, Anesthesia
A rapid point-of-care genetic test and decision support tool that allows physicians to precisely tailor the use of opioids for pain management.

Hector Wong, MD, Division of Critical Care Medicine
A diagnostic biomarker (IL-27) for rapid and early identification of sepsis in patients.

Finding Could Prevent Central Line Infection

In a study published in July online in *The Journal of Infectious Diseases*, Margaret Hostetter, MD, and a team of researchers revealed that they have found an agent that could potentially prevent the *Candida* infections that often afflict hospitalized patients on central lines.

Earlier research by Hostetter's team showed that the heparin fed through central lines to prevent clotting binds with the *Candida albicans* yeast that lives on and in all of us. *Candida* uses the binding to elude the body's immune response and to form biofilms – communities of microorganisms that grow on the inside surface of the catheters. Biofilms are the first step in bloodstream infections with the yeast.

Hostetter and her team developed an antibody that prevents *Candida albicans* from binding with heparin and thereby stops biofilm formation in a rat model of catheter-associated infection.

"Understanding how the medications in catheters facilitate biofilm formation by microbes can lead to new strategies for prevention of line infections,"says Hostetter.

Her collaborators on the study included researchers from Duke University Medical Center, the University of Cincinnati, and the University of Wisconsin. When the antibody is modified to be compatible with humans, clinical trials of the treatment can begin in humans.

‘Back to Basics’ for New Immuno-biology Director

Harinder Singh, PhD, joins Cincinnati Children’s this fall as Director of Immunobiology. Singh is an expert on regulatory proteins that enable self-renewing pluripotent hematopoietic stem cells to generate various cells of the immune system. His laboratory focuses on genetic and molecular analyses of transcription factors that regulate the differentiation of immune cells.

Before coming to Cincinnati Children’s, Singh worked in the Department of Discovery Immunology at Genentech in San Francisco, where he oversaw drug discovery and development projects in Immunology. Prior to that, he was a member of the faculty of the University of Chicago as Louis Block Professor of Molecular Genetics and Cell Biology, Investigator with the Howard Hughes Medical Institute, and Chair of the Committee on Immunology.

Singh says he accepted the appointment at Cincinnati Children’s in large part because he was interested in returning to the front end of the biomedical enterprise with a focus on the analysis of human diseases, particularly those that afflict children, and in developing new therapeutic approaches for them.

“Deep down, I’m really a basic scientist. Curiosity about biological systems and processes in health and disease stimulates my thinking,” Singh says. “I’ve seen and experienced the whole biomedical spectrum of basic, translational and clinical research and I believe that the fundamental research needed to enable generation of transforming new drugs is best done in the academic sphere.”

One of Singh’s goals is to build a Center for Systems Immunology that will harness approaches from Systems and Synthetic Biology to better understand the abnormal functioning of human immune cells in inflammatory and autoimmune diseases and eventually to use molecularly engineered immune cells for therapeutic purposes.

Singh obtained his PhD from Northwestern University in 1984, working with Lawrence Dumas in Biochemistry and Molecular Biology. He was a Jane Coffin Childs postdoctoral fellow with Phillip Sharp at the Massachusetts Institute of Technology (MIT) from 1984 to 1988. Singh’s interests in Molecular and Developmental Immunology were spawned by research collaborations with David Baltimore’s laboratory, while at MIT.

Singh served as editor of *Molecular and Cellular Biology* from 1997-2007. He has been a member of the Board of Scientific Counselors for the National Cancer Institute (2002-2007) and an advisor to the California Institute for Regenerative Medicine (2006-2009).

Anti-Rejection Drug Also Reduces Seizures

Everolimus shows new promise for patients with tuberous sclerosis complex

A drug originally developed to prevent the rejection of transplanted organs has dramatically reduced seizures in patients with tuberous sclerosis complex (TSC). A genetic disease characterized by benign tumors on multiple organ systems, TSC is estimated to affect more than 1 million people worldwide.

The study is the latest to demonstrate the effectiveness of everolimus for TSC patients. Previous studies at Cincinnati Children’s showed that the drug reduced tumors in the brain and kidneys.

The newest study, led by Darcy Krueger, MD, PhD, a pediatric neurologist and researcher at Cincinnati Children’s, has been published online in the *Annals of Neurology*. Krueger conducted the research in collaboration with a team at Texas Children’s Hospital in Houston.

The study included 20 patients, median age of 8 years, who were treated with everolimus. Half were enrolled at Cincinnati Children’s and half at Texas Children’s Hospital.

Everolimus reduced seizure frequency by at least 50 percent in 12 of the 20 children in the study. The drug also reduced seizures in 17 of the 20 children by a median rate of 73 percent. Four were free of seizures and seven had at least a 90 percent reduction in seizure frequency. The children’s parents reported other positive changes including improved attention and behavior.

“The treatment reduced seizure frequency and duration for patients whose seizures previously did not respond to treatment,” says Krueger. “The improvement in seizure control was associated with a better quality of life, and side effects were limited.”

Studies in the 1990s traced the cause of TSC to defects in two genes, TSC1 and TSC2. When these genes malfunction, the cell has higher activity of mTOR, a protein known to trigger uncontrolled tumor cell and blood vessel growth. Everolimus shrinks tumors by inhibiting mTORC1, and appears to reduce seizures in TSC patients in the same way.

Krueger says work is already underway to confirm the results in a follow-up, phase III clinical study. Whether the drug will have the same positive effect on other types of epilepsy remains to be seen.

“It is unclear whether the benefit of everolimus in treating epilepsy might extend beyond that observed in TSC,” says Krueger. “Additional clinical trials might tell us whether everolimus would benefit patients with epilepsy not related to TSC.”

Funding for the study was provided by Novartis Pharmaceuticals and the Clack Foundation.

Program Improves Antibiotic Prescribing

A program of education and technological intervention successfully reduced inappropriate antibiotic prescribing for community-acquired pneumonia (CAP), according to a study published in *Pediatrics* in May 2013.

Lilliam Ambroggio, PhD, MPH, Division of Hospital Medicine, was lead author on the study.

The goal of the program was to increase adherence to the appropriate antibiotic therapy for CAP as recommended in the Pediatric Infectious Disease Society/Infectious Disease Society of America national guidelines.

Ambroggio's team tracked patients' antibiotic therapy starting six months prior to implementing their first intervention and for nine months after. A total of 217 children with pneumonia were eligible for the study. Within six months of introducing the program, providers at Cincinnati Children's were meeting the antibiotic recommendations from the guideline for CAP in 100 percent of patients.

"Changing the antibiotic prescribing habits of providers is difficult. To say that our results were better than anticipated would be quite an understatement," Ambroggio says.

The team educated physicians on the new antibiotic recommendations and created a quick reference guide. They also updated the hospital's electronic medical records to default to the recommended antibiotics when a patient was diagnosed with pneumonia. Before the change, the default antibiotic was a broad spectrum drug.

Ambroggio reports that the hospital has maintained near-perfect adherence to the guideline recommendations, which she attributes to a culture that is open to change, the defaults in the electronic records system and other high-reliability interventions. Her team is now investigating the health outcomes associated with adherence to the antibiotic recommendation.

Cincinnati Cancer Center Appoints Director

Shuk-Mei Ho, PhD, will lead the Cincinnati Cancer Center, a new collaborative endeavor encompassing the activities of the Cancer and Blood Diseases Institute at Cincinnati Children's, the University of Cincinnati (UC) Cancer Institute and UC Health. The CCC aims to create a comprehensive, collaborative center designated by the National Cancer Institute that leads in innovative research to eliminate cancer.

Ho is Jacob G. Schmidlapp Chair of Environmental Health at the UC College of Medicine. She is known for her study of the role of hormones, endocrine disruptors and epigenetics in cancer development as well as her exploration of the interaction between genes, the environment and cancer. She will continue this work while overseeing the CCC's research activities, which will focus on programmatic themes of discovery, translational and population sciences.

Study Expands Use of Biomarker Test to Diagnose Acute Kidney Injury

A biomarker test developed at Cincinnati Children's to identify early acute kidney injury (AKI) in patients following surgery has now proven successful in broader clinical use.

In a study published in the September *Clinical Journal of the American Society of Nephrology,* the test, which measures the biomarker neutrophil gelatinase-associated lipocalin (NGAL), was used to successfully diagnose AKI in adult patients with a variety of illnesses who were admitted to hospital from the emergency department.

Prasad Devarajan, MD, Director, Division of Nephrology and Hypertension, developed the test and led the study, with collaborators at Fernando Fonseca Hospital in Portugal.

The study demonstrated that the NGAL test, which uses a single drop of blood and provides results within 15 minutes, could accurately distinguish AKI from transient reversible kidney dysfunction. Of 616 patients who participated in the study, individuals who were subsequently diagnosed with true AKI had the highest levels of NGAL measured at the time of hospital admission. The study also identified a cutoff point in NGAL levels above which the risk of acute kidney injury increases tenfold.

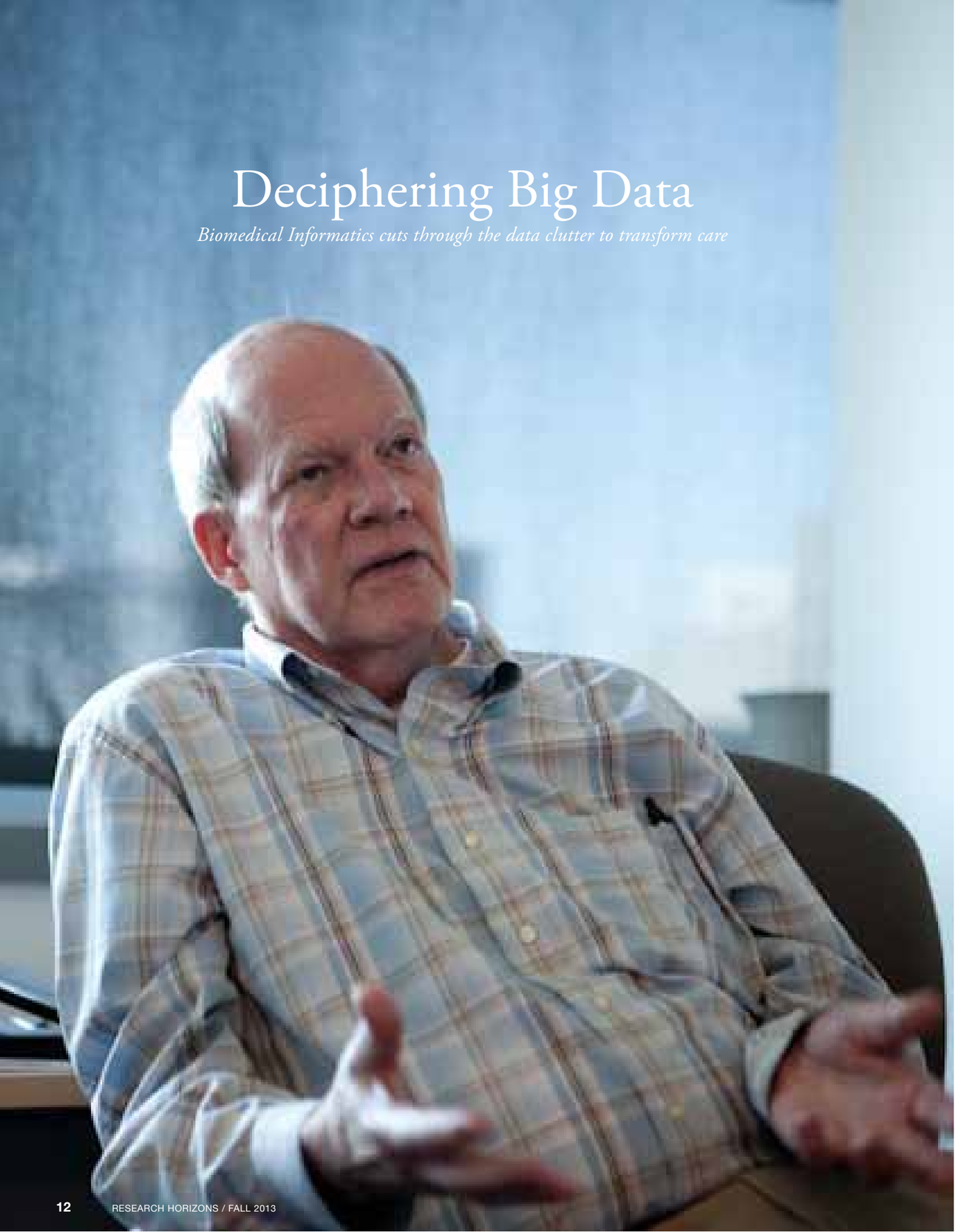
Results of a study previously published (2008) by Devarajan showed that the NGAL test predicted AKI in pediatric heart surgery patients within hours instead of days, allowing treatment that prevented serious damage to kidneys. Prior to the NGAL test, serum creatinine was the only reliable method for detecting kidney damage; however, the long wait for results often resulted in permanent kidney damage.

With a growing number of patients coming to emergency rooms with community-acquired AKI, Devarajan says having a rapid, reliable method of detecting kidney injury is increasingly important.

"This latest study showed that this simple laboratory test provides an accurate prediction of acute kidney injury and its severity in a heterogeneous clinical setting," says Devarajan. "The identification of biomarkers that differentiate intrinsic AKI from transient reversible forms of renal dysfunction and predict outcomes is a high priority."

Deciphering Big Data

Biomedical Informatics cuts through the data clutter to transform care



Nearly two decades ago, a few Cincinnati Children's board members made a transformative decision.

"They saw how the digital revolution was affecting business, and realized that healthcare and research were not major players," says John Hutton, MD (*left*).

So the Division of Biomedical Informatics at Cincinnati Children's was created, just in time for the onslaught of technology that would digitize patient records, allow physicians to enter orders into computers at the bedside, and automate the dispensing of drugs.

And just in time for the completion of the human genome project, which made a vast compendium of human genetic data accessible to researchers worldwide.

This explosion of health information, coupled with the medical center's growth, soon made it clear that one unit could not support both clinical and research needs, Hutton says. So Biomedical Informatics focused on supporting research, and the Department of Information Services focused on supporting clinical and business operations.

But the lines between clinical care and research would continually blur.

"We were created to provide computational resources to faculty and to conduct innovative research in biomedical informatics,"says Hutton, who directs the Division, "But it was also clear that we needed to collaborate closely with the clinical side."

That collaboration has earned them national recognition.

"We are nationally known for being closely integrated with the hospital," Hutton says, a reputation he attributes to an expertly trained and talented team. "It's the ability of our faculty who are trained in computer science to understand and work within a medical environment."

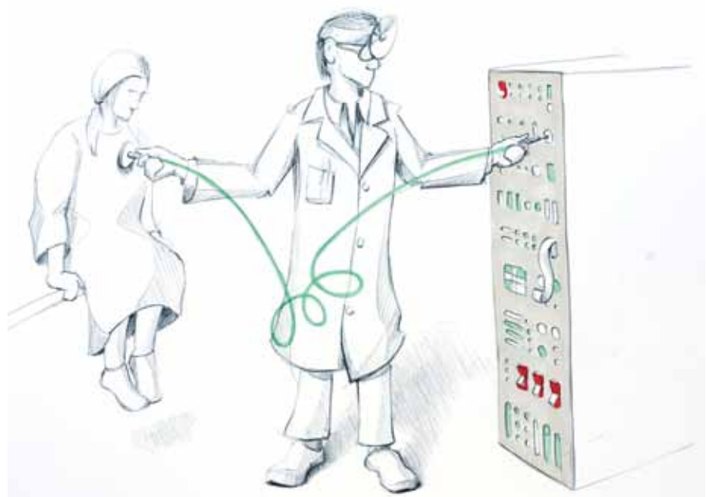
The Division has 60 staff members and 24 faculty, many with graduate degrees in bioinformatics as well as medical degrees. A number are practicing pediatricians or specialists who work in the hospital.

All use their skills to solve research questions and clinical problems aimed at improving the care of children, says Hutton.

"We have embedded throughout the medical center our ability to handle data – to capture, organize, analyze, and protect it. We do it on the research side and in clinical operations. But our goal in both is, how do we make life better, how do we improve therapies, how do we help clinicians and researchers understand what improves the quality of care and outcomes? All of that is data-based; you have to have proper data sets to get outcomes that are believable and statistically credible. That's where we come in."

The stories in this issue represent just some of the ways in which the Division of Biomedical Informatics is changing the delivery of medical care – and the outcomes for patients – here at Cincinnati Children's.

For more information about the Division's work: www.cincinnatichildrens.org/research/divisions/b/bmi/



Alert Fatigue

Researchers look to reduce 'noise' of alerts to make care safer

The move from paper charting to electronic health records, although an enormous improvement in efficiency and safety in patient care, has not been without its challenges.

One of the features of electronic recordkeeping is computerized provider order entry (CPOE), in which providers enter orders for medications and tests into a computer. CPOE is designed to make ordering easier for doctors and safer for patients. But its assistance is not always welcome.

When doctors enter an order for medication that the system perceives as a potential error, it sends an alert.

"We know that our providers are overriding alerts 90 percent of the time," says Eric Kirkendall, MD. "Nine times out of 10, people are making the judgment that the information they are being presented is not useful or accurate."

Kirkendall knows this because he is part of a team working to improve the electronic ordering system so that it becomes a truly useful tool for doctors instead of a nuisance.

The project is being led by Andy Spooner, MD, a pediatrician and Chief Medical Information Officer in the Division of Biomedical Informatics at Cincinnati Children's. He, Kirkendall, and Michal Kouril, PhD, a computer scientist in Biomedical Informatics, are tackling what Spooner says is a problem that goes beyond healthcare and pediatrics.

"The problem is information overload," Spooner says. "We design systems with information that is supposed to help us, but it becomes too much to process. So when we do things like set up alerts for dose of a drug, people in their overwhelmed state ignore it."

NOT DESIGNED FOR KIDS

The problem is even worse in pediatrics. Dosing decision support systems have largely been designed around adult patients and are sometimes a poor fit for children. Adapting the systems to a pediatric environment, where medication dosing is determined largely by weight, has resulted in an even greater number of pop-up messages.

The result is "alert fatigue" – a phenomenon in which doctors become so inured to alerts that they ignore them altogether, whether they are delivering helpful information or not.

When a doctor enters an order for medication into the hospital's electronic medical record system, it scans its vast collection of rules – its "clinical decision support" (CDS) - for allergies, interactions, and dosing irregularities. If the doctor enters an order at a dosing level the system doesn't deem appropriate, it sends up an alert challenging the dose. The system is designed so that doctors can override the alerts, and often, that's what happens.

"The question for our research is, how much risk are we exposing patients to by ignoring the decision support?" Spooner asks. "Is it truly noise or are we ignoring important things?"

DEFINING REASONABLE

To find out, Kirkendall and Kouril have spent the better part of the past year analyzing millions of order entries in our system.

"We're trying to measure what happens when people place orders and are presented with alerts, and what reasonable rates of alerts should be,"

Computer scientist Dr. Michal Kouril has analyzed millions of order entries to distinguish intentional system overrides from actual errors in medication prescribing. Kouril and others are using the information to reduce the number of false alerts.

To get doctors to pay attention to alerts, says Dr. Eric Kirkendall, his team is trying to determine what is a reasonable level of warning.

Kirkendall says. "We think that overriding alerts 90 percent of the time is not appropriate. So how can we tone the alerts down and get people to heed the system?"

DEVELOPING NEW RULES

One way of toning down the alerts has been the time-consuming process of creating custom dosing rules, says Kouril. Many medications in common use have not been approved by the FDA for use in children, so there are no approved dose ranges built into the system, resulting in high numbers of false alerts.

As a result, Kouril says, Cincinnati Children's Information Systems' team, including pharmacist Tom Minich, RPh, had to create thousands of new dosing rules.

"These custom rules supersede the rules provided by the system," Kouril says. "We chose them because they are high-risk medications – the ones most important to get right."

The researchers had to comb through the data to determine real alerts from what Kouril terms "false positives."

To do that, they focused on the big overdose alerts - variations of as much as 500 to 10,000 percent or more in excess of what the computer thinks are appropriate dosing amounts.

REAL MISTAKES – OR NOT?

"We are worried about what appear to be big overdoses," Kouril says. "How many of them actually are errors or were they intentional overrides? And if they were errors, did we catch them, and where?"

The team narrowed their review to the 20 medications most frequently entered into the system as overdoses. Were they actual mistakes in ordering, or were they simply doctors prescribing doses outside the range limits in the database?

"We believe most of these so-called 'overdoses' are actually intentional overrides by prescribers," Kirkendall says. "And we should be able to analyze the information to make changes to the system that would prevent them from being [recognized as] overdose orders in the first place."

Once the researchers complete their data gathering and analysis phase, they will publish their findings. The information could help fill the current enormous literature gap in CDS related to pediatric dosing.

Their next step will be to develop a simulation system based on their findings.

"We are constructing an analytic framework that will model what a real system does," Kirkendall says. "Before we put it into practice, we want to model simulations to see how it will work. We have to study it to understand true user behavior and test it to see if what we are developing is as safe as possible."

Dosing decision support systems are designed primarily for adult patients, not for children. Dr. Andy Spooner *(preceding page)* and his team want to make the system more useful in the pediatric environment.

The Gap Between Rules and Practice

A major reason for the unusually high rate of alerts in pediatric medication ordering is that vendor-supplied electronic rules ("eRules") are built around prescribing for adults, not children. In a study conducted at Cincinnati Children's, Spooner and Kirkendall looked at seven months of medication orders and alerts for thirty medications, across five age ranges and five dosing parameters. Their findings showed that the electronic dosing rules were inaccurate for children more than half the time. They found even greater variability among dosing rules for newborns. The study was published online in June in the *Journal of the American Medical Informatics Association* (JAMIA). Kirkendall, Spooner and others at Cincinnati Children's continue their research into the effects of these discrepancies on safe prescribing for children.

Healthcare, Only Different

Project redefines the doctor-patient relationship

Patients with chronic illnesses spend more time maneuvering through the healthcare system, more time concerned about symptoms, more time thinking about their medications and worrying about their health. But for all that time and energy, they don't fare as well as they could.

"We know from the literature that doctors deliver about half of indicated care and patients do about half of what they should to stay healthy," says Michael Seid, PhD.

And neither doctor nor patient is happy about it.

"No doctor gets up in the morning and says, 'I'm only going to give my patients half of what they need.' And patients want to be healthy."

So Seid, a psychologist at Cincinnati Children's who studies behavioral and social science in medical settings, teamed up with Peter Margolis, MD, PhD, a pediatrician and epidemiologist in the James Anderson Center for Health Systems Excellence, to do something about it.

Four years ago, they were awarded a "Transformative R01" grant from the National Institutes of Health that set them on a course to transform the way patients with chronic illness receive care.

The project was one of just 42 projects nationwide selected to receive such a grant, chosen specifically because it challenged the traditional top-down approach to care delivery.

"Chronic illness kills too many and costs too much," Margolis and Seid stated in the grant application. "What if there was a way to create a vastly better chronic illness care system by harnessing the inherent motivation and collective intelligence of patients and clinicians?"

Margolis and Seid used the grant funding to launch the Collaborative Chronic Care Network (C3N) Project to create that better system. Inspired by collaborative social platforms like Wikipedia and Firefox, the researchers wanted their new model to blend the best ideas of patients and caregivers with technology that was truly useful.

CREATING THE MODEL

They chose to develop the prototype for this new model of care with an established chronic care network, Improve Care Now (ICN). The network includes more than 50 gastroenterology sites around the country that care for kids with inflammatory bowel disease (IBD) - Crohn's disease and ulcerative colitis. The network had already improved the remission rate for their patients by 20 percentage points, just by sharing data and best practices.

"We knew that clinicians could collaborate and do better. And patients were finding each other on the Internet," Seid says. "But there wasn't any space where clinicians, patients and researchers could get together on the same platform. "

FROM MERE DATA TO USEFUL INFORMATION

One of the most daunting challenges faced by the project was creating a shared database of patient information. The data had to be secure enough to protect patient privacy but accessible enough that clinicians and patients could use the information in new and helpful ways.

With a $12 million, three-year grant from the Agency for Healthcare Research and Quality (AHRQ), experts in the Division of Biomedical Informatics at Cincinnati Children's created an "enhanced registry" for the project. The registry allows clinicians at each participating site to enter patient data into the electronic health record just once. The patient's complete identified information is stored at the site, while a de-identified copy of the data is automatically sent to the C3N database for use by participants.

NO MORE PASSIVE PATIENTS

Re-imagining the traditional model of care in which patients passively receive care from a doctor was another challenge taken on by the C3N team – a challenge that demanded the involvement of patients and parents.

"With a chronic condition, most care takes place outside the clinic, by the patients or parents themselves," Seid says. "A better way to think about health care is shared work. It takes everybody to create health."

They invited patients to create a Patient Advisory Council, which now consists of more than 30 teens and young adults with IBD. PAC members participate in design meetings and on research teams, create webinars and write for the blog.

Alex Jofriet is one of those kids. Diagnosed with Crohn's disease at age 9, he has struggled with medications, with surgeries, and with ac-

By combining the knowledge and experience of patients, parents and caregivers with the ease of new technology, Dr. Michael Seid (at left) and colleague Dr. Peter Margolis want to transform care for kids with chronic illnesses.

cepting the fact that his illness made him different. Getting involved with the ICN network and the C3N project – including writing for its blog – changed his perspective about living with a chronic condition.

"Opening up and focusing on advocacy brought me a new love for life, and made me a stronger person, healthier and less stressed," he says. "I like to think that I provide inspiration and hope to others."

Now 17 and a high school junior, Alex has not only accepted his condition but credits it with helping him become stronger and more resilient. It has also helped him decide to become a gastroenterologist. As he wrote in a blog post, "Life will always be full of obstacles but the way you deal with them is what determines whether the roadblock will be turned to a strength or a weakness."

A Parent Working Group is also part of the C3N Project. These parents share their experiences and ideas with clinicians and some serve on the ICN board of directors and its research committee. They help write grants, make welcome packets for newly diagnosed patients and talk with families who want to hear from someone who's "been there." This summer, parents helped launch an awareness campaign for the network.

Seid and Margolis hope that the success of the C3N Project's work with the Improve Care Now network will serve as a prototype for other chronic illnesses. At a time when caregivers are pushed to the limit and patients demand a more active voice in their care, the approach is a big win for both sides.

"Clinicians are already working as hard as they can, and patients and parents are the most under-utilized workforce in healthcare. Many want to do more," Seid says. "The idea is to shift to a collaboration where everyone works together. We want patients to feel healed, and we want doctors to feel healed too, because the system isn't working for them either." ■

Alex Jofriet (below) blogs about his condition for the C3N project and advises doctors and others about what patients and families need. Alex is one of a number of young people helping researchers develop a new model of care for people with chronic illness.

The Doctor Will Text You Now...

The C3N project explores new ways for doctors and patients to communicate

Making the Most of an Office Visit

This approach asks parents how their child is doing and what they want to discuss in advance of an office visit. Patients can enter information between visits that feeds directly into the doctor's visit planner. Prior to an appointment, clinicians will see what has gone well or not so well, and can address these concerns during the visit.

The app displays clinical data such as blood levels and lab test results in a simple visual format so patients can better understand what their numbers mean. It generates alerts about patients who are having difficulties between visits, as well as information about those who are doing fine and might be able to wait longer until their next visit. Patient and doctor are prepared in advance, and the time spent in the visit is as productive and helpful as possible.

Tracking Day to Day Activities

A "Personal Learning System" app allows patients to track diet, exercise, medication taking, and more. The information is captured so patient and doctor can reference the information at the next visit. The app lets patients set up reminders and link to other health-related apps such as RunKeeper. The app is web-based only for now, but as part of a partnership between CCHMC and Vital Reactor, LLC, the C3N Project is developing a mobile platform.

Learning a Patient's Patterns

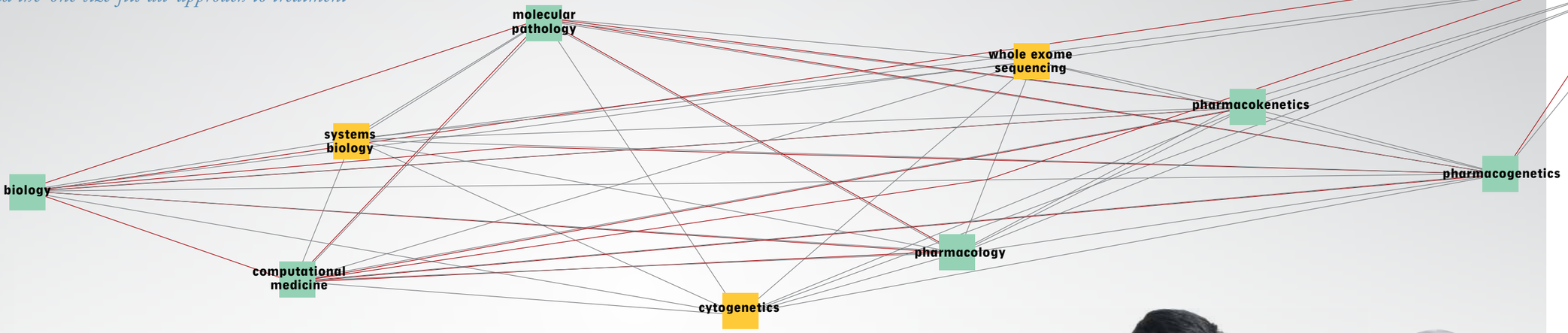
Next up: an app that will use a mobile phone's GPS system to learn participants' behavior patterns and understand deviations from patterns. The goal is to send patients alerts when it senses a change in behavior to identify potential "flares" of their disease. Seid is working on a grant to test the idea. He foresees that the app could send a patient a message allowing the patient to avoid a flare of his illness.

C3N

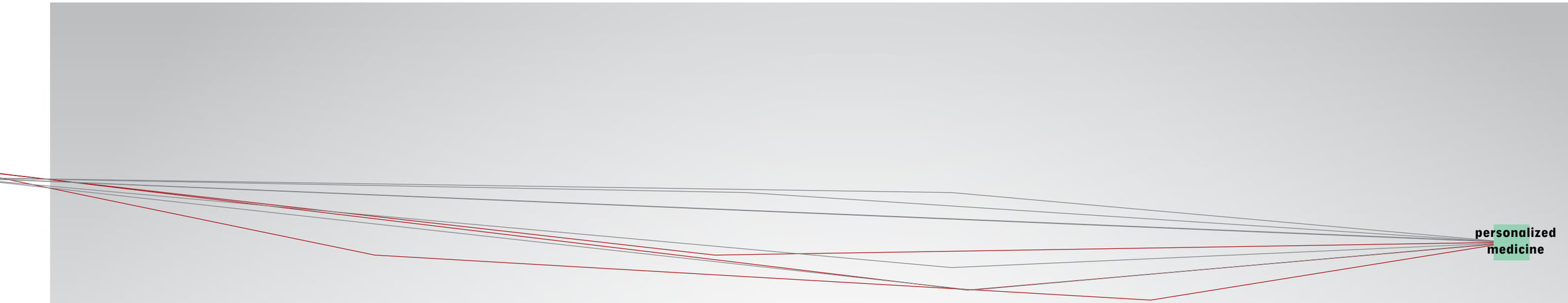
The C3N Project is supported by the National Institute of Diabetes and Digestive and Kidney Diseases, and housed at Cincinnati Children's. Aiming to transform care for people with chronic disease, C3N's pilot project is with Improve Care Now, a network of clinics treating kids with Inflammatory Bowel Disease.

Personalized Medicine Changes the Game for Clinical Practice

Beyond the 'one-size-fits-all' approach to treatment



From left to right: Drs. Anil Jegga, Bruce Aronow, David Witte, Sander Vinks, David Hooper and John Perentesis. All are using biomedical data to predict patients' response to treatment and prescribe more accurately and effectively.



Ever since the Human Genome Project produced the first complete map of a human genome in 2003, futurists have predicted that a doctor could use a patient's personal blueprint to customize treatment. For a fast-growing number of children, that day has arrived.

At Cincinnati Children's, many children who receive kidney transplants and every child who suffers a cancer relapse or needs certain psychiatric medicines already benefits from what some call the "Holy Grail" of advanced healthcare.

"For thousands of children, personalized medicine isn't 'just around the corner' anymore, it's here and it's saving lives," says Sander Vinks, PharmD, PhD, Director of Clinical Pharmacology.

CUSTOMIZED CHEMOTHERAPY MAKES TREATMENT SAFER

When initial rounds of chemotherapy or radiation no longer keep cancers in remission, children from all over the world come to our Cancer and Blood Diseases Institute (CBDI). Taking on complex cases has given CBDI faculty great experience in customized care. Now, advancing technology is taking things to a new level.

"Systems biology – what we used to call bioinformatics -- is turning out to be at the center of all the advances we are making in cancer therapy," says John Perentesis, MD, FAAP, CBDI Executive Co-Director. "We are using next-gen sequencing not only to gather genomic information about our patients but also to sequence the genes of the tumors themselves."

Perentesis is working with Vinks and Bruce Aronow, PhD, co-director of our Computational Medicine Center, on a study exploring the cancer-fighting abilities of sirolimus, an mTOR inhibitor originally developed as an immune suppressor.

The study uses a gene chip designed to analyze nearly 2000 variants in 225 genes known to influence metabolism to see how patients react to sirolimus. Eventually this work could help predict whether a specific tumor is likely to respond to a specific drug – and at what dose.

"This is a unique and powerful foray into personalized medicine," Aronow says. "Nobody else has really nailed this issue of differential drug toxicity and optimization."

To destroy cancerous tumors, doctors typically give patients the highest chemotherapy doses they can tolerate. But that approach has its shortfalls.

"We have drug regimens for Hodgkin's disease that offer a 97 percent cure rate – without a bone marrow transplant – even for children with stage IV disease," Perentesis says. "However, the chances of growing up to develop a life-threatening side effect such as heart disease or lung damage is much higher than the 3 percent risk of the drug failing to kill the cancer."

At least five multi-drug cocktails can cure Hodgkin's disease, Perentesis says, but each poses risks. The promise of personalized medicine is that doctors would no longer have to guess at which patients should use which regimens.

"If we can spot those patients most likely to have a side effect, we can use a lower dose or switch drugs while still achieving a therapeutic result," Perentesis says.

Between the sirolimus study and other projects, the CBDI has sequenced tumors for more than 100 children with relapsed cancers in the past year.

BETTER DRUG LEVEL MONITORING TO PREVENT ORGAN REJECTION

Obtaining quick, accurate test results to confirm that a drug is working as intended is another crucial part of personalized medicine.

Vinks is working with a team of clinicians and researchers to develop a web-based decision support tool to help doctors track whether kidney transplant patients are getting ideal doses of the anti-rejection drug mycophenolate mofetil (CellCept).

"The therapeutic window for this medication is quite narrow. If the levels stay too low, the transplanted organ can be rejected. If they go too high, the patient can suffer side effects," Vinks says. "But the dose required to stay within that narrow window can vary widely between individuals."

Cincinnati Children's pathology lab already conducts drug-level tests for transplant recipients and a few other serious conditions to determine if children are fast, normal or slow metabolizers. But the process is complicated, expensive and not widely available.

"We want to do all of this in a much more automated fashion, and present the information in an easy-to-use way," Vinks says.

The nephrology team plans to begin evaluating a beta version of the decision-support tool this fall. If successful, similar tools could be developed for infectious diseases, chronic pain control, cystic fibrosis, lupus and other conditions.

"So far, our doctors have loved the initial prototype," says David Hooper, MD, a pediatric nephrologist in the Division of Nephrology and Hypertension. "It logically organizes everything the physician needs to know in a single location and in a way that facilitates clinical decision making. Having this form available has significantly reduced the time needed to plan for medical visits, and has increased efficiency in the clinic."

The tool uses color coding to alert doctors to issues of concern, recommends "suggested actions" and allows users to give feedback about the suggestions. In the past several months, more than 80 percent of suggested actions were followed, Hooper says. And over time, the care patients are receiving has become more predictable and requires fewer suggested actions to be made.

"With this tool, doctors don't have to rack their brains to remember their patients' lab test schedules or other routine details. That gives them more time to focus on decisions only they can make at the bedside with their patients," Hooper says.

POWERFUL TESTS FUEL PREDICTIVE MEDICINE

In psychiatry, researchers have known for years that several frequently prescribed medications are affected by a few gene variations along a common metabolic pathway. These fairly-simple-to-detect variations can result in big differences in how children respond to treatment.

Cincinnati Children's established a genetic pharmacology service in 2004 to run gene tests that help set a child's starting dose for these medications. More than 10,000 children since have received the "psychiatric panel" as a standard part of care. In 2006, a spin-off company called AssureRX Health Inc. was founded to produce a commercial version of the test.

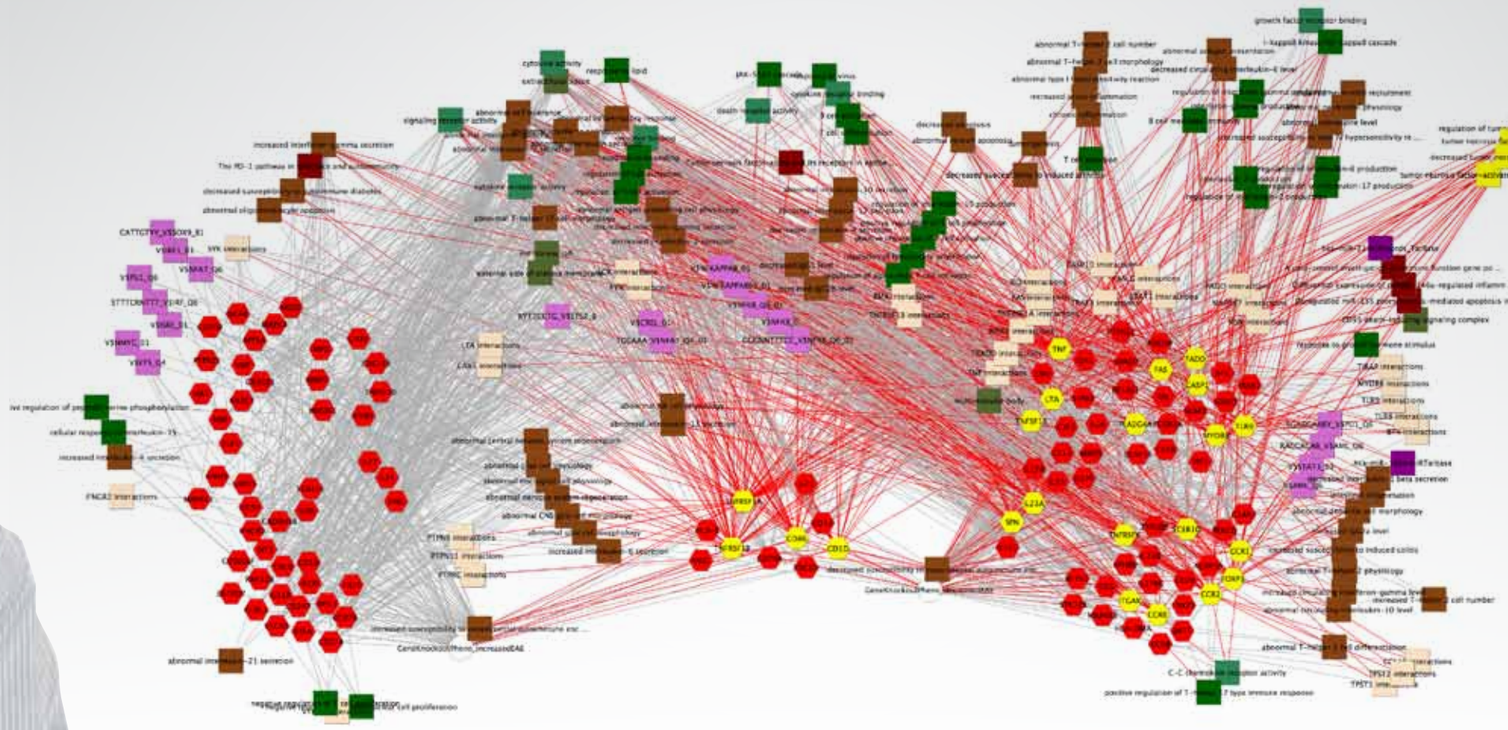
Since then, genetic testing for clinical and research purposes has leaped even farther forward.

In July, the Molecular Genetics Laboratory at Cincinnati Children's announced ExomeSeq, a whole-exome test developed to diagnose rare and complex conditions by scanning the important coding regions of 20,000 genes. Meanwhile, research scientists here are using even more powerful whole-genome sequencing techniques to hunt for the causes of disease and improved therapies.

Although the information generated by these powerful tests is already transforming how medical care is delivered, adapting them to widespread clinical use will take some time.

"The amount of data we can put together to analyze is staggering," Aronow says. "But in terms of having widely available technology to interpret the results of all this high-level analysis, we're still just scratching the surface."

Powerful, free tools accelerate research



Anil Jegga, DVM, and Bruce Aronow, PhD, both in the Division of Bioinformatics, have developed a powerful set of systems biology research tools called "ToppGene Suite" and GATACA.

The software tools – which are free for academic use – enable scientists to rapidly explore the relationships between diseases, drugs and the molecular pathways they affect.

The software organizes massive libraries of data about tens of thousands of genes in humans and in mice. Researchers can look up a wide range of "enriched" gene annotation information including disease-gene associations, drug-gene interactions, protein interactions, transcription factor binding sites, miRNA-target genes, corresponding mouse phenotypes and more.

In addition to detailed lists of information, the software can produce color-coded relationship maps that allow users to visualize communities of diseases and related networks of genes.

"This is very similar to what Amazon or Netflix does with their recommendation systems. Those consumer services use large collections of descriptors about movies and books to determine if you bought this product, you might be interested in these other products," Jegga says. "It's the same with genes. We collect 17 categories of information about gene functions and relationships, which in turn can point to other genes we didn't think about, but actually may play a role in a particular disease."

These tools are increasingly used in combination with next-gen sequencing to accelerate disease gene prediction and drug discovery.

"For example, if a whole genome or whole exome scan detects 200 genes that are down-regulated among people with a certain condition, then you can use ToppGene to rank them according to those most likely to have clinical importance," Jegga says.

For more information about these tools, go to http://toppgene.cchmc.org/ or https://gataca.cchmc.org/gataca/.

Keeping Watch

Algorithms created by Dr. Imre Solti will allow computers to keep constant watch over tiny newborns in the NICU and warn of problems before they occur.

They don't need sleep. They don't get distracted. When it comes to improving patient safety, computers might just be what the doctor ordered.

In most aspects of medical care, there is no match for the human touch. But in one crucial area - the battle to protect against medical errors - technology just might trump human frailty.

That is what researchers from our Division of Biomedical Informatics are exploring with doctors and other clinical staff from our Neonatal Intensive Care Unit (NICU), where the stakes of medical errors are about as high as they come.

"We already have systems in place to prevent errors," says Kristin Melton, MD, a neonatologist in the NICU. "Our error rates are not high, but you are relying on a human system, so errors do occur. We are trying to recognize those times when they do occur and prevent them."

So Melton and Imre Solti, MD, PhD, a researcher in our Division of Biomedical Informatics, are leading a project funded by a two-year, $500,000 grant from the National Institute of Child Health and Human Development. They are working with a team of experts from Biomedical Informatics and the NICU to develop a sort of digital guidebook for the wary - algorithms that will allow computers to continuously scan patient records for potential problems.

"Our goal is to build a database of adverse events and errors that the computer can search for and identify before they occur," says Solti, who is principal investigator on the study.

ERRORS WITH GREATEST POTENTIAL FOR HARM

The researchers are focusing on two types of errors with the most serious consequences for babies in the NICU – the ordering and delivery of medications, and "unplanned extubations," incidents when a baby's breathing tube is accidentally dislodged.

"If it works for the NICU, which is one of the most complex environments, it should work for other areas as well."

Neonatologist Dr. Kristin Melton identified two of the most serious errors that can happen in the NICU - errors in medication dosing and accidental extubations - for a study that uses computers to monitor for and warn against such occurrences.

Research team members spent the past year reviewing two types of data entered into the electronic health record. For medication errors, they examined "structured data" such as vital signs and other information that is entered routinely into the charting system.

For extubation errors, the annotators pored over clinical notes, the more subjective narrative provided by caregivers about the care and status of each patient. Nearly 750 infants were cared for in our NICU this past year, which generated more than 30,000 "patient days" of notes. The annotators' job was to identify all the ways in which caregivers describe the errors so that the terms can be included in the algorithms.

DOING NO HARM

While no error is acceptable in patient care, some have more serious consequences than others. In the coming year of the study, Solti says, the researchers will focus on the errors that resulted in harm to patients.

"As we detect errors in the electronic health records, we will also look at whether these errors contributed to harm to the patient," Solti says. He adds that creating "categories of harm" will help prioritize which mistakes carry the most serious consequences. The researchers will incorporate this information into their algorithms.

"We don't ever want errors to happen, but we do want to prioritize which errors should get most of our attention, " adds Melton. "Harm categories help us prioritize which are the most critical problems to focus on."

ON-THE-SPOT WARNINGS

Once the algorithms are developed, the research team hopes the next step will be putting in place real-time identification of high-impact errors that will send immediate alerts to caregivers. So if a nurse begins to give the wrong dose of medication, an alert would warn that it was not the same as the ordered dose.

The key to making such a system work well is cutting through the clutter of the noise in busy hospital units.

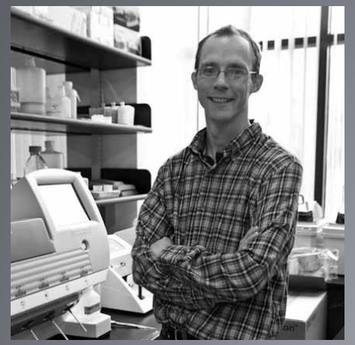
"We want to make sure the alerts are for something significant, and that they fire only if there is a reason," says Solti. "We don't want them to be another alert that no one pays attention to."

Automating the search for potential errors in the NICU should be a significant step forward in improving safety and removing one of the many tasks caregivers must perform. But Solti emphasizes that no automated system will ever replace the need for human judgment.

"The capacity to continuously and rapidly scan the entire record is certainly an advantage," he says. "But you will always need someone to look and see if something is truly an error or adverse event."

Solti and his team believe the project can become a model for other intensive care settings.

"If it works for the NICU, which is one of the most complex environments, it should work for other areas as well, adjusted and customized for that particular environment," he says. "We hope to test it in another institution and see how well our algorithms work there, then roll out to other NICUs on a larger scale."



"Our goal, on both the research side and the clinical side, is how do we make life better, how do we improve therapies, how do we help clinicians and researchers understand what improves the quality of care and outcomes?"

John Hutton, MD
Director, Division of Biomedical Informatics

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