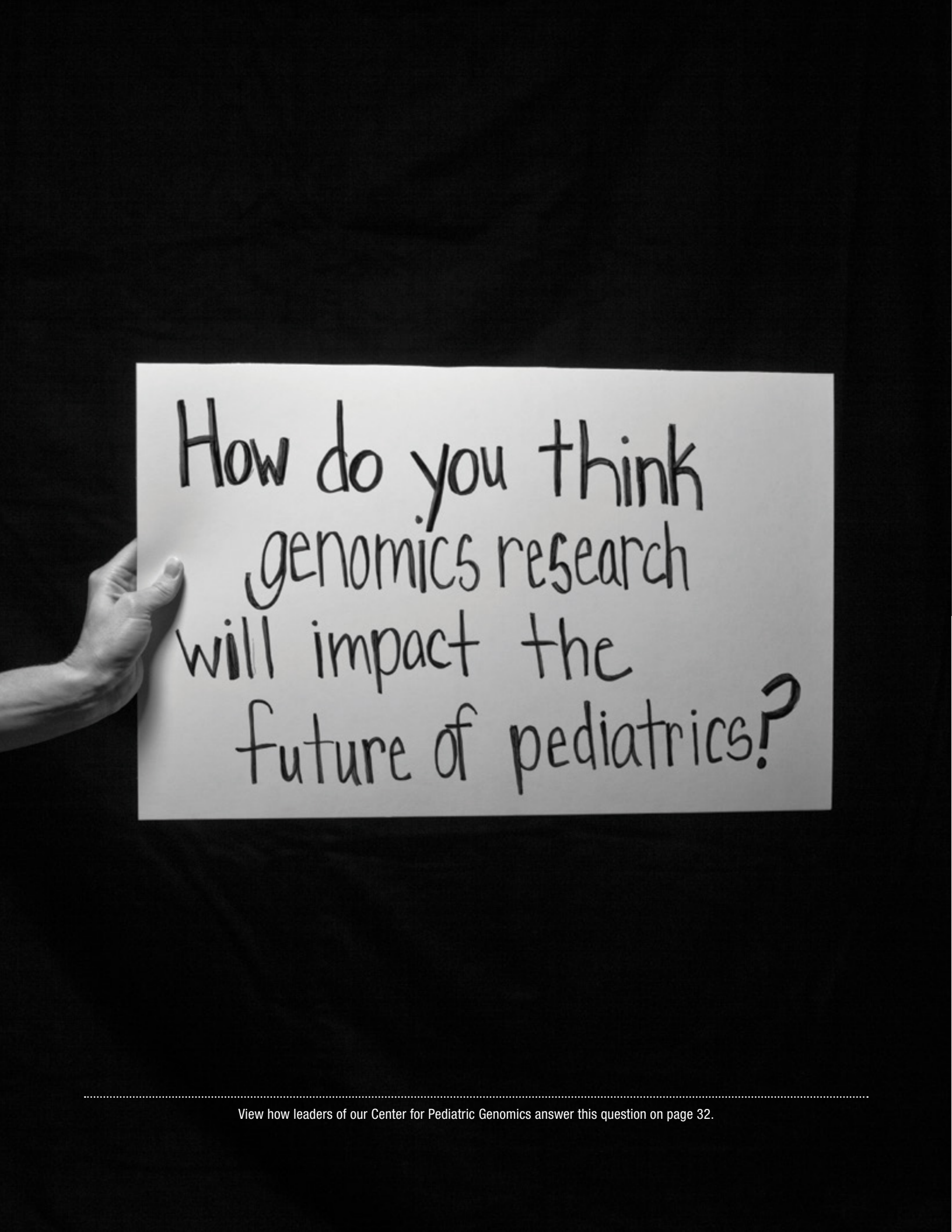
# Research Horizons

A PUBLICATION OF THE CINCINNATI CHILDREN'S RESEARCH FOUNDATION
**SPRING 2016**

## Genomics

To Harness a Whirlwind

Cincinnati Children's

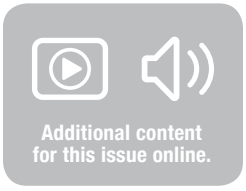



View how leaders of our Center for Pediatric Genomics answer this question on page 32.

# Research Horizons

## SPRING 2016






**Cover:** Flocks of starlings in mesmerizing murmurations. Swirling schools of mackerel. Nature's wondrous versions of "Big Data" in motion inspired the cover image and other art elements in this issue of *Research Horizons.*

# HONORS

## Frank Biro, MD,

**Director of Research, Adolescent and Transition Medicine,** received the 2015 Cincinnati Pediatric Society's Founders' Award, which honors career achievements in basic or clinical research and distinguished contributions to child health. Biro's career at Cincinnati Children's spans 31 years. He is nationally recognized for research on pubertal maturation. He was elected to the Cincinnati Children's Hall of Honor in 2014.

## Samantha Brugmann, PhD,

**Plastic Surgery,** is one of only 105 winners nationwide this year of the Presidential Early Career Award for Scientists and Engineers. Brugmann was honored for her studies of avian models of human craniofacial development.

## Andrew Dauber, MD,

**Program Director and Director of Translational Research, Cincinnati Center for Growth Disorders,** received the 2015 Young Investigator Award from the European Society for Paediatric Endocrinology, which recognizes outstanding research by society members aged 40 or younger.

## Prasad Devarajan, MD,

**Director, Nephrology and Hypertension,**
and Kasper Hoebe, PhD,
**Immunology,** were listed among Thomson Reuters' Highly Cited Researchers 2015. This list includes influential researchers in 21 scientific fields who are ranked in the top one percent of the most cited writers within their field.

## Anna Esbensen, PhD,

**Developmental and Behavioral Pediatrics,** an expert in the lifespan development of individuals with Down syndrome, was named in October 2015 as a fellow of the American Psychological Association.

## Robert Frenck Jr., MD,

**Interim Director, Infectious Diseases,**
and Paula Braverman, MD,
**Director, Community Programs, Adolescent and Transition Medicine,** received the Leonard P. Rome Award from the Ohio Chapter of the American Academy of Pediatrics. They were honored for developing the Teen Immunization Education Sessions Program, which is part of a national effort to increase HPV vaccination rates in teens. The Ohio Department of Health recently committed to re-fund the program through the end of 2016.
In another achievement, Frenck was elected, effective Nov. 1, 2015, to the Executive Committee of the American Academy of Pediatrics Section on Infectious Diseases.

## Patricia Fulkerson, MD, PhD,

**Allergy and Immunology,**
and Ellen Lipstein, MD, MPH,
**Adolescent and Transition Medicine,** have been selected as 2015 Schmidlapp Women Scholars. Fulkerson's research focuses on defining the regulatory network that drives eosinophil development. Lipstein's work focuses on family-centered medical decision making. The Fifth Third Bank/Charlotte R. Schmidlapp Women Scholars Program selects women faculty in a competitive application process and provides funds to support their academic career development.

## Satoshi Namekawa, PhD,

**Reproductive Sciences,** received the 2015 New Investigator Award from the Society for the Study of Reproduction, which recognizes outstanding research by society members who complete and publish within 12 years after earning a doctoral degree.

## Shari Wade, PhD,

**Director of Research, Physical Medicine and Rehabilitation,** received the inaugural Dr. Jane Gillett Award at the first International Paediatric Brain Injury conference held by the International Paediatric Brain Injury Society and the International Brain Injury Association. The award recognizes outstanding contributions to improving the lives of children impacted by brain injury.

## Sing Sing Way, MD, PhD,

**Infectious Diseases,** was awarded the E. Mead Johnson Award for Pediatric Research, considered among the most prestigious honors in pediatric research, and the inaugural Gale and Ira Drukier Prize in Children's Health Research from Weill Cornell Medical College.

## Gary Webb, MD,

**Director, Cincinnati Adolescent and Adult Congenital Heart Disease Program,** received the 2015 Lifetime Achievement Award from the International Society for Adult Congenital Heart Disease (ISACHD). In 1980, Webb became Co-Director and then Director of the Toronto Congenital Cardiac Center for Adults, one of the first ACHD centers in the world. He was the founding president of ISACHD and has held leadership roles in numerous ACHD organizations. He has co-authored more than 160 manuscripts and has edited two major textbooks.

# Cincinnati Children's Appoints Six Endowed Chairs

Cincinnati Children's honored five faculty members as chairs of the Research Foundation and another faculty member as the new Michael and Suzette Fisher Chair. The awards were presented Sept. 24, 2015, to these distinguished honorees:

## Research Foundation Endowed Chairs

### Maria Britto, MD, MPH,

**Director and Founder, Center for Innovation in Chronic Disease Care**

Britto's research looks to develop and evaluate new methods of care delivery for patients with cystic fibrosis, asthma and sickle cell disease. She serves as president of the Society for Pediatric Research and is a member of the American Board of Pediatrics Research Advisory Committee. She joined Cincinnati Children's in 1995.

### Tracy Glauser, MD,

**Associate Director, Cincinnati Children's Research Foundation**

An expert in pediatric neurology, pediatric epilepsy, clinical pharmacology and pharmacogenetics, Glauser serves as Director of the Comprehensive Epilepsy Center and Co-Director of Genetic Pharmacology Service. He also is vice-chair of the Cincinnati Children's Institutional Review Board. Glauser has authored or co-authored more than 130 articles and book chapters.

### Peter Margolis, MD, PhD,

**Director of Research, James M. Anderson Center for Health Systems Excellence**

A leader in healthcare quality improvement, Margolis is the national chair of the PCORnet Steering Committee, a $100 million initiative of the Patient-Centered Outcomes Research Institute (PCORI). He also chairs the Health Services Research Collaborative. Margolis joined Cincinnati Children's in 2006.

### Sander Vinks, PharmD, PhD,

**Director, Clinical Pharmacology, and Scientific Director, Pharmacy Research**

An expert in therapeutic management and the biochemical and physiological effects of medications, Vinks chairs the Clinical Pharmacology and Translational Research committee of the American Association of Pharmaceutical Scientists and serves on the Board of Regents of the American College of Clinical Pharmacology. He has published more than 140 peer-reviewed manuscripts and 18 book chapters.

### Katherine Yutzey, PhD,

**Director, Molecular and Developmental Biology Graduate Program**

Yutzey studies the regulation of heart development, and is internationally renowned for research on the control of valvulo-septal development. Yutzey was the first recipient of the Fifth Third Bank/Charlotte R. Schmidlapp Women Scholars Award. She holds positions on the American Heart Association National Peer Review Steering Committee and the Student Grievance Committee. She joined Cincinnati Children's in 1995.

## Michael and Suzette Fisher Chair

### Stephen Muething, MD,

**Vice President for Safety and Associate Director, James M. Anderson Center for Health Systems Excellence**

Muething leads Cincinnati Children's strategic goal of eliminating all serious harm for patients and employees. He serves on multiple national pediatrics safety groups, including Children's Hospitals' Solutions for Patient Safety, a network that includes more than 88 pediatric hospitals.

## Other New Chairs

These distinguished faculty members also have recently been awarded endowed chairs at Cincinnati Children's:

### Lori Stark, PhD,

**Director, Behavioral Medicine and Clinical Psychology**, was awarded the Arnold Strauss Chair in Mentoring.

### Carolyn Kercsmar, MD,

**Co-Director, Pulmonary Medicine**, was awarded the Luther Foundation Research Chair of Pediatric Pulmonary Medicine.

# GRANTS

## Artem Barski, PhD,

**Allergy and Immunology,** will study the direct epigenetic reprogramming of T cells, using a five-year $2.3 million grant from the National Institute of General Medicine Sciences.

## Frank Biro, MD,

**Director of Research, Adolescent and Transition Medicine,** was awarded a one-year, $3.8 million grant from the National Institute of Environmental Health Sciences to continue his studies on the environmental impact of puberty.

## Claire Chougnet, PhD,

**Immunobiology**, will study the homeostasis and function of regulatory T cells in the aging process, using a two-year, $2 million grant from the National Institute of Aging.

## John Clancy, MD,

**Pulmonary Medicine,** will study the translation of personalized cystic fibrosis research with a four-year, $1.9 million grant from the Cystic Fibrosis Foundation.

## Lawrence Dolan, MD,

**Endocrinology,** will use a five-year, $1.8 million grant from the national Centers for Disease Control and Prevention to continue his work with the "SEARCH for Diabetes in Youth Registry," a multi-site system for analyzing new cases of diabetes.

## Chandrashekhar Gandhi, PhD,

**Gastroenterology, Hepatology and Nutrition,** will study the mechanisms of nonalcoholic steatohepatitis with a three-year, $1.3 million grant from the U.S. Department of Defense.

## John Harley, MD, PhD,

**Center for Autoimmune Genomics and Etiology,** received a four-year, $3.4 million grant from the National Human Genome Research Institute to study the role of genomics in informing policy and improving healthcare outcomes.

## Bin Huang, PhD,

**Biostatistics and Epidemiology,** will study patient-centered adaptive treatment strategies with a three-year, $1.5 million grant from the Patient-Centered Outcome Research Institute, an independent nonprofit, nongovernmental organization based in Washington, DC.

## James Heubi, MD,

**Director, Center for Clinical and Translational Science and Training,** was awarded the Clinical and Translational Science Award, part of a five-year, $2.8 million grant from National Center for Advancing Translational Sciences.

## Eric Kirkendall, MD, MBI,

**Hospital Medicine,** received a four-year, $1.5 million grant from the National Library of Medicine to study ways to improve the safety of intensive-care medications.

## Qing Richard Lu, PhD,

**Scientific Director, Brain Tumor Center,** will study the molecular mechanisms of oligodendrocyte differentiation and myelination with a five-year, $2.4 million grant from the National Institute of Neurological Disorders and Stroke.

## Melinda Mahabee-Gittens, MD, MS,

**Emergency Medicine,** will study intervention strategies to reduce second-hand smoke exposure using a five-year, $2.9 million grant from the National Institute of Child Health and Human Development.

## Peter Margolis, MD, PhD,

**Director of Research, James M. Anderson Center for Health Systems Excellence,** received a one-year, $1.4 million grant from ImproveCareNow, Inc., for his work with its improvement collaborative, a team of physicians from numerous institutions who specialize in inflammatory bowel diseases.

## Patrick McGann, MD, MS,

**Hematology,** was awarded a five-year, $1 million grant from the National Heart, Lung and Blood Institute to study the therapeutic response and adherence related to hydroxyurea treatment.

## Lou Muglia, MD, PhD,

**Perinatal Institute,** will study maternal temperament, stress and inflammation in preterm birth, with a two-year, $2.2 million grant from the National Institute of Child Health and Human Development.

## Marc Rothenberg, MD, PhD,

**Allergy and Immunology,** will study the genetic and immunological dissection of eosinophilic esophagitis, using a five-year, $2.5 million grant from the National Institute of Allergy and Infectious Diseases.

## Richard Ruddy, MD,

**Emergency Medicine,** received a four-year, $2.4 million grant from the Health Resources and Services Administration to continue his work on improving EMS services through the Pediatric Emergency Care Applied Research Network (PECARN).

## Bruce Trapnell, MD, MS,

**Pulmonary Medicine,** received a four-year, $2.7 million grant from the National Heart, Lung and Blood Institute, for his continued work with the Rare Lung Diseases Consortium, a network of physicians and patients working to accelerate clinical research and improve treatment.

## Ronald Waclaw, PhD, MS,

**Experimental Hematology and Cancer Biology,** will study signaling pathways that regulate oligodendrocyte development, using a five-year, $1.9 million grant from the National Institute of Neurological Disorders and Stroke.

## Kathleen Walsh, MD, MSc,

**Director of Patient Safety Research, James M. Anderson Center for Health Systems Excellence,** received a three-year, $1.4 million grant from the Agency for Healthcare Research and Quality to study human and systemic factors in medication error and injury.

## Yui-Hsi Wang, PhD,

**Allergy and Immunology,** will use a three-year, $1.6 million grant from the U.S. Department of Defense to study interlukin-9-producing mast cell precursors and their impact on food allergies.

## Sing Sing Way, MD, PhD,

**Infectious Diseases,** will study maternal regulatory T cell antigens specificity, using a five-year, $2 million grant from National Institute of Allergy and Infectious Diseases.

## James Wells, PhD,

**Endocrinology,** received a five-year, $1.2 million grant from the National Institute of Allergy and Infectious Diseases to study intestinal organoids as a model system for studying enteric disease.

## Hector Wong, MD,

**Critical Care Medicine,** will study the novel diagnostic and stratification tools for septic shock, using a three-year, $2.3 million grant from the National Institute of General Medicine Sciences.

## Yutaka Yoshida, PhD,

**Developmental Biology,** received a five-year, $1.6 million grant from the National Institute of Neurological Disorders and Stroke to study synapse elimination in the central nervous system.

## Basilia Zingarelli, MD, PhD,

**Critical Care,** will study age-dependent mechanisms in metabolic recovery with a four-year, $1.5 million grant from the National Institute of General Medical Sciences.

# Ultrasound Zaps Dangerous Fat

Chuck Dumoulin, PhD

Someday, ridding ourselves of risky excess fat might be as simple as zapping it with ultrasound.

Using MRI-guided, high-intensity focused ultrasound (MR-HIFU), researchers in the Imaging Research Center at Cincinnati Children's removed visceral fat tissue from overweight rats without a knife cut or needle puncture. Visceral fat collects around organs such as the liver, kidneys and pancreas, and contributes to hypertension, heart disease, diabetes, stroke and other diseases.

"The unique abilities of MR-HIFU and the critical role of visceral fat in obesity and disease suggest that MR-HIFU could be used to reduce the metabolic activity of fat in people who are overweight," says Chuck Dumoulin, PhD, Director of the Imaging Research Center and senior author of a study published online Aug. 18, 2015, *Magnetic Resonance in Medicine*.

On average, the rats lost 7.5 percent of their body weight after treatment, despite having only 1.5 percent of visceral fat removed. The researchers believe MR-HIFU might not only combat medical complications of obesity, but also serve as a safe and non-invasive alternative to bariatric surgery.

# Air Pollution Associated With Higher Risk of Preterm Birth

Exposure to high levels of small particle air pollution is associated with an increased risk of preterm birth — before 37 weeks of pregnancy, according to a study published online Jan. 15, 2016, in the journal *Environmental Health*.

The study, by researchers at Cincinnati Children's and the University of Cincinnati, identified a 19 percent increased risk, with the greatest risk when high exposure occurred during the third trimester of pregnancy. Preterm birth rates were higher among mothers exposed to above-standard levels of airborne particle pollution, as well as among mothers 40 or older, black mothers, and women with no prenatal care or with lower education level.

"Although the risk increase is modest, the potential impact is robust, as all pregnant women are potentially at risk," says Emily DeFranco, DO, a physician-researcher at the Center for Prevention of Preterm Birth at Cincinnati Children's. "We estimate that decreasing the amount of particulate matter in the air below the EPA's standard threshold could decrease preterm birth in women exposed to high levels of small particulates by about 17 percent, which corresponds to a 2.22 percent decrease in the preterm birth rate in the population as a whole."

Emily DeFranco, DO

# Shorter Moms, Smaller Babies

Above: Louis Muglia, MD, PhD
Below: Ge Zhang, MD, PhD

Scientists have long observed that shorter mothers have shorter pregnancies, smaller babies, and higher risk for preterm birth. Research published online Aug. 18, 2015, in *PLoS Medicine*, connects this phenomenon to height-associated single nucleotide polymorphisms (SNPs). SNPS are the most common genetic variations among people.

The study looked at 3,485 Nordic women and their babies, and found that maternal height directly influenced the length of the pregnancy.

"The explanation for how this happens is unclear, but could be related to height reflecting the size of the uterus and pelvis, or to the mother's metabolic rate and the amount of nutrition she can supply to the growing baby," says Louis Muglia, MD, PhD, primary investigator of the March of Dimes Prematurity Research Center Ohio Collaborative and co-director of the Perinatal Institute at Cincinnati Children's. Muglia and Ge Zhang, MD, PhD, collaborated on the study.

The doctors say further confirmation is needed in additional cohorts. And the findings may not apply to low- or middle-income countries where nutrition can restrict growth.

# Stronger Links Between Autism, Maternal Obesity

A new study from Cincinnati Children's shows that scientists can use electronic medical records and birth information to verify and strengthen an already suspected link between autistic children and pregnant mothers with obesity and diabetes.

The findings, posted online Jan. 29, 2016, in *Autism Research*, reveal that pregnant mothers with obesity or gestational diabetes were 1.5 times more likely to have a child with ASD compared to other mothers. The increased risk of ASD for pregnant mothers with both obesity and gestational diabetes was two-fold.

The findings fit well into an increasing body of evidence that obesity and gestational diabetes may be associated with autism development.

"Although previous studies report a link between maternal obesity and diabetes during pregnancy to autism, we demonstrate that electronic medical data can verify and establish the extent of this link across large populations," says Katherine Bowers, PhD, MPH, study senior author and a member of the Division of Biostatistics and Epidemiology at Cincinnati Children's.

Katherine Bowers, PhD, MPH

# Working with E-Scrap Increases Lead Exposure

The disposal and recycling of electronic devices has increased exposure to lead and other toxicants, says Nicholas Newman, DO, MS, and pediatricians should talk with parents about potential hazards.

In the July 17, 2015, *Morbidity and Mortality Weekly Report*, Newman reported findings on two children, ages 1 and 2, whose father worked at an "e-scrap" recycling company. His job required crushing old leaded cathode ray tubes from televisions and computer monitors. His children had dangerously elevated blood lead levels. Within three months after the father left the job, the children's lead levels decreased.

"This is an opportunity to avoid take-home exposures of lead, other metals, and toxicants that may be present at work," says Newman, who directs the Environmental Health and Lead Clinic at Cincinnati Children's. "Preventing is key because decontaminating homes and vehicles isn't always effective. Normal house cleaning and laundry methods are inadequate, and decontamination can lead to hazardous exposures among workers doing the cleaning."

Newman's report outlines steps that parents can take if their jobs put them at risk. The national Pediatric Environmental Health Specialty Unit network provides a list of potentially risky occupations.

Nicholas Newman, DO, MS

# Software Predicts Success of Cochlear Implants

A new computer program may be able to predict whether hearing-impaired children will develop language skills after cochlear implant surgery.

A study published Oct. 12, 2015, in *Brain and Behavior,* details how the program analyzes functional magnetic resonance images (fMRI) to show how regions of infants' brains respond to auditory stimulus tests given before surgery. The computer model was produced by a team led by Long (Jason) Lu, PhD, and Scott Holland, PhD, of the Pediatric Neuroimaging Consortium.

"This study identifies two potential biomarkers for predicting cochlear implant outcomes," Lu says.

The model detects heightened activity in the left hemisphere's speech-recognition and language-association areas, and physical variations in the right cerebellar structures. After fMRI data is collected, the computer algorithm uses a process called Bag-of-Words to predict which children are good candidates for cochlear implants.

"This is one of the first successful methods for translating data from fMRI of hearing-impaired children into something with potential for practical clinical use," says Lu.

Above: Long (Jason) Lu, PhD
Below: Scott Holland, PhD

# Bariatric Surgery for Teens Shows Long-Term Benefits

Two studies by Cincinnati Children's researchers demonstrate the promise of gastric bypass surgery for severely overweight teens.

At the November 2015 American Heart Association meeting, doctors reported on 50 patients who had the surgery as teens eight years prior. Their BMI had decreased by 32 percent, and cholesterol and triglycerides decreased from 85.7 to 38.3 percent.

By comparison, just eight of 30 teens in a non-surgical, medically supervised weight management program continued their program after 12 months. Their BMI increased by 6.2 percent overall after eight years, and lipids were unchanged.

Amy Shah, MD, Division of Endocrinology, and Tom Inge, MD, surgical director, Surgical Weight Loss Program for Teens, will monitor whether the lipid improvements seen in the surgical patients will reduce atherosclerosis and cardiovascular disease over time.

In another report in the Nov. 6, 2015, *New England Journal of Medicine*, doctors reviewed the multi-center Teen-LABS (Longitudinal Assessment of Bariatric Surgery) study. Teen-LABS enrolled 242 teens ages 13 to 19 who weighed an average of 325 pounds before surgery. Three years after surgery, their average weight had decreased by more than 90 pounds. Type 2 diabetes was reversed in 95 percent and kidney function normalized in 86 percent; hypertension and lipid abnormalities also reversed in many patients.

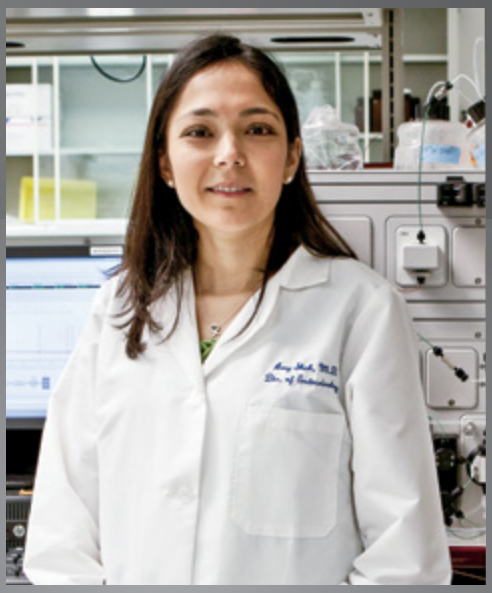
The promising results may underscore the advantages of earlier surgical intervention for obesity, researchers say.

"The remission rates for diabetes and hypertension were greater in teens than those we see in adult bariatric surgery patients," says Inge. "It is possible that earlier intervention could lead to better outcomes."

The surgery is not without challenges. Thirteen percent of patients required additional abdominal surgery, most commonly gallbladder removal, during the three-year period.

"Once teens are in these extremes of obesity, only 25 percent of them can achieve weights in the normal range after surgery, and over half remain severely obese even after surgery," says co-author and bariatric surgeon Michael Helmrath, MD, MS.

With numbers of obese teens growing, gastroenterologist and co-author Stavra Xanthakos, MD, MS, says, "The study will help doctors have informed discussions with teens and families about the benefits and risks of bariatric surgery."



Tom Inge, MD, and Amy Shah, MD

# Reinvigorating Older Progenitors

Exposing older nephron progenitors to younger ones appears to keep the older cells productive for a longer time.

A research team led by Raphael Kopan, PhD, exposed older nephron progenitor cells to a younger progenitor cell niche, extending the older cells' capacity to self-renew. The study involved heterochronic transplantation of young and old progenitor cells and used single cell mRNA analysis to study their behavior.

The researchers published their findings Oct. 12, 2015, in *Developmental Cell*.

In an interview in *Nature Reviews Nephrology*, Kopan noted that the findings were unexpected and seemed related to exposure to the younger progenitors. "... we observed an in-between result — some of the old progenitor cells preferentially exited the cap mesenchyme niche, but approximately 30 percent of the cells remained and continued to contribute to nephron production for up to one week."

Kopan's team plans to determine the molecular pathways underlying the progenitor cells' signaling mechanism, which eventually could lead to methods for increasing nephron numbers among premature and low birthweight infants.

Raphael Kopan, PhD

# New Asthma Treatment Reflects Years of Research

Cincinnati Children's played a major role in bringing about the November 2015 FDA approval of mepolizumab, the first new asthma drug in more than a decade.

The drug successfully targets severe asthma in people 12 years and older.

The drug's availability is a credit to institutions and researchers around the world who have been studying asthma for more than 30 years, says Marc Rothenberg, MD, PhD, Director of the Division of Allergy and Immunology and the Cincinnati Center for Eosinophilic Disorders.

"A tremendous amount of work has been done not only by Cincinnati Children's but also by many others," he says.

Researchers found a pathway involving the protein interleukin 5, which fuels severe asthma caused by inflammatory cells called eosinophils. Mepolizumab inhibits interleukin 5 and blocks the production of eosinophils.

Besides identifying the molecular target for mepolizumab, Cincinnati Children's also conducted clinical trials of its safety and efficacy, for patients with asthma as well as eosinophilic disorders such as eosinophilic esophagitis.

Marc Rothenberg, MD, PhD

# Amniotic Fluid Could Be Key to Safer Deliveries

A pregnant woman's amniotic fluid could predict when it is safe to deliver a premature baby.

Researchers have identified a way to test RNA and genetic signatures in amniotic fluid to see whether fetal lungs – and other organs – are mature enough for a safe delivery. The findings were published Oct. 22, 2015, in *BMC Medical Genomics*.

By isolating RNA in amniotic fluid at different times during pregnancy, researchers identified 257 genes that were expressed differently in late preterm (34-36 weeks) compared with full-term fetuses. The genes expressed preterm were linked to underdeveloped lungs, decreased lean body mass and immature feeding patterns.

Because the study involved only 16 women, the authors plan to confirm results with a larger group. They also plan to develop a test for fetal maturity that will use the mother's blood or urine, to avoid amniocentesis.

The research team included lead author Beena Kamath-Rayne, MD, MPH, senior authors Nathan Salomonis, PhD, and Yan Xu, PhD, and investigators in Neonatology, Pulmonary Biology, Bioinformatics, and Maternal-Fetal Medicine.

From above: Beena Kamath-Rayne, MD, MPH, Nathan Salomonis, PhD, and Yan Xu, PhD

# Cincinnati Children's Collaborates with Adare Pharmaceuticals on Innovation Fund

Adare Pharmaceuticals, Inc., and Cincinnati Children's are joining forces on a project to optimize medications for children.

The collaboration combines the experience of Cincinnati Children's with Adare's expertise in enhancing medications and their delivery to improve patient care.

"Collaborations like these drive innovation, and we look forward to working with Cincinnati Children's to bring better options to infants and children, who have a special set of needs," says John Fraher, President and CEO of Adare Pharmaceuticals.

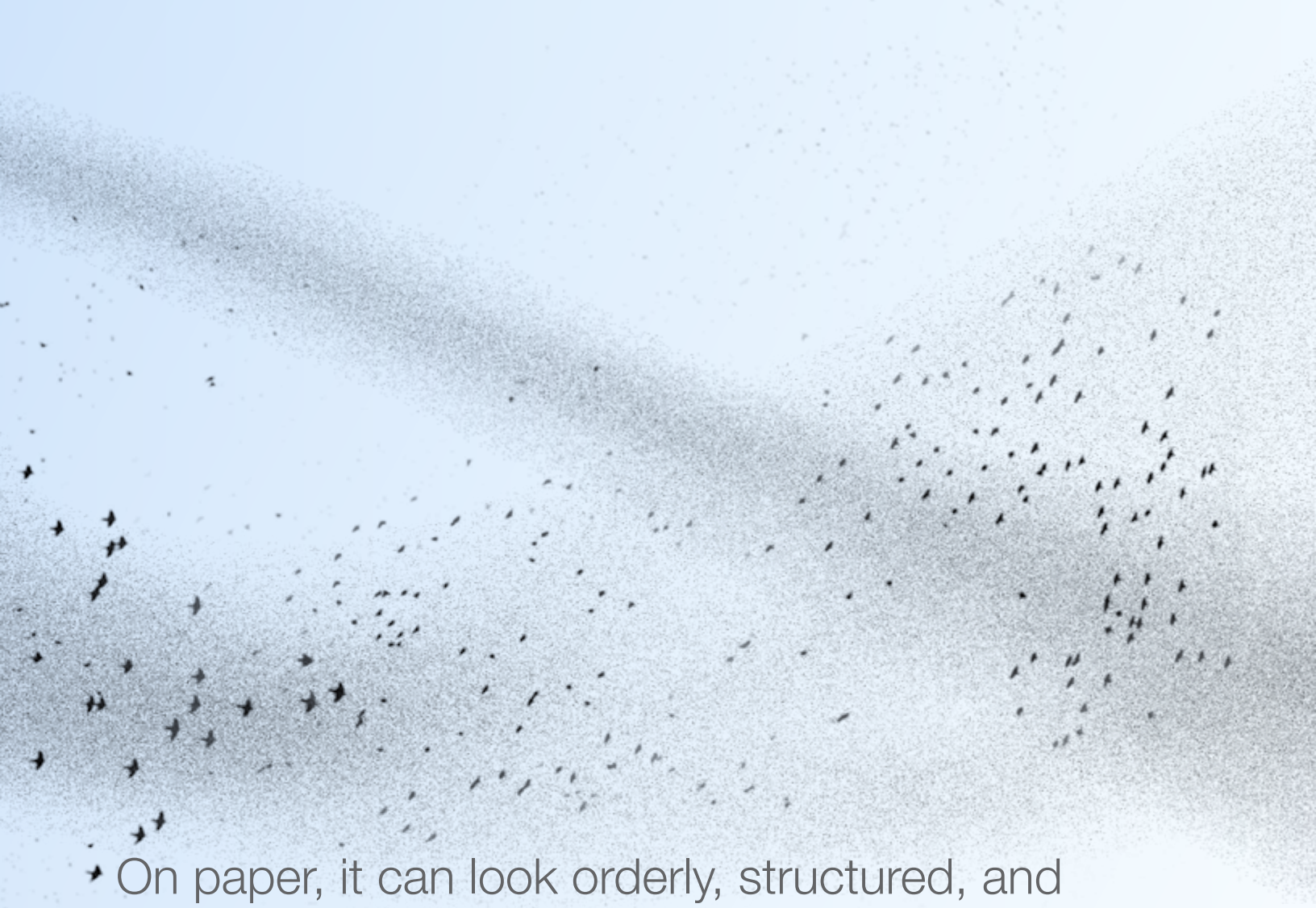
According to the agreement, Adare will be part of the review committee for Cincinnati Children's annual Innovation Fund, which identifies and sponsors research of special merit and potential. Following completion of the chosen research, Adare will have the option of entering into a licensing agreement and will be responsible for further clinical development and commercialization of products arising from the collaboration.

"We are pleased to partner with Adare to identify and advance improved treatments for our patients," says Margaret Hostetter, MD, Chair of Pediatrics and Director, Cincinnati Children's Research Foundation.

# To Harness a WHIRLWIND

## CENTER FOR PEDIATRIC GENOMICS APPLIES STRUCTURE TO A SURGING FLOW OF DISCOVERY

*by Tim Bonfield*



On paper, it can look orderly, structured, and almost simple. But the cycle of discovery fueled by the revolution in genomic science is more like a cyclone, surging forward, spinning faster, and changing everything in its path.

The enormous potential of genomics to transform medicine makes these exciting times to be working in biomedical science. The breakneck pace of new developments, however, makes it all the more urgent to fully understand the implications of this evolving field and be prepared for the changes to come. This is the goal behind the new Center for Pediatric Genomics at Cincinnati Children's - to usher in a sea change in the relationship between research and clinical practice.

"Our capacity to explore ideas about how things work has changed so much that we're doing experiments today that were impossible two years ago," says John Harley, MD, PhD, who co-directs the center with Peter White, PhD. "The databases we have at our disposal are vastly larger and growing exponentially, which offers tremendous opportunity. But bringing utility to all this takes a new level of concerted, dedicated effort."

Says White: "Five years from now, genomics will be considered much more a standard part of clinical practice. Yet there's tremendous uncertainty about the changes genomics will bring, not just for patients and families, but also for clinicians. The uniqueness of the center is that it seeks to establish genomics as a community of practice across an entire institution."

Cincinnati Children's launched the Center for Pediatric Genomics in 2014, but the center actually reflects more than 15 years of investment to acquire the latest gene sequencing and gene editing technologies, to expand computing power, to develop ethical methods for mining electronic medical records, and most importantly, to recruit a world-class team of experts to put it all together to improve outcomes for children.

So, what is the Center for Pediatric Genomics? On one level, the center functions as an incubator for innovation that


John Harley, MD, PhD, (left) and Peter White, PhD, co-direct the Center for Pediatric Genomics at Cincinnati Children's.

has already provided support to more than 20 new and promising projects. (See pages 30 and 31). On another level, the center serves as a catalyst for integrating genomics into everyday medicine.

## UNDISCOVERED FRONTIERS

The projects supported by the center reflect the wide range of ways genomics will influence the future of pediatric medicine. Some projects seek cures for rare, almost untreatable conditions. Others search for solutions to stubborn complications that occur in cancer treatment and organ transplantation. Some seek to scale up the entire field to take on common but far more genetically complex conditions such as epilepsy, diabetes and asthma.

Still other projects explore more foundational questions, such as studying the formation of chromatin loops and the role they play in regulating gene expression, or searching for better methods to distinguish a risk-causing gene mutation from a "variant of unknown significance."

Harley says no one can predict where the work may lead.

"If you could stretch out a full strand of DNA, it would be about three meters long. But the strands of the DNA in our chromosomes are actually boxed up into a ball so tiny that we cannot see it. Indeed, there are about 10 trillion of these in the adult human body," Harley says. "We used to think there was no particular significance to the way that folding occurs, but now we know that it matters very much. That's just one aspect of genomics that remains minimally understood. It may take the rest of the century to figure out what exactly causes the many differences in our genome, and why."

## NEW KINDS OF CARE TEAMS

Some of the center's work explores how all this new science will play out as more clinicians become involved in using and communicating genomic information and more families face decisions based on that information.

The emergence of genomics and the promise of personalized, precision medicine is driving new relationships between clinicians and research scientists. In addition to working directly with patients, this may mean that physicians must also interact effectively with a behind-the-scenes army of experts, including computational biologists, cytogeneticists, biostatisticians, programmers, advanced laboratory technicians, bioethicists and others.

Working out the best ways to work together will be a massive undertaking, which is why the center expects to play a major role in training and raising awareness in the clinical world about resources available on the research side.

## FORGING MASSIVE NETWORKS

Harley and White emphasize that translating the potential of genomic innovation into improved medical practice will depend heavily on research centers working together at institutional levels. Cincinnati Children's already leads several big research collaborations and participates in many others. (Read more about eMERGE on page 24).

An important role for the center will be to support even more multi-center projects.

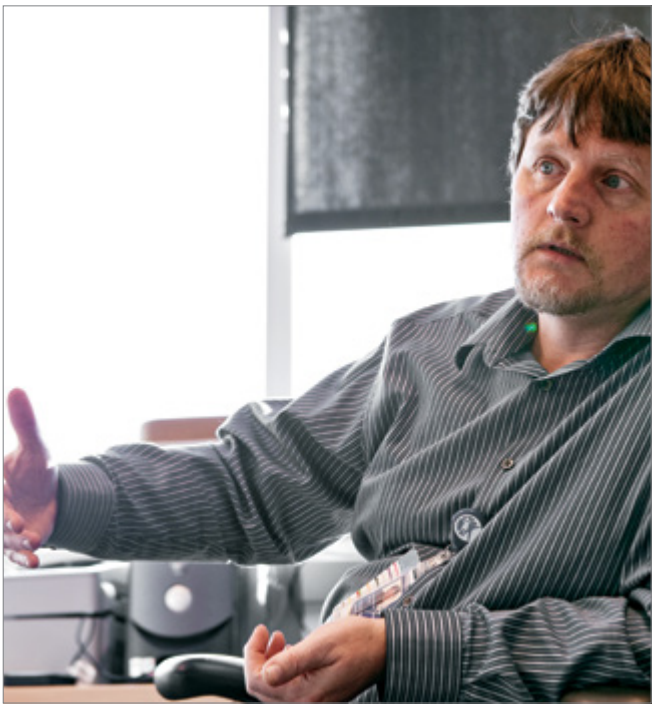
"Our challenge is that the complexity of genomics precludes the old models for conducting research and providing care," White says. "Very few, if any, advances in this field will come from researchers in isolated labs, or even from single institutions. This truly is the era of team science." ■


A cyclone of discovery: Innovation in genomics swirls along a path that begins with patients and touches all aspects of medical research.

# Of Mice & Men

Emerging Use of Mouse "Avatars" Accelerates Precision Medicine

*by Tim Bonfield*



One of the most exciting trends in genomics has been the emergence of the human-to-mouse-to-human approach to diagnosing and treating rare conditions.

Until very recently, the cost and complexity of conducting whole genome and whole exome sequencing made these tools impractical for use in patient care. Now these research devices are evolving into clinical life-savers.

At Cincinnati Children's, Kenneth Kaufman, PhD, is pursuing a two-track genomic strategy to do battle against the rare lung disease hereditary pulmonary alveolar proteinosis (hPAP).

One track reflects an accelerated but traditional research model: gather samples from people diagnosed with the condition. Conduct genetic analysis to generate a list of suspicious DNA variations. Conduct further tests, usually in animal models, to confirm which polymorphisms are most likely to be disease-related. Publish a paper detailing new therapeutic targets.

Under this model, the hoped-for result would be that a future generation of children might benefit from faster technology speeding up the process of discovering disease-related variants that eventually could lead to new medications.

The other track, however, is far more individualized. Kaufman and colleagues in the Transgenic Animal and Genome Editing (TAGE) core laboratory at Cincinnati Children's are creating highly custom mouse models that reflect the genomic disease profiles of specific children. The technology has become so quick that custom lines of humanized mice can be generated in as little as three months. These mouse avatars can allow clinician-scientists to explore various possible treatments without risk to the patient, then recommend the most effective option for actual use.

The improving speed of this process has made the avatar approach an increasingly attractive option when treating children with rare, severe, high-cost conditions. At Cincinnati Children's, mouse avatars already play important roles in treating children with relapsed cancers and in research related to mitochondrial diseases (see story on page 18). This is precision medicine in action.

## A FAMILY AFFAIR

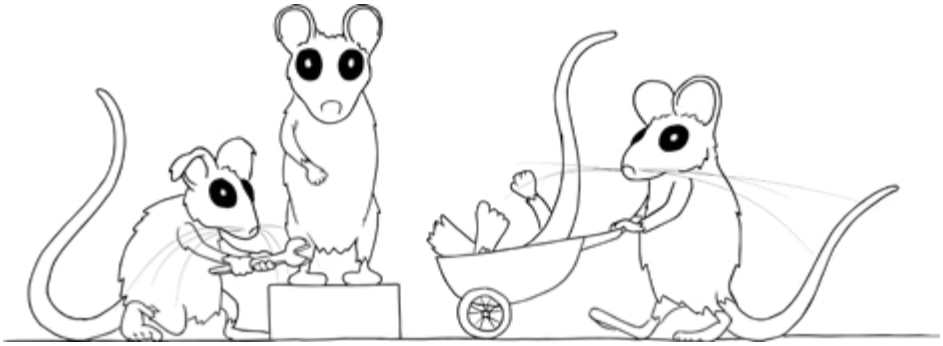
Kaufman's work involves studying a Kuwaiti family that includes a sister and a brother who share a rare gene deletion associated with hPAP, but surprisingly, only the girl has developed the disease. Whole-exome sequencing has revealed that the girl possesses a second polymorphism, in a gene specifically expressed in lung tissue, that appears to explain why she developed the disease but her brother did not.

As the team continues its work, it may someday be possible to transplant edited versions of the girl's own lung stem cells so that they lack the second polymorphism, Kaufman says. Such a result may never lead to a blockbuster drug, but the effort could close the loop for a child like this, giving her a chance to grow up without enduring whole-lung lavage treatments, the primary therapy for her condition.

## A REWARDING FEELING

The outcome in this case remains uncertain. But just the possibility of playing a direct role in saving a child's life, even if they never meet face-to-face, inspires Kaufman.

"When we conduct whole exome sequencing, most of the polymorphisms we find have no causative relationship with the disease. Even when we find an association, in most cases, it does not mean a person is certain to develop the disease. It only means that the risk is elevated," he says. "But sometimes we can find the culprit. And when that leads to an effective therapy, it can be a very rewarding feeling." ■



Custom-built mice: Gene sequencing and editing technology has become so quick that clinician-scientists such as Kenneth Kaufman, PhD, (shown left) can use mouse avatars to refine diagnoses and test-drive precision treatment plans.


Dr. Sonata Jodele's research into the functionality of gene variants has provided insight into why some children with stem cell transplants are more susceptible to thrombotic microangiopathy than others. She credits the strong sense of collaboration at Cincinnati Children's and delights in sharing former patients' photos with the lab researchers so integral to her work.

# Bridging the Pathways of TMA

Complication of stem-cell transplantation appears rooted in genetic variants, the fingerprints that – until now – have long eluded researchers

*by Tom O'Neill*

In children who have undergone stem-cell transplantation, some forms of thrombotic microangiopathy (TMA) can progress from manageable to potentially fatal with elusive silence.

TMA does, however, leave one crucial clue: a genetic fingerprint of susceptibility.

That discovery is driving new strategies for early diagnosis and treatment at Cincinnati Children's, led by Sonata Jodele, MD, Division of Bone Marrow Transplant and Immune Deficiency.

In a prospective study published online Nov. 24, 2015, in the journal *Blood*, Jodele's team used gene-expression profiling to find the functional significance of gene variants found among 77 patients who underwent genetic testing. Of the group, 34 had TMA, and of those, 65 percent had genetic variants in at least one gene compared with only nine percent of patients without TMA.

## PROGRESS IN EARLY DETECTION

TMA is a fairly common complication of hematopoietic stem-cell transplantation. If left unchecked, symptoms can cascade from anemia and platelet consumption to thrombosis and, in some children, multiple organ failure and death.

Cincinnati Children's is the only center in the U.S. that performs the full array of molecular and cellular diagnostic testing for TMA. Yet until recently, there was no data addressing individual susceptibility to TMA, nor any pre-transplant screening that could alter risk-assessment and transplant regimens.

"Our study reveals important differences in genetic susceptibility based on genotype," Jodele says. "Now, we are looking at how these markers in the blood line up over time, the role of genetics and complement gene defects."

The new study, which involved scientists from the divisions of Human Genetics and Biomedical Informatics, follows up on a July 24, 2014, study, also published in *Blood*. In that study, Jodele's team established a new algorithm for early diagnosis, and showed the potential of eculizumab therapy, a humanized monoclonal antibody that functions as a terminal complement inhibitor.

Last year, Cincinnati Children's awarded Jodele one of its 11 Innovation Fund awards to build upon her work in TMA.

## PICTURES OF SUCCESS

Jodele's office walls are a tapestry of another type of award: art and photos of the children whose lives she has helped save.

"It's very rewarding," Jodele says, "because we see kids who are suffering and dying. But then you see them go home and go back to school, it's wonderful."

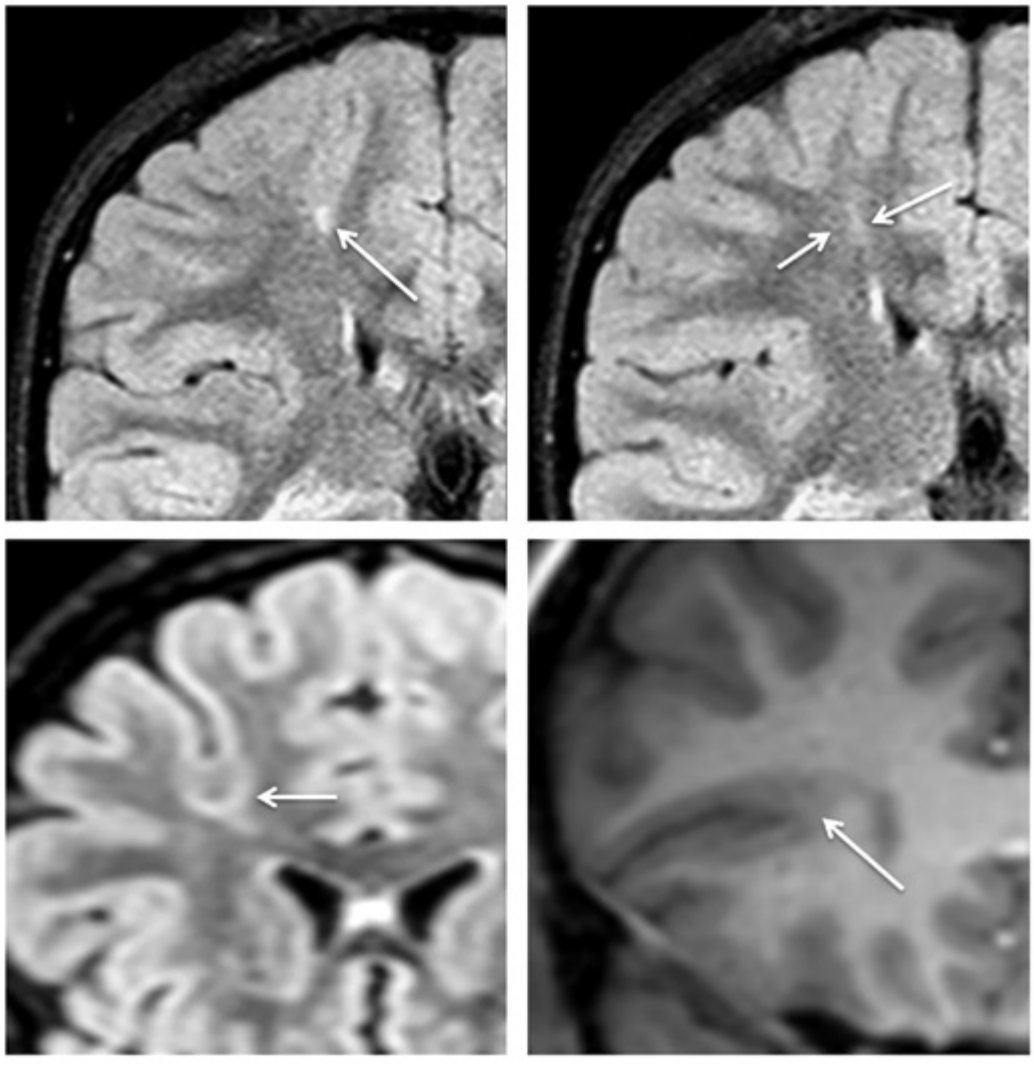
One of those kids is Ava Pannozzo, 7, of upstate New York. She was treated in 2013-14 at Cincinnati Children's for hemophagocytic lymphohistiocytosis (HLH), a disorder of the immune system. She developed severe TMA, was days or weeks from dying, and now is a first-grader taking ballet dance lessons.

Told of Jodele's art and photo collection, her father, Chris, paused. "That's tremendously humbling," he says. "I think we should have a shrine to *her*."

# Predicting Surgical Outcomes

## Genomic Research May Help Identify Best Candidates for Anti-Seizure Surgery

*By Heide Aungst*



MR imaging findings of cortical dysplasia in three patients. Top row: Two adjacent coronal T2 FLAIR images demonstrating focal signal along the bottom of a frontal lobe sulcus (left) and adjacent tapering signal abnormality extending into the white matter (right). Bottom row: Coronal T2 FLAIR image (left) demonstrating an abnormally deep sulcus with associated abnormal cortical signal and cortical thickening. A Coronal T1 image (right) demonstrating an abnormally deep sulcus, with associated cortical thickening and adjacent heterotopic gray matter. While findings of cortical dysplasia may be diagnostic, imaging findings are often subtle. In many children with pathologically proven cortical dysplasia, MRI may be normal. Images are courtesy of James Leach, MD, Cincinnati Children's.

When neurologist Hansel Greiner, MD, meets with families of children who are about to undergo brain surgery for epilepsy, they usually have one important question for him: "Why?"

As Co-Director of the Epilepsy Surgery Program at Cincinnati Children's, that crucial question also haunts Greiner's research: Why do some children develop seizure-causing focal cortical dysplasia (FCD)? Why can some children be treated successfully with medication, while others need surgery? Why does surgery work best for children with one kind of FCD, but not the other?

While wrestling with these questions, Greiner knew he wanted to go beyond understanding only why some children develop FCDs. He also wanted to develop a minimally invasive diagnostic tool that could help him determine — before surgery — if a child had FCD, and, if so, if it was the type that could be helped most by surgery. To do all that, he knew, would take a different kind of research than he had ever done before.

## EXPERT IN EPILEPSY, NEW TO GENOMICS

"I noticed some of my colleagues really get some good information on rare diseases using high-powered genomic sequencing, and I thought, 'Why can't we do that?'" Greiner says.

About four years ago, Greiner began collecting brain tissue and blood samples from patients, ages newborn to 30, who were undergoing FCD surgery performed by neurosurgeon Francesco Mangano, DO, at Cincinnati Children's. Once he had samples from about 20 patients, he wanted to move forward with exome sequencing, but he wasn't exactly sure how to take the next steps.

That's when he applied for and received a pilot project award from the Center for Pediatric Genomics (CpG). In addition to providing funding to sequence his samples, CpG connected Greiner with other collaborators within Cincinnati Children's to help him find the best solutions for processing and storing his data.

## CENTRAL DATA COMMONS ADDS VALUE

In fact, one of CpG's key objectives is to create a central data commons — ¡VIVA! — a one-stop place where researchers can process, store and access genomic data for their studies. Ultimately, ¡VIVA! also will allow for collaboration outside of Cincinnati Children's, promoting powerful genomic research.

"This convenient access to data will allow us to raise genomic literacy, foster collaboration, and build multidisciplinary teams to tackle complex genomic disorders," says Peter White, PhD, Director of the Division of Biomedical Informatics and Co-Director of CpG, who is working with a steering committee to develop the data repository.

Although Greiner is still gathering initial data, he's excited about using genomics to answer those tough questions about FCD, which he hopes will lead to new diagnostic tools and therapies.

"One of the biggest challenges for me has been to learn how to design an experiment using genomics that can yield results," Greiner says. "There are so many things we can learn with genomics. And the most important is 'How can we improve a patient's life?'" ■

Hansel Greiner, MD

# When Diagnosis Brings Relief

## Genomic Data Helps Family Understand Son's Mysterious Symptoms

*by Tim Bonfield*

It took a revolution in medical science to provide the answers the Brunner family had been seeking for nearly 13 years.

When Tyler was born in 1999, it seemed like an early surgery to correct a birth defect involving his stomach would largely resolve his medical troubles. However, by age 2, Tyler developed seizures that seemed like an emerging case of epilepsy. By age 6, he was exhibiting bladder and bowel dysfunctions that suggested an autoimmune disease. As Tyler grew, he struggled to gain weight, became exhausted by normal activity and highly intolerant to heat. Strength faded from his legs to the point that he began using a wheelchair for relief.

"Not knowing what was going on was awful," says Tyler's mother, LaTonya Brunner. "He was sleeping on the couch constantly. His hands and feet would suddenly turn bright red and nobody could explain it."

By 2013, however, increased speed and reduced costs had made whole-mitochondrial genome testing significantly more accessible as a diagnostic tool. In addition, Cincinnati Children's had recently recruited an expert who knew exactly what to look for. It turns out that Tyler has a rare mitochondrial disease.

### IMPROVING DIAGNOSIS

Taosheng Huang, MD, PhD, a geneticist from the University of California Irvine, arrived in fall 2012 to direct the new Mitochondrial Disease Program at Cincinnati Children's. Known as the "powerhouses" of cells, mitochondria produce over 90 percent of the energy required by a cell. However, when dysfunctions occur, a wide variety of neurological and organ system complications can result. The new program, based in the Division of Human Genetics, integrates genetic testing, translational research, and clinical care for these children.

Tyler's condition occurs once in every 5,000 births, scientists estimate. If there was ever a set of conditions that needed the power of high-throughput genomic analysis and the promise of personalized medicine, this is it.

"This is the time for improving diagnosis," Huang says. "With more precision, we have a better chance of finding more effective treatments."

Tyler has already benefitted from better genetic testing. He takes a vitamin cocktail known to help improve energy levels for some children with "mito." Over time, researchers hope to find treatments that can more directly address specific forms of mitochondrial disease.

The Huang lab has identified many new mito disease-causing genes. For example, in July 2015, Huang's team published findings in *Nature Genetics* based on whole exome analysis of four families from different countries who share an identical set of gene mutations that have caused an unusual combination of optic atrophy and peripheral neuropathy affecting their vision and their legs, respectively. The team managed to produce a zebrafish model, and has recently begun work to produce a mouse model to resolve how these genetic abnormalities lead to the patient's symptoms.

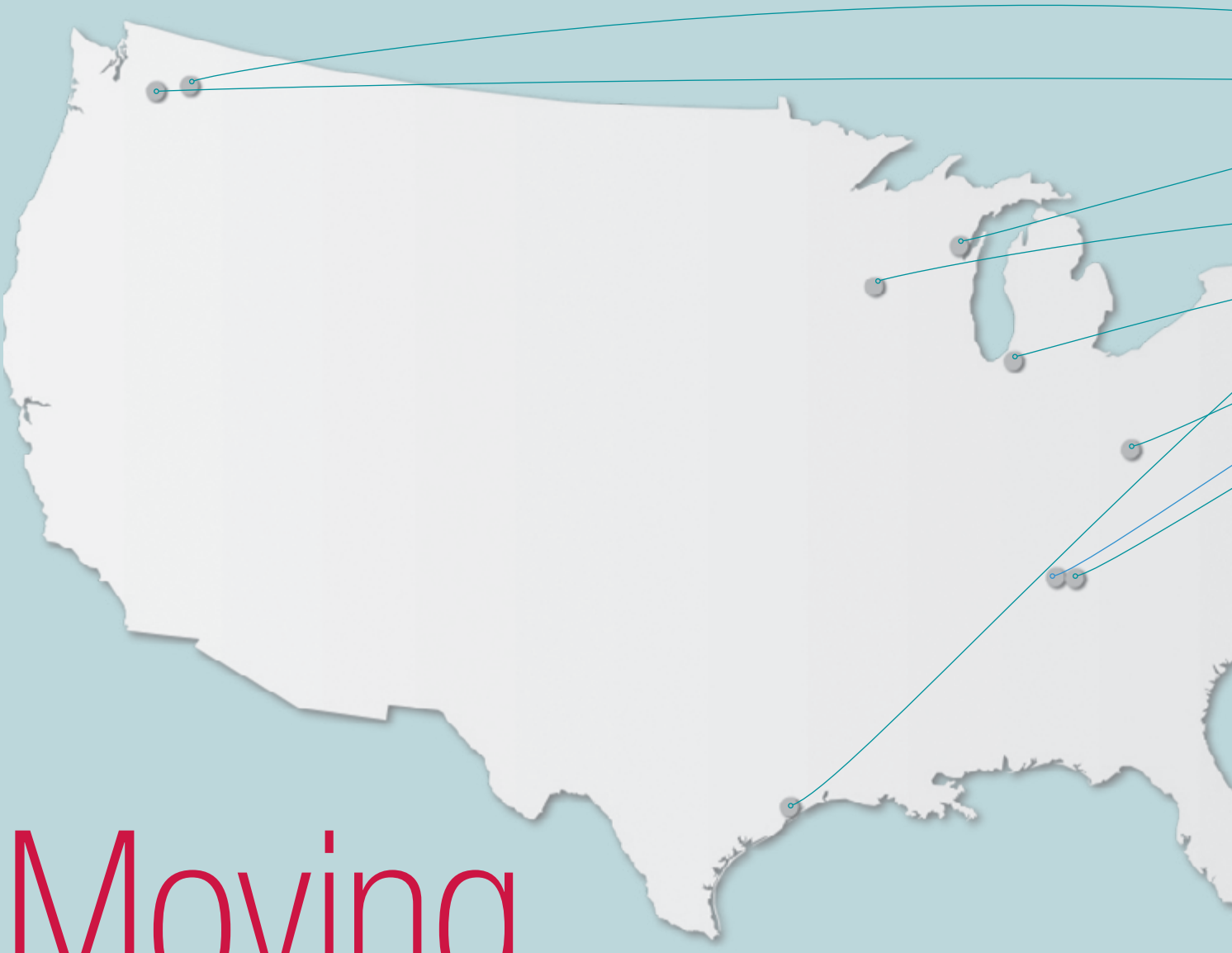
## PATHWAY TO TREATMENT

Eventually this work could lead to a new drug compound, or possibly a stem cell transplant approach, that could improve mitochondrial function across a wide range of variations. "This would be a remarkable advancement for both science and the patients suffering from mitochondrial diseases," Huang says.

LaTonya Brunner says she hopes that Tyler may personally benefit from a breakthrough treatment, but even if that does not happen, participating in the research work has been valuable.

"A couple of years ago, we didn't know anything about mito. It's a very hard disease to explain to other people," she says. "Now the word is starting to get out." ■

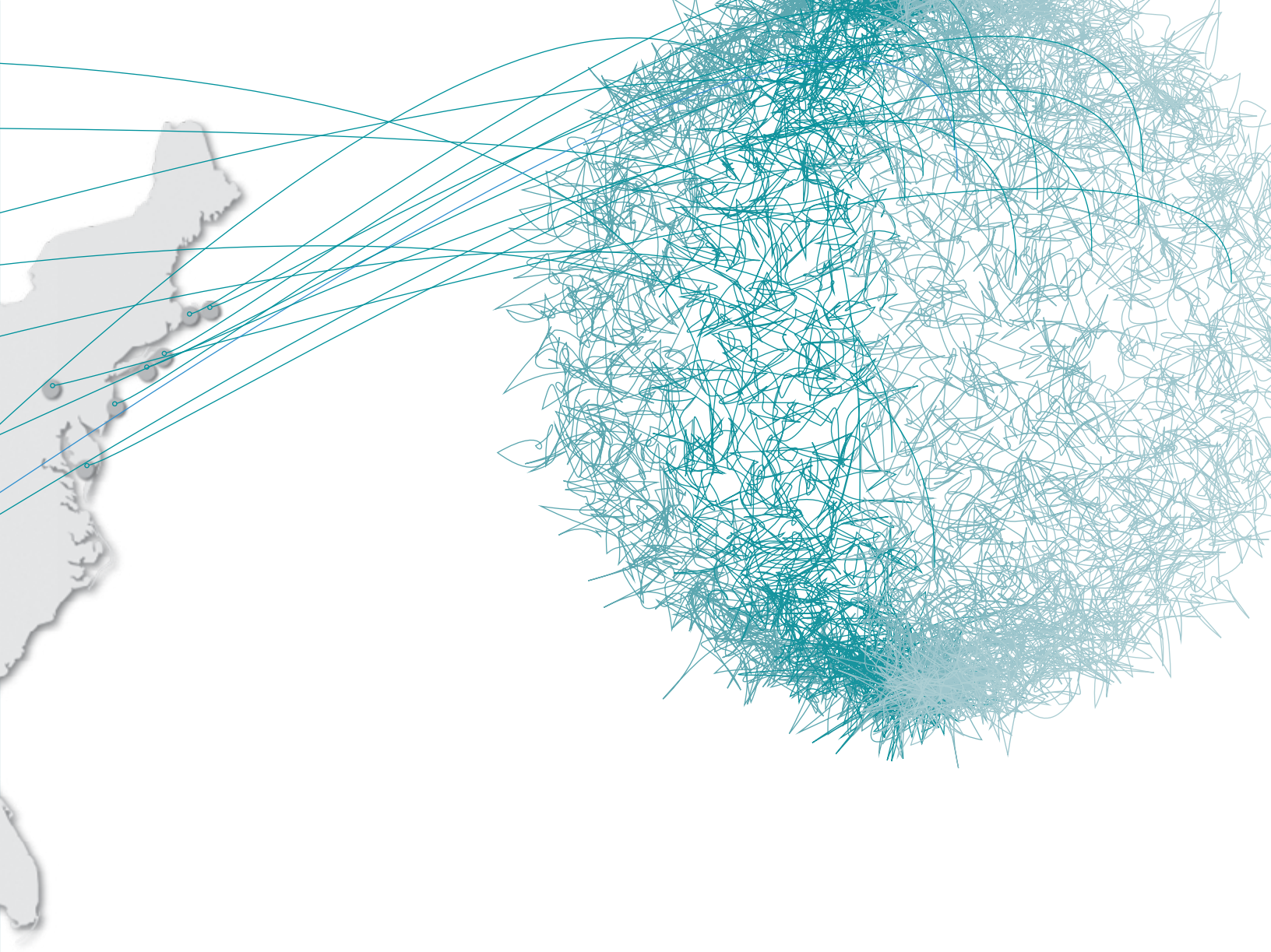
Solving mysteries: Taosheng Huang, MD, PhD, explains to Tyler Brunner and his mother, LaTonya, how the teen's unusual symptoms might be caused by a rare mitochodrial disease, which occurs in approximately one in every 5,000 births.



# Moving Innovation into Practice

## eMERGE PROJECT COMBINES GENOMIC RESEARCH WITH ELECTRONIC HEALTH RECORDS TO IMPROVE CARE

*By Jill Schlabig Williams*



Senthilkumar Sadhasivam, MD, is tapping into the power of genomics multiplied by the power of electronic health records (EHRs) to make pain management in children safer and easier.

As a post-surgery pain management specialist and researcher, Sadhasivam is searching for solutions to a long-standing issue in pain control. While most children respond well to medications like codeine, some receive little to no pain relief from typical dosages. Meanwhile, an unlucky few suffer severe drug reactions, including brain damage or death from opioid-induced respiratory depression.

Controlling post-surgical pain in children has long been a complex challenge. Codeine, a common pain medication for adults, is no longer recommended for children undergoing outpatient tonsillectomy because of its wildly variable effects. Sadhasivam is working to find better and alternative analgesic options by developing a genomics-based method that can predict how individual children are most likely to react to opioid pain medications.

Sadhasivam's project is among several genomics-based clinical efforts receiving a boost from the Electronic Medical Records and Genomics (eMERGE) project, a federal initiative that supports work at Cincinnati Children's and nine other sites. The goal: to develop methods and best practices for using electronic health records to move genomic research into clinical care.

Sadhasivam and colleagues have developed a genetic test that helps predict how children are likely to respond to pain medications. Through the eMERGE project, he is working with an informatics team to merge those test results into patient records to help surgeons provide more accurate dosing and optimize pain relief.

## CONNECTING CLINICIANS & RESEARCHERS

The National Human Genome Research Institute launched eMERGE in 2007. Pediatric sites including Cincinnati Children's were added in May 2012. A new four-year, $52.4 million phase (eMERGEIII) was launched in September 2015.

This initiative represents one of the largest cross-divisional efforts in translational medicine at Cincinnati Children's. Overall, eMERGE involves 17 distinct aims involving more than 50 faculty scattered among many Cincinnati Children's research divisions.

Plans include collecting the DNA sequences of more than 100 genes, most of which are known to have serious pathological

The multicenter eMERGE study includes 17 distinct aims. A novel post-surgical pain management project involves Senthilkumar Sadhasivam, MD, (left), Victor Garcia, MD, (upper right) and Roxanne Anderson, MSN.

variants, from 3,000 Cincinnati Children's patients. That data will become part of a collection of 30,000 sequencing records from the entire eMERGE network.

The genomics of specific diseases will be studied, with a special focus on identifying somatic mutations, which are not inherited and randomly occur in life. Other aspects of the eMERGE project include addressing ethical concerns, supporting clinical decision making, and developing best practices for returning genomic results to patients and families.

John Harley, MD, PhD, director of the Center for Autoimmune Genomics and Etiology (CAGE) and the principal investigator on the project, aims to leverage eMERGE to make clinical implementation of genetic results routine. "This effort is an infrastructure project," he says. "We are putting the tools in place to help our clinicians and researchers work together to find practical utility from the tsunami of genomic data that is being generated."

He describes the eMERGE project as a suite of options that can connect researchers and clinicians, allowing them to mine EHRs for clinical clues that inform genomic research, and then, for those that do, to use those same EHRs to return genetic results and guide care decisions. He also emphasizes that eMERGE is constantly seeking new opportunities to use genomics and the EHR to improve care.

## HUNTING FOR COMPUTABLE PHENOTYPES

At the heart of eMERGE are activities to define and develop algorithms that can identify distinct groups of patients who share certain characteristics or conditions (phenotypes), along with developing tools in the electronic medical record to support clinical decision-making.

First, investigators select conditions that have attractive properties for genomic study. Pain management is just one of several conditions to be studied through the eMERGE project. Another project will focus on non-alcoholic steatohepatitis (NASH), commonly called 'fatty liver,' which is increasing in frequency along with the epidemic in childhood obesity.

Then, the researchers transform raw EHR data into a computable format. They also write complex computer algorithms and often use natural language processing tools to hunt through that data, including free text from clinical notes, to find groups of patients with similar conditions. The EHR data of these patients are analyzed along with their genomic data in order to determine whether any of the genetic markers are causal.

These algorithms for "computable phenotypes" are shared and validated at the other eMERGE sites and are also being used locally to help deliver targeted decision support to clinicians.

All of these activities are supported by a multi-disciplinary team that includes Yizhao Ni, PhD, Todd Lingren, MS, and Keith Marsolo, PhD, from the Division of Biomedical Informatics; collaborators from the Department of Information Services; input from clinical experts; along with Harley, Bahram Namjou-Khales, MD, Kenneth Kaufman, PhD, and Beth Cobb, MBA, from CAGE.

## IDENTIFYING CAUSATIVE GENES

Namjou-Khales is organizing these activities with the goal of using genome-wide and phenome-wide association studies to hunt down causative genes in a wide range of disorders.

For the pain medication project, researchers grouped patients who had adverse reactions to codeine and other opioids into cohorts with

Bahram Namjou-Khales, MD, is a member of our Center for Autoimmune Genomics and Etiology (CAGE). He supports the eMERGE project by organizing searches for disease causing genes.

similar characteristics. By analyzing the biological samples, researchers identified causative genetic variants for each phenotype and used that knowledge to create a genetic test to identify patients likely to suffer adverse reactions.

In another eMERGE initiative, more than 80 genes that can affect individual responses to drugs due to differences in metabolic pathways have been sequenced in 9,000 samples across the eMERGE network. Algorithms are being developed to help target drugs more closely to individual needs.

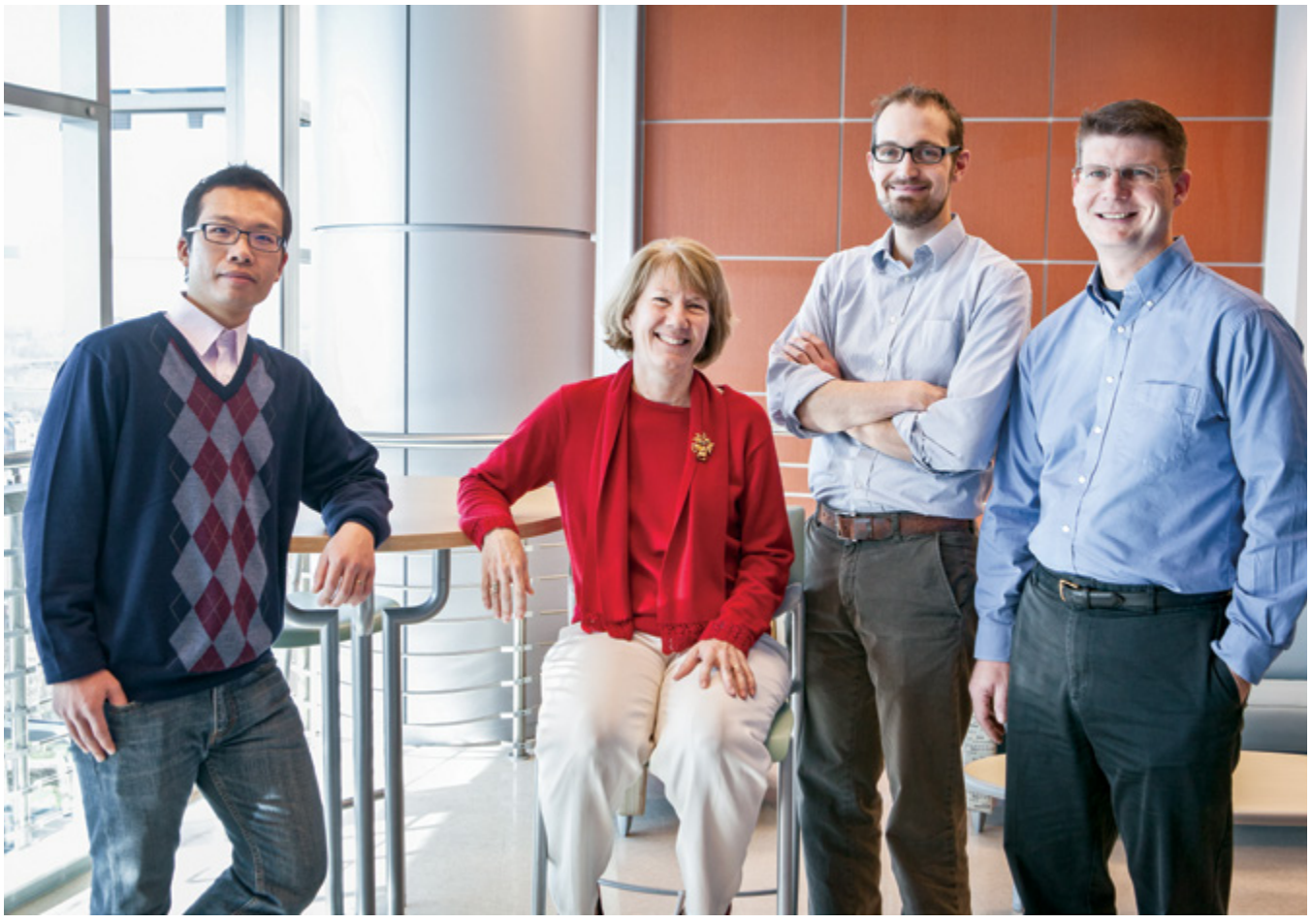
## TAKING IMPLICATIONS INTO ACCOUNT

The ethical, legal, and social implications of genomic work are front and center in the eMERGE project.

Cindy Prows, MSN, APRN, manages several projects in the Division of Human Genetics. She and colleagues, including Melanie Myers, PhD, MS, are exploring how and when to return genomic results to patients. What are the best ways to share findings with doctors, patients, and guardians? Should all results be shared? Or only those that are actionable, where a change in care can improve the outcome? How do the wishes of adolescents and their parents fit into the picture?

Armand Antommaria, MD, PhD, Director of the Ethics Center at Cincinnati Children's, is collaborating with colleagues in the University of Cincinnati College of Law on a project exploring responsibilities for re-analysis of genetic sequencing results. "As our knowledge expands, the interpretations of these results change over time," says Antommaria. "Are there moral and legal obligations to reanalyze results? On the provider side, what is the responsibility for communicating evolving results?"

Costs of treatment also will be studied. While Sadhasivam's codeine project did not have an economic focus, he did find that using an inexpensive genetic test to guide pain medications resulted in shorter lengths of stay for patients in the post-anesthesia care unit, saving an average of $160 per patient. The eMERGE team at Cincinnati Children's is considering a more formal cost-benefit analysis of genetic tests used to guide treatment of babies with neonatal abstinence syndrome.



A team including (left to right) Yizhao Ni, PhD; Cindy Prows, MSN; Keith Marsolo, PhD; and Todd Lingren, MS, supports the eMERGE project by hunting for computable phenotypes and studying how best to share genomic data with patients and clinicians.

### LOCAL EXPERTISE, NATIONAL SCOPE

The promise of precision medicine is to tailor treatments to individuals. The eMERGE project seeks to help fulfill that promise both locally and nationally.

Locally, the team at Cincinnati Children's is well-equipped to lead the way into this brave new world. The Cincinnati Biobank Core Facility contains DNA samples from more than 60,000 patients. Several on-site laboratories run increasingly sophisticated gene panels and other tests. And a state-of-the-art data center provides the secure, scalable computational power needed to work with huge genomic data sets.

With its national scope, the eMERGE project helps researchers across the country share data to maximize statistical sampling power and tap into larger cohorts to study diseases. By playing a lead role in this project, Cincinnati Children's has gained a seat at the table where decisions about the future of genomics and healthcare are being made.

All for the benefit of our patients.

## Get Involved

**IT'S NOT TOO LATE TO PLAY A ROLE IN SHAPING THE FUTURE OF GENOMIC MEDICINE.**

Interested scientists and clinicians can join the eMERGE project in various ways, including serving on working groups on topics ranging from phenotyping to data integration to ethical implications.

*For more information:*
*Contact* eMERGE *project manager Beth Cobb at Beth.Cobb@cchmc.org.*

## Key Aims of eMERGE III

- Help identify at least 100 genes to be included in a DNA sequence analysis panel to be run on more than 30,000 samples provided by eMERGE research sites.
- Provide consented biological samples from at least 3,000 Cincinnati Children's patients to be sequenced and included in a national database.
- Reinterpret 4,000 targeted gene panels previously run at Cincinnati Children's to identify candidate gene variants.
- Generate computer algorithms to mine electronic health records (EHRs) to identify genomic subgroups in disorders including appendicitis, hypermobility, migraine, primary pulmonary hypertension, and pyloric stenosis.
- Explore variants in the eMERGEIII gene panel to discover new disease patterns.
- Test EHR-based algorithms against the PCORnet Common Data Model, a standardized approach to managing medical data.
- Apply an eMERGE algorithm to data from the Million Veterans Project.
- Study how patients, guardians, and physicians learn about genetic results; develop tools to assess adolescent preferences; assess the value of MyChart as a portal for returning results.
- Evaluate the genetics of outpatient pain after tonsillectomy.
- Assess the economic impact of CYP3A5 genotype-guided dosing of tacrolimus, an immunosuppressant medication used after organ transplantation.
- Integrate clinical decision support processes into the EHR to guide treatment decisions.
- Explore and integrate ethical, legal, and social considerations.

# FUNDING INNOVATION

The Center for Pediatric Genomics (CpG) at Cincinnati Children's fosters and incubates outstanding and innovative scientific and translational genomics projects. These projects have received funding for pilot studies:

## 2016 Awardees

### Vidya Chidambaran, MD
**Anesthesia**
Genetic-Epigenetic Approach to Predict Chronic Post-Surgical Pain in Children

### Andrew Dauber, MD
**Cincinnati Center for Growth Disorders**
Confronting the Dreaded VUS: Validation of Exome Sequencing Candidates in Human Growth Disorders Using Genome Editing

### David Haslam, MD
**Infectious Diseases**
Fecal Metagenomics as a Tool to Identify and Mitigate Risk of Bloodstream Infection in High Risk Children

### Hong Ji, PhD
**Asthma Research**
Epigenetic Mediation of Genetic Effects in Childhood Asthma

### Andrew Lindsley, MD, PhD
### Artem Barski, PhD
**Pediatrics**
Epigenetic Mechanisms of Humoral Immune Deficiency in Kabuki Syndrome

### Q. Richard Lu, PhD
**Brain Tumor Center**
Functional Genomic Analysis of Oncogenic Pathways in Primary and Recurrent Medullablastomas

### Melanie Myers, PhD
**Genetic Counseling Graduate Program**
A Decision Aid for Return of Results across Genomic Sequencing Studies

### Mihaela Pavlicev, PhD
**Pediatrics**
The Contribution of Non-Coding Genome to Placental Defects: The Establishment and Application of a Novel Tool to Reliably Map and Quantify Active Enhancers

### Matthew Weirauch, PhD
**Center for Autoimmune Genomics and Etiology**
Etiology of Inflammatory Diseases Revealed by Shared Molecular Mechanisms

### Susanne Wells, PhD
**Epithelial Carcinogenesis and Stem Cell Program**
HPV Infection of Human Epidermis: Single Cell Resolution & Metabolomic Consequences

## 2015 Awardees

### Hansel Greiner, MD
**Neurology**
Biomarker Development in Focal Cortical Dysplasia

### Taosheng Huang, MD, PhD
**Human Genetics**
Mutations in SLC25A46 Cause Autosomal Recessive Optic Atrophy and Axonal Peripheral Neuropathy

### Sonata Jodele, MD
**Bone Marrow Transplant and Immune Deficiency**
Genetic Predisposition for Thrombotic Microangiopathy

### Kenneth Kaufman, PhD
**Center for Autoimmune Genomics and Etiology**
Validation of Arg>Cys 77 AGER Polymorphism in Hereditary Pulmonary Alveolar Proteinosis

### Kasiani Myers, MD
**Bone Marrow Transplant and Immune Deficiency**
Inherited Bone Marrow Failure: Mechanisms and Therapy Through Gene Discovery

### Derek Neilson, MD
**Human Genetics**
Genomic Approach to Prevent a Painful Syndrome: Ehlers Danlos Hypermobility Type

### Steve Potter, PhD
**Developmental Biology**
Genetics of Hepatoblastoma and Congenital Kidney Disease

### Senthilkumar Sadhasivam, MD, MPH
**Pain Management**
EMR Machine Learning and Validation of Genetic Associations and Postoperative Pain and Opioid Outcomes in Children Undergoing Tonsillectomy

### Rolf Stottman, PhD
**Human Genetics**
Forward Genetic Analysis of Congenital Craniofacial Malformations

### James Wells, PhD
**Developmental Biology**
Generating Corrected Beta Cells from Patients with Genetic Forms of Diabetes

### Chunyue Yin, PhD; Alexander Miethke, MD
**Gastroenterology, Hepatology & Nutrition**
Identification and Functional Relevance of Gene Variants in Progressive Familial Intrahepatic Cholestasis Patients

## Meet Our Steering Committee and Support Team For the Center of Pediatric Genomics


Photo collection based on the Genetics Portrait Project (www.thegeneticportraitproject.com) created by Stefan Petranek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