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FILLING IN THE FUTURE

2014 Research Foundation Annual Report

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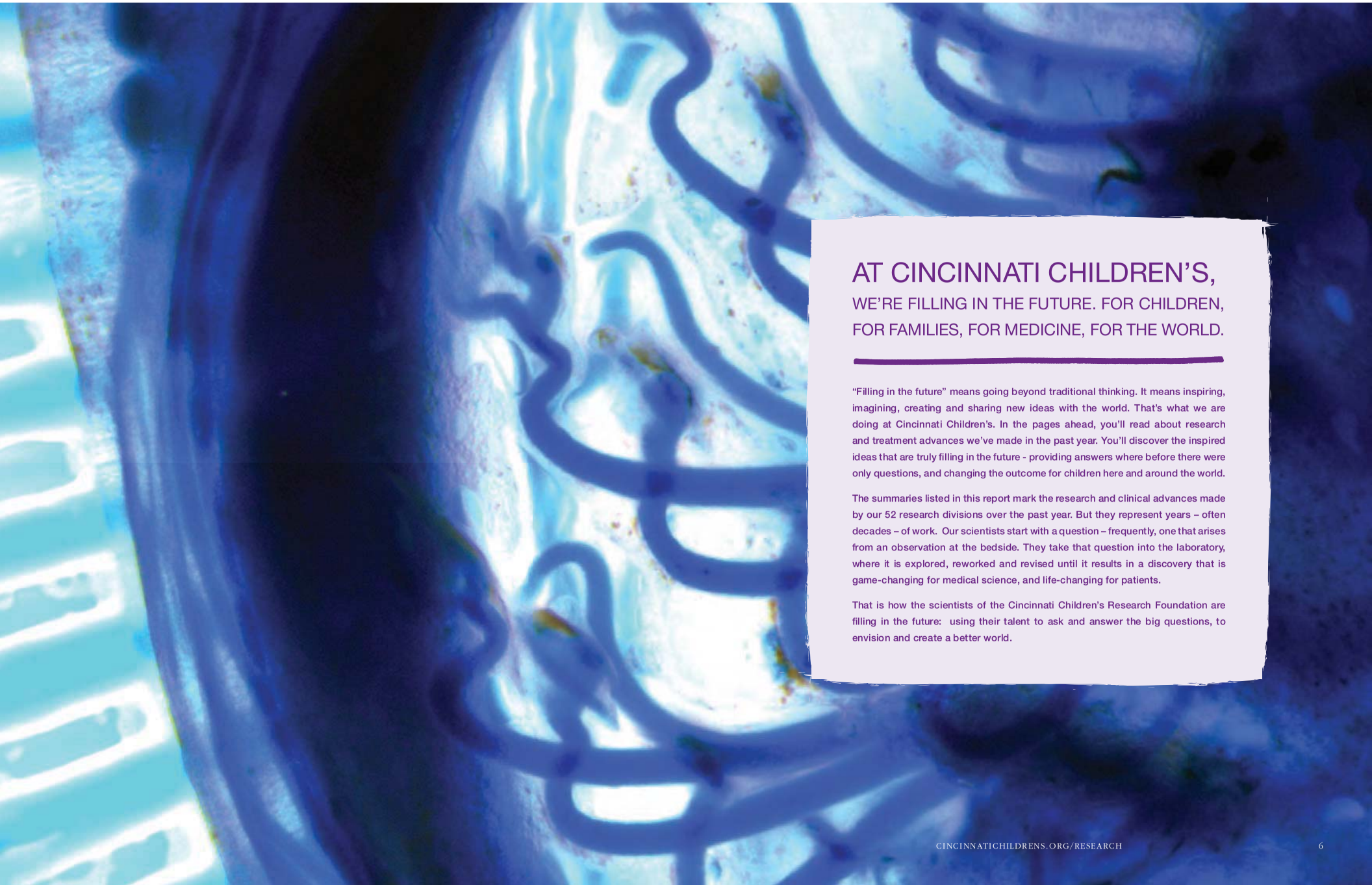


AT CINCINNATI CHILDREN'S,

WE'RE FILLING IN THE FUTURE. FOR CHILDREN, FOR FAMILIES, FOR MEDICINE, FOR THE WORLD.

"Filling in the future" means going beyond traditional thinking. It means inspiring, imagining, creating and sharing new ideas with the world. That's what we are doing at Cincinnati Children's. In the pages ahead, you'll read about research and treatment advances we've made in the past year. You'll discover the inspired ideas that are truly filling in the future - providing answers where before there were only questions, and changing the outcome for children here and around the world.

The summaries listed in this report mark the research and clinical advances made by our 52 research divisions over the past year. But they represent years – often decades – of work. Our scientists start with a question – frequently, one that arises from an observation at the bedside. They take that question into the laboratory, where it is explored, reworked and revised until it results in a discovery that is game-changing for medical science, and life-changing for patients.

That is how the scientists of the Cincinnati Children's Research Foundation are filling in the future: using their talent to ask and answer the big questions, to envision and create a better world.

FROM THE DIRECTOR

This issue of the Research Annual Report should encourage us to reflect on the stellar contributions of Arnold W. Strauss, MD, seventh B.K. Rachford Professor, Chair of the Department of Pediatrics, and Director of the Cincinnati Children's Research Foundation.

During his seven-year tenure, Dr. Strauss recruited 21 division directors and one center director, attracted hundreds of faculty to our research and clinical missions, and presided over a rise in annual NIH funding from $93.7 million to $143 million. Dr. Strauss strengthened our research pipeline by inaugurating the Office of Faculty Development and the Office of Pediatric Clinical Fellows and by renewing our Child Health Research Career Development Award from NICHD. He led the Board of Trustees to approve millions of dollars in funding for internal programs such as the Trustee Awards, the Gap Awards and the Redesign and Research Innovation Pilot (RIP) funding programs.

He worked tirelessly to advocate for pediatric research networks throughout Ohio and the nation. Our new Clinical Sciences Building (Location T), now nearing completion, brings our usable research space to nearly 1 million square feet -- the most of any pediatric institution in the U.S.

Dr. Strauss' foresight set in motion the accomplishments highlighted in this publication. As we move forward with exciting initiatives in discovery science, clinical research, and educational programs, we confront the future of pediatric research with confidence and inspi ation.

That future will see us build upon our unique blend of clinical, research and educational achievement. Our mission of improving child health and transforming care will be strengthened by our national and international research collaborations, clinical partnerships around the globe, and training programs that prepare doctors to work anywhere in the world. Our spirit of innovation and collaboration attracts the best and the brightest, the leaders of tomorrow who are already building a brighter future for child health.

Thank you, Arnie.

Margaret K. Hostetter, MD
B. K. Rachford Professor
Chair, Department of Pediatrics
Director, Cincinnati Children's Research Foundation
Cincinnati Children's Hospital Medical Center

FROM THE BOARD

Too often in the world of medical research a scientist can labor for months, even years, without encountering the children living with the diseases they are working to cure. Too often families never see the immense effort happening beyond the hospital room to help change the outcome for their kids.

At Cincinnati Children's we believe in creating closer connections between the laboratory and the bedside. We constantly encourage collaboration between investigators, clinicians and families as we strive to create a brighter future for children here and around the world.

This year's Research Foundation Annual Report highlights the many strides we have taken to fill in more of the blank spaces in our understanding of childhood disease and development. Indeed, the summaries contained in this report present an impressive picture of progress.

Thanks to research advances by our faculty, doctors can rapidly analyze a child's entire genetic blueprint to find the perfect balance of cancer chemotherapies, or provide the precise amount of anti-rejection medication after an organ transplant, or pinpoint the exact moment in embryonic development that can lead to a serious birth defect. We are using stem cells derived from adult skin and blood cells to grow organoids of intestine and stomach tissue that will transform our research. We are developing gene therapies to combat sickle cell disease and other inherited conditions.

And yet, despite these and other awe-inspiring advances, we are reminded every day of the gaps that still exist, of the cures that remain undiscovered, of the children who face uncertain futures. The emerging universe of genomic research may offer enormous potential to improve the lives of our children, but with the high hopes of a brighter tomorrow comes the immediate need for resources to support the effort.

Cincinnati Children's demonstrates its commitment to biomedical research every day. Our new Clinical Sciences Building — set to open in June 2015 — will make us the largest pediatric research center in the U.S. We continue to hire more of the world's top experts in their fields. And we are fueling their quests for cures with more than $200 million in external research funding received in the past year.

Yes, we've had a very good year. But now we are taking our efforts to accelerate innovation to a new level as we launch a $250 million fundraising campaign, the largest in the history of Cincinnati Children's. This ambitious campaign comes with ambitious goals. The money raised will be invested in supporting research with global impact and in community partnerships that will help the children of Cincinnati become the healthiest in the nation. We believe the high-impact research happening at Cincinnati Children's is providing the outlines of a brighter future for the children and families we serve.

Thank you for your continued support of research, discovery and innovation at Cincinnati Children's.

Pictured in photo, from left: Nancy Krieger Eddy, PhD, Research Chair; Thomas Cody, Chairman, Board of Trustees; Michael Fisher, President and CEO of Cincinnati Children's

ADOLESCENT AND TRANSITION MEDICINE

No infants born with HIV in 8 years

The Family Care Center, led by Corinne ("Corki") Lehmann, MD, MEd, provides healthcare and follow-up testing of infants, children, adolescents, and young adults exposed to or infected by HIV. The team includes nursing, social work, physician, and community case management services through Caracole, an agency that provides housing and support for people living with HIV/AIDS. The center works closely with the HIV Perinatal Collaborative, which includes physicians, nurses and social workers from Infectious Disease, Gynecology/Obstetrics, and Pediatrics. Through the work of the Perinatal Collaborative, no infant has been born infected with HIV in the last eight years in the Greater Cincinnati area. The Family Care Center evaluates nearly 24 infants per year and has an ongoing caseload of 40 patients.

Eating disorders program also supports siblings

The Eating Disorder Program, directed by Laurie Mitan, MD, has expanded its clinical and research endeavors to include support for siblings living in a family affected by eating disorders. Funded by a generous anonymous philanthropic gift, the program was able to recruit Abigail Johnson, PhD, to lead this expansion. In addition, using the division's Change the Outcome funds, the Eating Disorder Program has started a treatment track for post-doctoral fellows in collaboration with the Division of Behavioral Medicine and Clinical Psychology.

Preventing sexually transmitted infections

Jessica Kahn, MD, MPH, Tanya Mullins, MD, and Lea Widdice, MD, conduct collaborative, international research to prevent sexually transmitted infections (STIs) in adolescents using emerging technologies and interventions, and to decrease racial, ethnic, and socioeconomic disparities in the incidence of STIs and their clinical consequences. Kahn examines the epidemiology and risk factors for HPV infection in adolescents; the influence of HPV vaccination on sexual attitudes and behaviors; the impact of HPV vaccination on the epidemiology of HPV in the community; and the safety and effectiveness of HPV vaccination in HIV-infected youth. Mullins studies the epidemiology of STIs among HIV-infected and HIV-uninfected youth, as well as clinician attitudes and intentions toward prescribing new biomedical HIV prevention methods, the results of which will inform the dissemination of such methods and thus improve adolescent access to effective HIV prevention strategies. Widdice combines epidemiological, behavioral, and health services research methods, and focuses on HPV natural history; uptake, use, and impact of point-of-care STI diagnostic devices in clinical and community settings; and development of clinical interventions to increase HPV vaccination and STI testing and treatment.

ALLERGY AND IMMUNOLOGY

Zeroing in on under-recognized allergens

Few people know as much about slime mold as Michelle Lierl, MD. Her recent study, published in the *Annals of Allergy, Asthma & Immunology*, suggests that myxomycete (slime mold) spores may be under-recognized as airborne allergens. However, conducting the research needed to reach this conclusion presented a significant challenge. No extracts of these spores are commercially available, so Lierl collects the spores herself and makes the experimental extracts needed for allergy skin testing. Having also discovered a lack of photographs available of these microscopic spores, she launched a website to share images of basidiomycete, ascomycete and myxomycete spores as a reference source. Now Lierl is testing methods for growing myxomycetes in bulk, a necessary step for wider-scale research.

Setting the guidelines for Ohio's SCID screening initiative

In July 2013, the state of Ohio added severe combined immune deficiency disease (SCID) screening to its list of mandatory infant screenings. This life-threatening genetic disorder causes a lack of functional T cells that makes children with SCID extremely vulnerable to infectious diseases. Kimberly Risma, MD, PhD, who developed Cincinnati Children's guidelines for responding to an abnormal SCID screening test, worked with members of the Ohio Department of Health Newborn Screening Laboratory and other pediatric immunologists to develop algorithms that will guide pediatricians' response statewide. The new testing requirement is a critical improvement in newborn screening and will allow physicians to identify patients with SCID prior to them becoming ill from exposure to bacterial, viral or fungal agents or to live vaccines such as those for rotavirus. The most common treatment for SCID is bone marrow transplantation (BMT), although recent gene therapy trials are showing promise.

Developing new diagnostics for rare food allergy

A team of researchers led by Ting Wen, PhD, and Marc Rothenberg, MD, PhD, developed a molecular diagnostic panel for eosinophilic esophagitis (EoE), a severe, often painful allergy that renders children unable to eat a wide variety of foods. Their recent study, published in *Gastroenterology*, demonstrated that the EoE Diagnostic Panel is accurate and reliable; can quantitatively measure the degree of disease activity; can identify patients who have been exposed to topical glucocorticoids; and can be done within hours after biopsy procurement. The test was recently licensed to Diagnovus, LLC, and is now commercially available as the ENGUAGE™ GI-EoE.

JAMES M. ANDERSON CENTER FOR HEALTH SYSTEMS EXCELLENCE

Learning networks

In a Learning Health System, patients and providers work together to choose care based on best evidence, and the process of discovery is driven as a natural outgrowth of patient care. The Anderson Center Learning Networks Core, led by Carole Lannon, MD, currently supports fi e national and international networks involving 120 organizations and 390 sites of care in the U.S. and the U.K. These networks simultaneously improve care and outcomes and support clinical, comparative effectiveness and quality improvement research.

- Solutions for Patient Safety achieved a 40 percent reduction in hospital-acquired conditions, a 20 percent reduction in readmissions, and a 25 percent reduction in serious safety events.
- ImproveCareNow has increased remission rates for IBD from 60 percent to 79 percent.
- The National Pediatric Cardiology Quality Improvement Collaborative has reduced cumulative interstage mortality for infants with complex congenital heart disease by 25 percent.
- Pediatric Rheumatology Care and Outcomes Improvement Network has increased the number of patients experiencing 6 months' remission to 45 percent.
- The Ohio Perinatal Quality Collaborative has engaged 105 (98 percent) of maternity hospitals and reduced elective deliveries before 39 weeks gestation by 70 percent, to 5 percent statewide.

This work is supported by the Patient Centered Outcomes Research Institute (PCORI) $100 million PCORNet program. Peter Margolis, MD, PhD, is the co-PI of PEDSnet, a network linking eight large children's hospitals, and chair of the PCORNet Program's steering committee. The ultimate vision is that a pediatric "network of networks" will transform clinical research and clinical care through collaborative partnerships between patients and providers.

Faculty leaders of learning networks include Jeffrey Anderson, MD, MPH; Bill Brinkman, MD, MEd, MSc; Esi Morgan DeWitt, MD, MSCE; David Hooper, MD; Heather Kaplan, MD, MSCE; Lisa Opipari, PhD; Michael Seid, PhD; and Lannon, who also leads the Learning Networks Core.

Partnerships drive children's health

Since its inception in 2010, the Anderson Center has achieved significant progress in partnering with many Cincinnati organizations to improve the health of children in our community. This has resulted in significant funding support, including a $3.2 million grant from Bethesda, Inc. to help develop partnerships with schools, health officials and community leaders. Key partners include public schools, health departments, neighborhood groups and social service agencies. Key early successes include a 20 percent reduction in asthma ED and inpatient services through care coordination, working with the Price Hill Health Center to develop same-day access to OB care for the highest risk women, and partnering with Santa Maria in Price Hill to reach every patient and work on healthy development.

Capacity and capability building

The Leadership Academy is designed to build a broader and deeper network of improvement leaders. Leadership topics such as the business case for quality, transformational leadership, chronic care improvement, patient safety, managing a portfolio of projects, implementation and sustainability as well as research and improvement are covered. In FY 2014, we completed our first External I2S2 class, with 17 graduates from organizations such as Vanderbilt University Medical Center and the American Board of Pediatrics. The Anderson Center is also building community capability in quality improvement through collaboratives with STRIVE and the Cincinnati Public School system.

ANESTHESIOLOGY

Productive research, growing fellowships

Our faculty set a record in the past year for providing national and international lectures, hosting visiting professorships, producing education and research publications, and securing new grants. We recruited 12 pediatric anesthesia fellows and nine advanced fellows in pain medicine, cardiac anesthesia, palliative care, research, education, quality and safety, and intraoperative neurophysiological monitoring. We also formed the Principal Investigators Leadership Group, which includes Steve Danzer, PhD, Michael Jankowski, PhD, Andreas Loepke, MD, PhD, David Richards, PhD, Senthilkumar Sadhasivam, MD, Anna Varughese, MD, MPH, John McAuliffe III, MD, MBA, and Nicole Sutton, business manager, Neurobiology.

Record volumes, declining infections

The Divisions of Anesthesiology, Palliative Care, Perioperative Pain Management, and Intraoperative Neuromonitoring set records for clinical encounters, driven by lengthy, high complexity cases. The palliative care division created a palliative pain service and palliative medical service to facilitate care and growth. We sustained improved processes of care, which decreased surgical site infections and serious airway events. We also are organizing around the perioperative microsystems to facilitate pre-operative communication. David L. Moore, MD, and Lisa Rice, business director, Pain Management, advanced the dental, cancer, and biopsy anesthesia service, which increased the quality of care and case volume of service. The cardiac service became a division apart from anesthesia; the cardiac division set a record for number of cardiac catheterizations.

Promotions and honors

Nick Pratap, MBBChir, Rajeev Subramayan, MBBS, MD, Rupi Mavi, MD, and Matthew Sjoblom, MD, became assistant professors; Richards and Mario Patino, MD, were promoted to associate professor; and Sadhasivam and Varughese were promoted to professor. Joseph Previte, MD, FAAP, Veronica Busso, MD, and Pornswan Ngamprasertwong, MD, MSc, were appointed clinical directors. Anne Boat, MD, is the hospital patient experience office . Karmella M. Franic-Everhart, CRNA, received a doctorate in nurse anesthesia.

McAuliffe serves as president of the American Society of Neurophysiological Monitoring (ASNM). Paul Samuels, MD, leads the Board Exam review course for the Society for Pediatric Anesthesia (SPA). C. Dean Kurth, MD, Anesthesiologist-in-Chief, is president of the SPA pediatric anesthesia leadership council and a board member for the society and its journal, *Pediatric Anesthesia*. SPA also awarded first prizes in research to Subramayan and Mavi for fellow and junior faculty categories.

ASTHMA RESEARCH

Genetic and environmental influences on asthma development systems

Gurjit Khurana Hershey, MD, PhD, is the principal investigator (PI) of an NIH-funded Asthma and Allergic Diseases Cooperative Research Center and serves on its steering committee. The Cincinnati Center is one of only 11 such centers in the United States. The Center has identified several epithelial genes with previously unrecognized roles in asthma. Further analyses suggest that some of these genes are specific to one epithelial surface and are associated with one allergic disease, while others are common to multiple surfaces and disorders. By identifying epithelial genes and pathways that predispose individuals to allergic disorders, we are advancing the search for novel, targeted therapeutics. Furthermore, integration of data will provide novel insights into a key question in allergy - what are the mechanisms underlying tissue-specific disease manifestations of allergic inflammation? We have made significant progress and several manuscripts have been published, with more in preparation.

Cincinnati Children's studies inner city asthma

Cincinnati Children's is one of nine contracted clinical research sites funded to study the treatment and prevention of asthma in inner-city asthma populations by conducting several clinical trials and mechanistic studies in order to understand the immunopathogenesis of the disease and to evaluate and develop effective interventions tailored to inner-city populations. Khurana Hershey is the PI of the Inner City Asthma Consortium (ICAC) at the Cincinnati site. The study's goals are to improve asthma control, to improve asthma phenotyping using biomarkers, to develop allergen immunotherapy approaches for cockroach allergy, to conduct further studies of asthma in the inner-city, and to develop, validate and implement the basic science methodology to support these objectives. ICAC is the nation's largest effort to study asthma in the inner city. To date, Cincinnati Children's has participated in three ICAC clinical trial studies and looks forward to participating in many more in the years to come.

Ohio children's hospitals collaborate to analyze asthma hospitalizations

Khurana Hershey has been working with fi e other children's hospitals in Ohio to develop the Ohio Pediatric Asthma Repository (OPAR) to identify practices that result in the best health outcomes for children with asthma. OPAR is being used to conduct observational, comparative effectiveness, and intervention studies for pediatric asthma. To date OPAR has enrolled 2,456 participants statewide.

We head the fi e-center Ohio Pediatric Asthma Repository (OPAR), which collaborates to identify best practices in asthma care. So far, the Repository has enrolled 2,456 participants statewide.

BEHAVIORAL MEDICINE AND CLINICAL PSYCHOLOGY

Cognitive behavior therapy helps children with migraines

An estimated 20 percent of children experience chronic pain and yet, children are one of the most underserved of all pain populations. Our researchers and clinicians have been leaders in developing evidence-based approaches to treating pediatric chronic pain. Last year, a randomized trial led by Susmita Kashikar-Zuck, PhD, showed that cognitive behavior therapy (CBT) produced strong improvements in daily functioning. This year, a randomized trial led by Scott Powers, PhD, ABPP, demonstrated that medication plus CBT resulted in a fi e-fold decrease in chronic migraines for children compared to medication alone. Anne Lynch-Jordan, PhD, also demonstrated that children with chronic pain treated with CBT in our clinical pain service showed rapid improvements in daily functioning even prior to pain reduction. Powers' findings were published as a featured article in the *Journal of the American Medical Association* (JAMA), which included online video interviews and an accompanying editorial highlighting the importance of these findings

Translating findings into practice

Our Outpatient Behavioral Pain Management Service is an ideal example of how we work to shorten the estimated 17 years it can take to move an innovative treatment into routine clinical care. Our program includes four psychologists who focus on treating pain, with additional psychologists and advanced trainees incorporating behavioral pain management into their clinical work. We also have pain psychologists embedded in the Division of Neurology's Headache Center and in the Department of Anesthesiology's Pain Management Center. Our outcome data show that 84 percent of outpatients treated with CBT for pain management demonstrate significant improvement in functioning and/or pain.

For inpatients with chronic intractable pain, Sara Williams, PhD, worked with Anesthesiology and Physical Medicine and Rehabilitation to develop an intensive pain rehabilitation program. In its first eight months, the program has demonstrated 80 percent success in improving patients' day-to-day functioning despite pain. Our pain psychologists also provide group-based behavioral pain management treatment as part of an intensive physical therapy summer program for youth with joint hypermobility.

Improving treatment adherence

Our Center for Adherence and Self-Management, launched in 2007 under the leadership of Dennis Drotar, PhD, has become the nationally recognized leader for treatment adherence and self-management research. Drotar stepped down this year as the center's director, but not before recruiting a team of talented researchers. The center's faculty members have secured $11.3 million in NIH funding in the past seven years and have trained 11 fellows, eight PhD-level graduate students, 14 research assistants and 57 undergraduate volunteers.

Avani Modi, PhD, has been named the new director of the Adherence Center. Kevin Hommel, PhD, has become associate director and will oversee the NIH award for the nation's only post-doctoral training program for treatment adherence. Meanwhile, Sandra Cortina, PhD, works with the Anderson Center and the Solid Organ Transplant Program to improve adherence and Ahna Pai, PhD, leads the Wellness Program for the Cancer and Blood Diseases Institute.

BIOMEDICAL INFORMATICS

Novel methods for studying disease

Bruce Aronow, PhD, focuses on the integration and mining of multiple sources of genomic, genetic, and biomedical data to derive models for pathways and processes underlying development, disease, and drug response.

Anil Jegga, DVM, focuses on gene regulatory networks and the interaction between genotype and phenotype using a variety of bioinformatics approaches. He has extensive experience in transcription factor and micro-RNA based gene regulatory mechanisms, gene polymorphism functional analysis, candidate disease gene identificatio and prioritization. His current interests include elucidating the regulatory mechanisms of p53 tumor suppressor network.

Jason Lu, PhD, is developing biomarkers to assess the risk of developing heart disease by combining proteomics experiments and computational prediction to discover subspecies in high density lipoproteins (HDL) that correlate with cardiovascular protection.

Nathan Salomonis, PhD, is breaking ground in pediatric cancer, cardiovascular disease and spinal cord injury by developing new software and algorithms to identify complex relationships from whole transcriptome data. The advent of single-cell genomic profiles has created many new opportunities for understanding how stem cells differentiate and how disease gene expression is regulated.

Jun Ma, PhD, is using computational tools to understand how cells in a developing embryo "know" where they are located and what they will become.

Learning healthcare systems

Keith Marsolo, PhD, and the learning networks informatics team have received a grant extension to expand and improve an electronic health record-linked registry they built for the ImproveCareNow Network. This 67-center group helps improve outcomes for children with Inflammato y Bowel Disease (IBD) by sharing learnings gleaned from collecting data at the point of care. The network's uses include identifying patients for clinical trials and supporting comparative effectiveness research. Marsolo and his team have also created several new versions of the pre-visit planning and population management reports that clinicians use for chronic care management.

Approaches for improving data-driven research, screening, and decision support

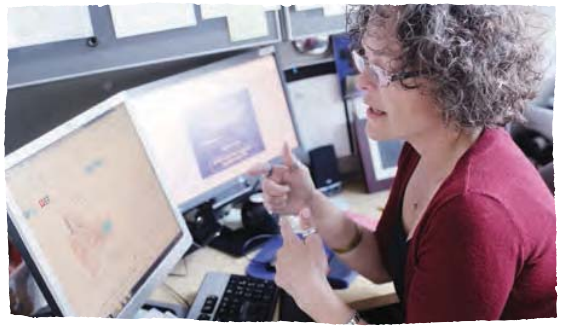
Michael Wagner, PhD, and colleagues launched the C-MIND database, which contains MRI and neuropsychological evaluation data on normally developing children. This resource is available to the public and can be used as a healthy control group in clinical studies. His team is also developing methods to integrate and disseminate longitudinal clinical, observational, and genomic data for newborn screening disorders on a national scale through the Newborn Screening Translational Research Network.

John Pestian, PhD, MBA, and colleagues have been issued a patent for processes that optimize medication dosages for patients with refractory epilepsy. Their software application analyzes clinical linguistic characteristics of patients and medical records to identify individuals who would best be treated by neurosurgery. Pestian has also launched a clinical trial to test a system that uses linguistics, acoustics and facial features to identify emergency room patients at very high risk of committing suicide.

Imre Solti, MD, PhD, and his team have applied the tools of natural language processing, machine learning and information extraction to develop an automated method for identifying patients for clinical trials and to detect medical errors in neonatal intensive care units. Solti's team also has developed algorithms linking genotypes and phenotypes in childhood obesity and autism.

Stephen Spooner, MD, MS; Michal Kouril, PhD; Eric Kirkendall, MD, MBI; and Judith Dexheimer, PhD, have collaborated to create a data warehouse to address growing concerns about alert fatigue. The data can be used to study how clinicians manage the load of decision-support alerts they receive when prescribing medications in the Cincinnati Children's system.

BIOSTATISTICS AND EPIDEMIOLOGY



Translating findings into practice

Our fi e-year strategic plan envisions playing a lead role as a catalyst for trans-disciplinary research and increased prominence in producing big data for little children. Our faculty and staff contributed to 178 scientific articles in the past year, up 32 percent from the prior year, including 38 published in high-impact journals and 18 that involved the development or application of novel quantitative methods. Our faculty or staff members were first authors of 24 papers and senior authors of 14. We participated in 88 research grants and contracts, with annual direct costs totaling $28M.

Our faculty's independent research included a stroke study led by Jane Khoury, PhD; a hearing loss study led by Jareen Meinzen-Derr, PhD; and a traffic pollution study led by Patrick Ryan, PhD, MS. Meinzen-Derr also received the 2014 Charlotte R. Schmidlapp Woman Scholar Award.

High-level data management and statistical support

Our Data Management Center, led by Rachel Akers, MPH, Cyndie Baker, and Matthew Fenchel, MS, supported 75 studies by assisting with grant application and protocol review, budgeting and resourcing for data management, case report form design, database development, data entry and documentation, discrepancy management, data cleaning and preparation for analysis. We also began four projects in Medidata Rave, a state-of-the-art clinical data management system acquired in FY13.

Our Biostatistical Consulting Unit, led by Mekibib Altaye, PhD, director, and Matthew Fenchel, MS, manager, supported 138 projects in 26 divisions and departments at Cincinnati Children's and the University of Cincinnati. The unit offers specialized expertise in meta-analysis, statistical process control, pharmacokinetics modeling and spatial-temporal data modeling. The team collaborates closely with the Data Management Center, the Division of Biomedical Informatics, and with the Center for Clinical and Translational Science and Training (CCTST) as part of "Research Central."

Our Scale Development Unit, led by Richard Ittenbach, PhD, PSTAT, assists investigators with the creation and validation of new measures for use in medical settings. During the past year, this unit grew to include fi e primary faculty/staff members and four affiliated faculty members and collaborated with investigators on 32 research projects in 13 divisions and institutes. Ittenbach also helped introduce modern theory techniques to empirical bioethics at UC.

A growing team

Our newest faculty members include Nanhua Zhang, PhD, whose research has covered clinical trial design and meta-analysis in studying environmental health and health disparities; and Lilliam Ambroggio, PhD, an infectious disease epidemiologist with interests in community-acquired pneumonia, metabolomics and antibiotic resistance.

We also added nine staff members including James Decker, MS, who led the Statistical Computing Group of P&G Pharmaceuticals; Yuanshu Zou, PhD, a statistician; and Nusrat Harun, PhD, who joined us from the MD Anderson Cancer Center in Houston.

Our faculty taught in the Colleges of Medicine, Pharmacy, and Arts and Sciences, and in the MS program in Clinical Science sponsored by the CCTST. Six students participated in the Graduate Statistics Internship Program led by Bin Huang, PhD, and Siva Sivaganesan, PhD, UC Department of Mathematical Sciences. We also are developing curriculum for a fellowship in Epidemiology and Biostatistics in Pediatrics. The first ellow selected was Samrat Yeramemeni, PhD.

CANCER AND BLOOD DISEASES INSTITUTE

The Cancer and Blood Diseases Institute (CBDI) includes the Divisions of Bone Marrow Transplantation and Immune Deficienc , Experimental Hematology and Cancer Biology, Hematology and Oncology.

ONCOLOGY:

Exome sequencing accelerates personalized cancer therapy

In a landmark investigation, Brian Turpin, DO, presented the CBDI/Oncology experience in targeted exome sequencing of more than 100 cases of high-risk and relapsed childhood cancers and leukemias at the International Society of Pediatric Oncology annual meeting in Hong Kong in 2013. This work represents the first and largest pediatric experience in tumor signatures. The research project has several key implications:

- It is the first and largest use of clinical tumor sequencing in children for "precision therapy" with targeted drugs, and produced exceptional tumor responses in highly drug-resistant cancers and leukemias.
- It identified mutations in more than 70 percent of patient tumors, where previous estimates had asserted that only a minority of patients would have alterations.
- Most of the mutations identified are targetable by new small-molecule anticancer drugs available or in development.
- Tumor mutations did not track with tumor histology, which suggests a new approach for treating patients by genetic signature.
- Drug-resistant pediatric tumors shared targetable genomic alterations common with aggressive adult cancers – a previously unappreciated observation, and critical information for future development of new anticancer drugs for children.

This work forms a foundation for personalized precision therapy of high-risk and relapsed pediatric cancers, augmenting our role as the nation's largest center for new anticancer drug development in children.

> Targeted exome sequencing shows promise in finding better ta geted treatments for children with high-risk and relapsed childhood cancers and leukemias.

EXPERIMENTAL HEMATOLOGY AND CANCER BIOLOGY:

A major step forward in rejuvenating hematopoietic stem cells

Many tissues in the human body require continuous replenishment from stem cells, but as people age their stem cells begin to decline in function. Now a study led by a Cincinnati Children's scientist has revealed a critical mechanism involved in this aspect of aging. The regeneration of haematopoietic stem cells (HSCs), which produce all types of blood cells, appears to be controlled by a shift from canonical to non-canonical Wnt signaling due to elevated expression of Wnt5a. The altered signaling triggers a cascade of events that erodes the regenerative capacity of HSCs. Controlling this signaling circuit could help refresh aged or diseased blood stem cells, which in turn could have significant impact on a variety of diseases. The study, published in *Nature*, was led by Hartmut Geiger, PhD, and included a team of scientists from Cincinnati Children's and the University of Ulm in Germany.

Novel therapy for Myelodysplastic Syndrome

The lab of Daniel Starczynowski, PhD, has identified a potential new approach to treating a collection of bone marrow disorders known as myelodysplastic syndromes (MDSs). These disorders arise from defective hematopoietic stem cells or progenitor cells that produce MDS-initiating clone cells. In a paper published in *Cancer Cell*, Starczynowski and colleagues report that the immune-modulating kinase, IRAK1, is overexpressed and hyperactivated in MDSs. Treating MDS clones in the lab with an IRAK1 inhibitor increased cell death among the MDS cells without affecting normal stem cells. They also found that a combined treatment to inhibit IRAK1 and BCL2 was even more effective at eliminating MDS clones. These findings support further investigation of treatments that target IRAK1.

HEMATOLOGY:

Hematology division rated 'excellent' for hemoglobinopathy research

The Division of Hematology has received a fi e-year, $8.9 million "Excellence in Hemoglobinopathy Research Award" from the National Heart, Lung, and Blood Institute. Led by Punam Malik, MD, the grant will focus on mechanisms that lead to cardiac and kidney damage among patients with sickle cell disease. Co-investigators include Theodosia Kalfa, MD, PhD, Charles Quinn, MD, MS, Jay Degen, PhD, and Jeffrey Towbin, MD. Other scientists in the Heart Institute also are collaborating.

Sickle cell research expands in Africa

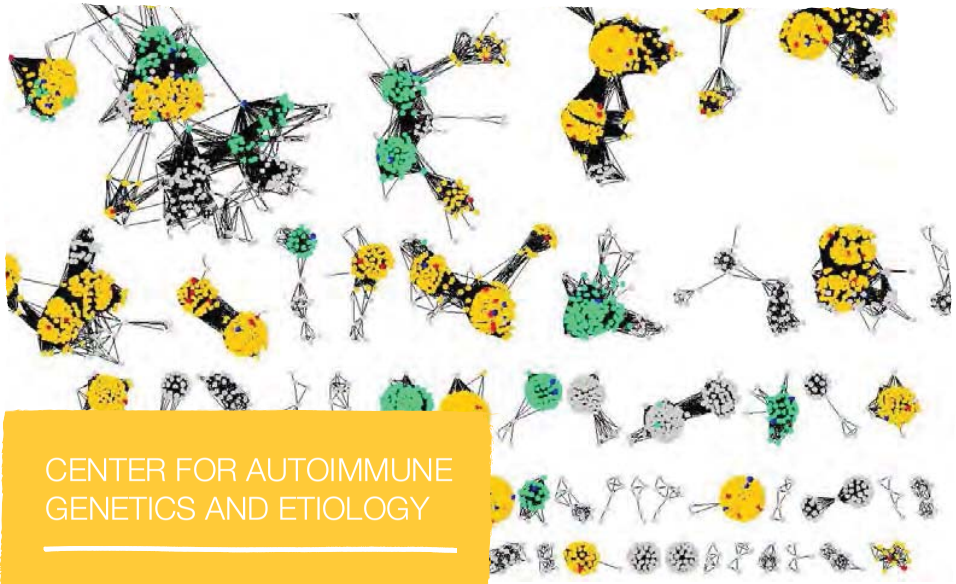
The recent recruitment of Russell Ware, MD, PhD, Director of Hematology, and Patrick McGann, MD, MS, is rapidly expanding the role of Cincinnati Children's in sickle cell research in sub-Saharan Africa. Ware and McGann recently led a highly successful newborn screening initiative in the Republic of Angola. They have since launched several more projects, including a hydroxyurea safety and dosing trial known as Realizing Effectiveness Across Continents with Hydroxyurea (REACH) and the Uganda Sickle Surveillance Study (US3).

BONE MARROW TRANSPLANTATION AND IMMUNE DEFICIENCY:

Study shows safety in radiation-free transplants

Our division completed a multi-center study showing that it is safe to perform bone marrow transplants in children with Fanconi Anemia without using radiation. We also established a comprehensive biological sample repository for transplant recipients, storing more than 30,000 samples annually. Our team also has identified genetic changes that increase the risk of post-transplant thrombotic microangiopathy.

> Research from Cincinnati Children's suggests a new way to refresh aged or diseased blood stem cells, which in turn could have significant impa t on a variety of diseases.



CENTER FOR AUTOIMMUNE GENETICS AND ETIOLOGY

Progress in understanding the roles of transcription factors

Transcription factors (TFs) play a key role in gene regulation by recognizing short genomic DNA sequences, called "motifs." Discovering how TFs work is crucial to understand genome function, in both normal and disease states. However, DNA sequence binding specificities are currently known for less than 2 percent of eukaryotic TFs. A recent study led by Matt Weirauch, PhD, describes a novel procedure that has identified 34 percent of TF binding motifs and is freely available. Weirauch and his colleagues also demonstrated how this tool can be used to identify TFs that might be affected by human disease-associated genetic variants.

Controlling Natural killer cells may be key to better vaccines

Natural killer (NK) cells help eliminate dangerous cells, such as some cancer cells. Stephen Waggoner, PhD, has learned that these cells also impair the immune response against some infections by neutralizing cells that fight the infection. The National Institute for Drug Abuse is funding his proposal in the fight against AIDS and HIV infection to develop more effective vaccines.

Celebrating our PhD students

MD-PhD candidate Sam Vaughn presented his findings on how PXK interacts with BCR, the immunoglobulin receptor on B lymphocytes, at the International Immunology Congress in Milan, Italy. Carolyn Rydyznski, who works on NK cell regulation of vaccine responses, won a travel award to visit the Scripps Institute in order to bring technology associated with reverse engineering of arenaviral vaccine vectors to Cincinnati Children's. Laura Brungs is applying knowledge gained at an NIH-sponsored workshop on analyzing next-generation sequencing data to her work examining rare *de novo* sequence mutations in juvenile idiopathic arthritis patients. Meanwhile, Rydynski, Ke "Coco" Liu and Xaioming Lu all won travel awards to the national meeting of American Association of Immunologists to present their research.

CENTER FOR CAREER DEVELOPMENT IN ACADEMIC PEDIATRICS

Schmidlapp Scholars provide a 21-fold ROI

Since the start of the Schmidlapp Women Scholars Program in 1997, 17 of the Scholars have been promoted, with fi e being promoted to professor and fi e awarded tenure. The Scholars have published 598 papers and have received extramural grants totaling approximately $35 million in direct costs. This is a 21-fold return on investment, indicating the success of this program.

Schmidlapp Young Women Fellows program

This year we received a new gift from the Charlotte R. Schmidlapp Fund of $500,000 to set up an endowment to support promising young women in our Summer Undergraduate Research Program (SURF). Female students hoping to break into this male-dominated field often need a little more support and inspiration beyond the personal training and real-life experience the SURF program offers. We hope to offer an extra incentive for the top women selected as Schmidlapp Fellows, pairing them up with our female researchers (including Schmidlapp Scholars) who can offer them personal guidance and the perspective of what it is like to be a female researcher in a male-dominated profession. Our hope is that some of these relationships may grow beyond the course of the summer, allowing an opportunity for strong mentor relationships that could greatly influence the li e course of these young women.

Undergraduate support

Over the past several years faculty and parents of undergraduates supported by the Center have donated more than $106,000 to support our future women researchers and clinicians, with 37 donors contributing more than $16,000 this fiscal ear.

CENTER FOR CLINICAL AND TRANSLATIONAL SCIENCE AND TRAINING

Ohio Clinical Trials Collaborative formed

The Center for Clinical and Translational Science and Training (CCTST) played an integral role in forming the Ohio Clinical Trials Collaborative, a statewide network of Clinical and Translational Science Award sites in Cincinnati, Columbus and Cleveland and six partnering institutions, including Cincinnati Children's. The Collaborative is establishing a clinical trials structure across Ohio to facilitate trials available through commercial clinical research organizations, the pharmaceutical industry, and government agencies.

Landmark collaborative IRB agreement reached

Hospitals and research institutions across Cincinnati and Northern Kentucky have formed a collaborative Institutional Review Board (IRB) agreement that will allow any of the six participating sites, including Cincinnati Children's, to serve as the IRB-of-record for human subject research that involves multiple participating study sites. All participants are members of the Consortium of Greater Cincinnati IRBs.

Design Thinking Research Awards established

Design thinking has been defined as "devising courses of action aimed at changing existing situations into preferred ones." Toward that end, the CCTST and the Live Well Collaborative established the Design Thinking Research Awards to support novel approaches to health care challenges by Cincinnati Children's faculty. Funds partially support studio projects utilizing design teams led by University of Cincinnati faculty and students who work with investigators and stakeholders to develop innovative solutions, tools and prototypes that can be readily evaluated. Leaders plan three funding rounds per year.

CENTER FOR TECHNOLOGY COMMERCIALIZATION

Rare Disease Collaborative launched with Alexion Pharmaceuticals

Cincinnati Children's and Alexion Pharmaceuticals have established a collaboration and fund for the advancement of research in rare diseases. The Alexion Rare Disease Innovation Fund is a focused opportunity within Cincinnati Children's broader Innovation Fund, which covers all therapeutic areas and technology types. The program, open to all Cincinnati Children's researchers, will focus on research that aligns with Alexion's specialty of developing new treatments for complex and rare diseases. The Center for Technology Commercialization (CTC) believes this type of collaboration will serve as a model for how industry and academia can better work together to bring health innovations from the bench to the bedside.

Commercialization-related revenue up 30 percent

The CTC generated more than $6.2 million in commercialization-related revenue and funds this year from a variety of sources, up approximately 30 percent over the previous year. Revenue from the CTC's licensing activity totaled roughly $1.2 million, with industry-sponsored research totaling $1.5 million. Approximately $500,000 was received for patent reimbursement from current licensees and $3 million was received in commercialization grants. The significant grant funding came from Ohio's Third Frontier for Cincinnati Children's start-up fund, which will be matched by the medical center for a total of $6 million for Cincinnati Children's new start-ups.

New start-up formed, existing start-ups hit major milestones

Persepsys Biomedical LLC, a new Cincinnati Children's start-up, launched this year based on research and technology from the lab of Hector Wong, MD, director, Critical Care Medicine. The company, still in an early stage, hopes to offer products that will help with the management and prognosis of severe sepsis and septic shock. They also see strong opportunities to use the technology as a diagnostic and quality outcomes tool.

Several other start-ups have achieved major milestones: Assurex Health was named an approved supplier to the U.S. and will soon offer their GeneSight psychotropic test to help doctors prescribe the best medications to treat patients with mental issues. Airway Therapeutics, working to help premature babies avoid developing bronchopulmonary dysplasia (BPD), was granted orphan designation by the U.S. Bexion Pharmaceuticals, focused on cancer therapeutics, recently submitted an Investigational New Drug (IND) application to the FDA in support of its upcoming Phase 1 clinical trial.

Cincinnati Children's received more than $6.2 million in commercialization-related revenue in 2014, up 30 percent over the previous year.

CLINICAL PHARMACOLOGY

New pharmacogenetic marker to predict morphine pharmacokinetics

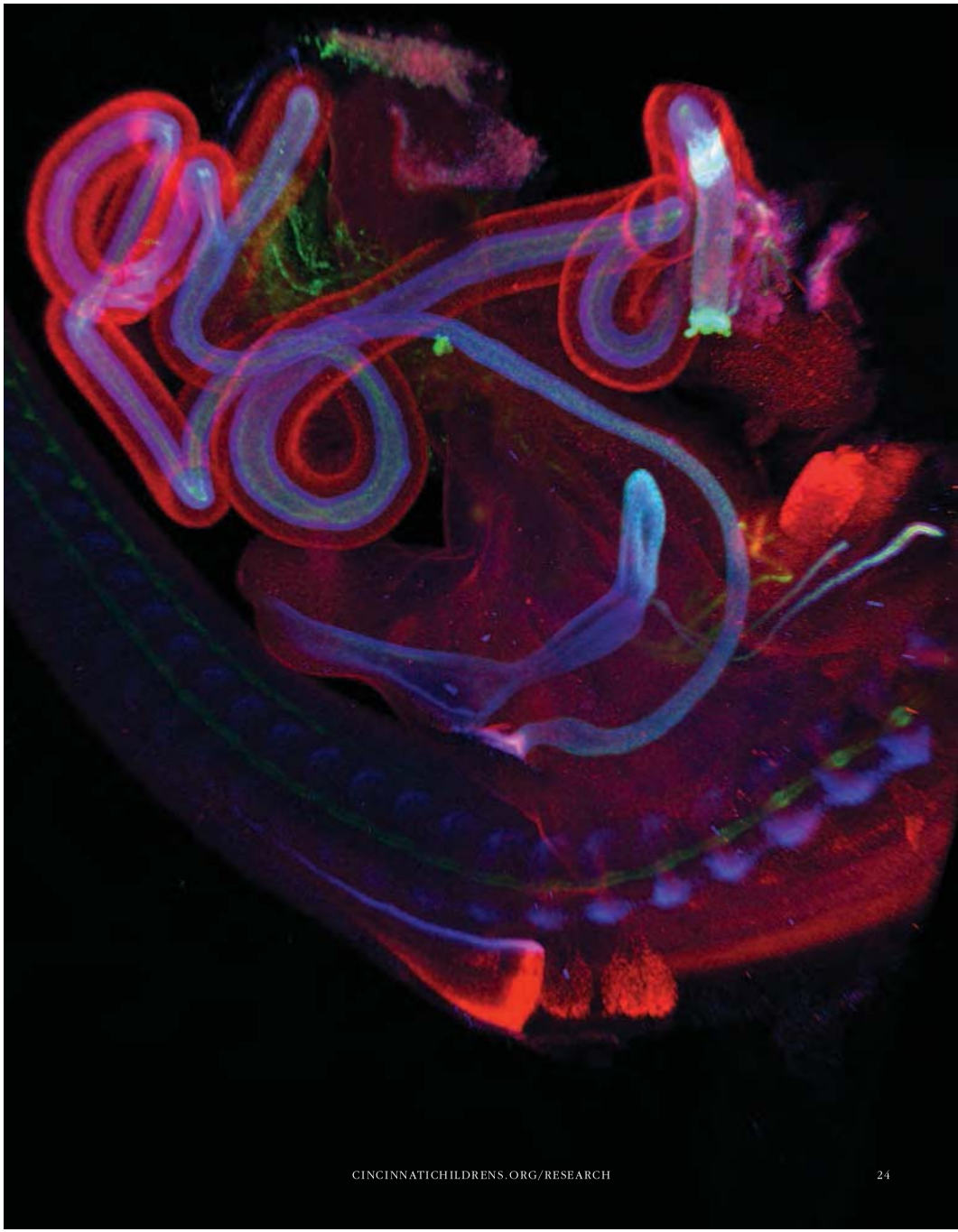
Tsuyoshi Fukuda, PhD, discovered novel pharmacogenetic polymorphisms in the Organic Cation Transporter (OCT1), one of the transporters involved in the pharmacokinetics of morphine. Relatively high allelic frequencies of defective OCT1 variants can explain why Caucasian children are slower to eliminate morphine from the body and experience higher rates of adverse events compared to African–American children. Fukuda's paper, published July 2013 in *Pharmacogenomics*, also was selected as the journal's scientific paper of the month. The study also has led to an internal translational research award to explore individualized morphine treatment in neonates. The study will be led by a multidisciplinary team including Joshua Euteneuer, MD, a Neonatology fellow who participates in the pediatric clinical pharmacology training program.

Pharmacometrics program revolutionizing how we perform drug studies in children

Our new Pharmacometrics Services Program provides special expertise that can improve pediatric drug development and enhance the success rate of pediatric drug studies. We provide consultation as part of several clinical trials, including studies evaluating sirolimus as a treatment for children with vascular anomalies, leukemia and lymphoma, and optimizing doses of melphalan in bone marrow transplantation. Our research explores the developmental characteristics and genetic polymorphisms of drug metabolizing enzymes and receptors. Among these projects, Chie Emoto, PhD, leads a study that focuses on developing a pharmacokinetic model for sirolimus.

First clinical fellows to graduate from pediatric pharmacology training program

We are one of three sites in the U.S. awarded a pediatric clinical and developmental pharmacology training grant from the National Institute of Child Health and Development. This postdoctoral program trains clinical investigators to assume leadership roles in evaluating pediatric therapeutics. Many medicines have not been studied for use in children and few medicines have been developed specifically to treat childhood diseases. One of our major goals is to support and train fellows in applying pharmacokinetics and pharmacogenetics/genomics to individualized therapy. This year's graduates were: Dawn Pinchasik, MD, Jason Wiles, MD, and Andrea Hahn, MD.



CRITICAL CARE MEDICINE

Divisional Teaching Award

Critical Care Medicine received the Divisional Teaching Award from the senior pediatric residents at Cincinnati Children's. This award is given annually to the division that has contributed the most to pediatric residency education.

Heartpedia interactive app

Our Critical Care Media Lab developed the Heartpedia interactive app, which was released to the public in 2014. The Media Lab also released a series of animated illustrations of congenital heart defects. The Media Lab team members are Ken Tegtmeyer, MD, and medical animators Jeff Cimprich and Ren Wilkey.

Nearly 60 percent reduction in serious harm events

Critical Care Medicine and the entire PICU team collaborated to reduce incidents of preventable serious harm in FY14, including ventilator-associated pneumonia (VAP), catheter-associated urinary tract infections (CAUTI), central line-associated bloodstream infections (CLABSI), and pressure ulcers. The focus was on daily multidisciplinary Safety Leadership Rounds and Prevention Standards compliance, including daily discussion of each patient's risks for harm. Events of harm decreased from 27 in FY13 to 11 in FY14, the lowest for the PICU in four years.

DENTISTRY

New faculty welcomed

New faculty member Elizabeth Gosnell, DMD, MS, has established a collaborative effort with the Tuberous Sclerosis clinic and serves as the National Tuberous Sclerosis Alliance spokesperson. Gosnell also has established collaborations with the craniofacial anomalies team.

Our teaching staff in the Advanced Program of Pediatric Dentistry training program includes part-time faculty Kyle Reynolds, DDS, MS; Guilia Pagano, DMD, MS; Lisa Rudolph, DMD; and Laura Goodell, DMD. Rudolph and Goodell are recent graduates of our program and Reynolds and Pagano are recent graduates of Nationwide Children's Hospital. Reynolds received the American Board of Pediatric Dentistry Pugh Award for scoring in the top 3 percent nationally on the written board examination.

We earned accreditation, and improved access to dental care

Sarat ("Bobby") Thikkurissy, DDS, MS, director of the training program, has guided the program through a successful accreditation site visit conducted by the Commission on Dental Accreditation (CODA). The training program achieved a "no reporting requirements" status. Thikkurissy has been instrumental in implementing many changes in the clinic operations to include popular "walk-in" chairs, which allow us to see up to 40 patients per day. Although our division is only scratching the surface of this demand, this change has greatly improved access to oral health care for underserved children in the community.

Our residency program was one of 10 selected nationally to lobby for oral health initiatives in Washington, D.C., on behalf of the American Association of Pediatric Dentistry (AAPD). Thikkurissy also is working with the Foster Care Clinic to provide a dental home to children in foster care with unreliable dental access.

Other collaborations include working with the University of Cincinnati oral surgery and advanced general education training program to provide oral health care to patients with special needs. We also have supported the Oral Health Network, which recently opened a school-based dental clinic. We also have collaborated with the divisions of Anesthesiology and Nursing to open a daily intravenous sedation clinic in the Dental Clinic, which offers immediate access to pharmacologic behavior management.

Division grows national profile

Several of our faculty members are involved in key national committees and continuing education courses. Stephen Wilson, DMD, PhD, is internationally recognized for behavior management and is editor of a forthcoming textbook on sedation in dentistry. Wilson and Thikkurissy serve as national educators on sedation for the AAPD. Both Rudolph and Goodell serve on the Junior League of Cincinnati, driving powerful oral health initiatives in the public health sector. Gosnell is a national consultant for school-based health initiatives program.

One consequence of these efforts is an increasing visibility and growing number of applicants to our training program. In 2013, the Division had 208 applicants for fi e positions. Furthermore, the program has been approved for increasing the number of resident positions by CODA.

DERMATOLOGY

Improved access

We are recruiting new faculty members to meet the strong demand for appointments from throughout the region. We now offer appointments at Cincinnati Children's Mason and Liberty Township outpatient locations, and we plan to expand to the Green Township location.

Excimer laser introduced

For children with certain skin disorders, such as psoriasis and vitiligo, standard therapy with topical medications is not effective, resulting in frustration and poor adherence. We now provide excimer laser treatment for these inflammato y skin diseases at the Burnet campus. The laser effectively treats these conditions by delivering painless, focused ultraviolet light to affected areas.

Clinical research

The division is expanding its role of promoting research in dermatologic diseases in children. We are involved in a clinical trial involving psoriasis, and are developing future research in atopic dermatitis and melanoma.

Patch testing

Allergic contact dermatitis is not uncommon in children, but identifying the allergen causing it can be difficul and frustrating. We now offer epicutaneous patch testing to evaluate reactions to a customized series of potential allergens, including nickel and other metals, sunscreen ingredients, fragrances, preservatives and other chemicals.

Advances in medical photography and dermoscopy

Our full-time medical photographer captures, creates and catalogs thousands of clinical images of dermatologic diseases to support patient care and clinical research. The images are particularly useful in monitoring children with melanocytic nevi or a history of melanoma who are cared for in our Pigmented Lesion Center. In addition, through the use of epiluminescence microscopy, we can obtain specialized dermoscopy images of melanocytic nevi and other cutaneous lesions that can facilitate diagnosis.

DEVELOPMENTAL AND BEHAVIORAL PEDIATRICS

Collaboration with CVG to improve air travel experiences

The Starting Our Adventure Right (SOAR) program is a collaboration between our division, the Cincinnati/Kentucky International Airport (CVG) and The Autism Society of Greater Cincinnati. The SOAR program was originally developed to identify ways that CVG airport could support families and prepare individuals with Autism Spectrum Disorders (ASD) for the airport experience. The inaugural SOAR event was held in October 2013, during which children with autism, and their families, participated in all of the steps required for boarding an airplane, including boarding an actual airplane, with support from our staff, who had also provided training to CVG and TSA staff. Using the airport location as a model, the SOAR program is being expanded to other locations (e.g., Cincinnati Museum Center, Cincinnati Zoo, Newport Aquarium, grocery stores, libraries, restaurants, movie theaters, sports venues, and amusement parks) as well as to other developmental disabilities beyond ASD. The SOAR program emphasizes the importance of working with community partners in innovative ways to promote safe, comfortable, and inclusive opportunities for individuals with developmental disabilities to participate and become more independent within their own communities.

Sharp reductions in wait times

In the past year, our division has focused extensively on improving access to first visits for patients. Within the field of Developmental/Behavioral Pediatrics, long wait times for visits are well known, and place an unacceptable burden on families. With support from the Anderson Center and technical support provided through the Autism Speaks-Autism Treatment Network, significant improvements in the time to first visit were made. For children under 6 years of age referred to us, time from referral to first visit has improved from a high of 175 days (in April 2013) to 46 days, as of June 2014. For children over 6 years of age, time from referral to first visit has improved from over 400 days (April 2013) to 54 days as of June 2014. These types of improvements are rare at best in comparable programs around the country, and we plan to continue to improve access to better serve our families.

Contributions to New York Times best-selling book 'About Boys'

Staff and faculty from The Kelly O'Leary Center for Autism Spectrum Disorders (TKOC) worked closely with author Rosalind Wiseman on her best-selling book, *Masterminds and Wingmen: Helping our Boys Cope with Schoolyard Power, Locker-Room Tests, Girlfriends,* and the *New Rules of Boy World.* Wiseman, author of *Queen Bees and Wannabees,* spent several days at TKOC interviewing staff and patients for her chapter on boys with special needs. One TKOC patient was highlighted in the chapter and served as an editor for the book. *Masterminds and Wingmen* provides valuable information to parents and professionals about the unique social lives and struggles of boys. The collaboration was rewarding for all involved.

DEVELOPMENTAL BIOLOGY

TAGE core formed to enhance research capabilities

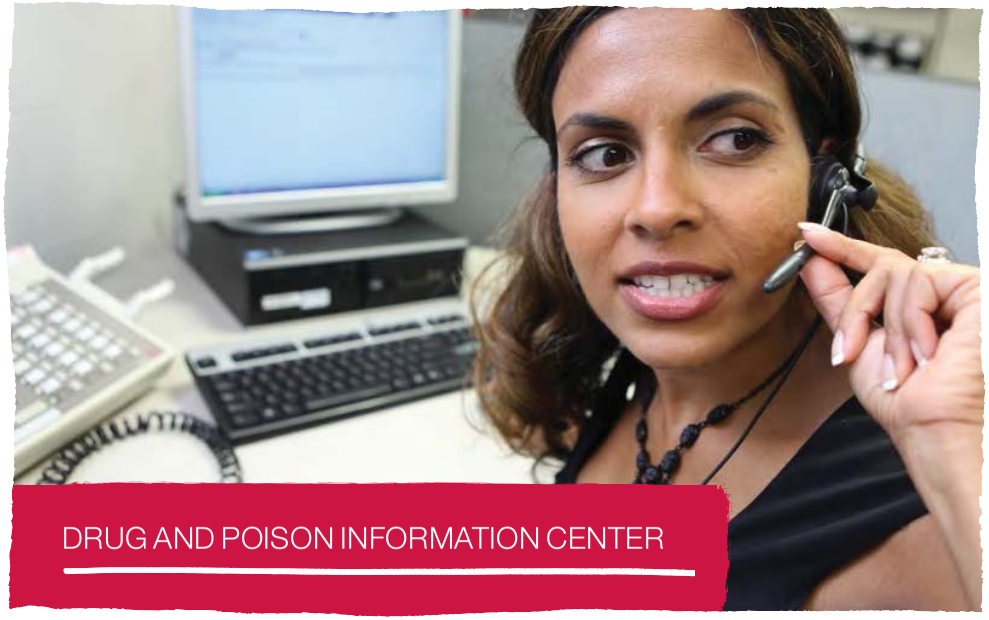
Our division was tasked with merging the Cincinnati Children's transgenic animal facilities, traditionally housed in Developmental Biology, with similar facilities at the University of Cincinnati. Yueh-Chiang Hu, PhD, was selected to direct the combined facility now called the Transgenic Animal and Genome Editing (TAGE) core. The TAGE core already has generated mutant mice using the CRISPR/Cas9 system and has numerous genome editing projects scheduled for the upcoming year. This critical enabling technology will help researchers across the medical center to improve their research product as well as compete more successfully for external funding. This core will be scaled up to support the new Center for Pediatric Genomics (CPG) at Cincinnati Children's.

Symposium focuses on systems biology

Our division hosted the symposium, "Emerging Leaders in Systems-Level Biology," in April 2014. Thirteen postdoctoral and early-stage investigators were invited to present their latest research in systems biology as it relates to developmental biology and relevant diseases, such as cancer. Three leaders in the field - David Sprinzak, of Tel Aviv University; Arjun Raj, PhD, of the University of Pennsylvania, and Rob Phillips, PhD, of the California Institute of Technology – were keynote speakers. Our division has initiated a faculty search for systems biologists studying developmental processes and related diseases, and this symposium helped set the standard for potential candidates.

Annual retreat attracts 175 participants

Our 15th annual retreat, held in Spring 2014, was the largest and most diverse to date. The event attracted 175 participating clinicians, basic scientists and students and included 75 posters from 20 research divisions at Cincinnati Children's. The volume of research presented is roughly on par with regional meetings of the Society of Developmental Biology and reflects the impressive size and depth of the developmental biology community at Cincinnati Children's.



DRUG AND POISON INFORMATION CENTER

Protecting the public

With 30 certified specialists in poison information and 51 staff certified in national incident management systems, our Drug and Poison Information Center is one of the largest in the country. This year, after the closing of the Northern Ohio Poison Center, our Center now serves a combined population of 5.8 million Ohioans. Our Center regularly collaborates with county, regional and statewide medical response and disaster preparedness programs. We also support the Ohio Disease Reporting Hotline. Additionally, the Center acted as the 24-hour Disease Reporting Line for the World Choir games. Our Health Alert Network sent alert faxes to 70 regional hospitals on subjects ranging from blue green algae in local rivers to fentanyl–contaminated heroin. Our team also continues to gather and evaluate safety data on public health issues such as poisoning, water quality, common household detergents, alcohol sanitizers and terrorism preparedness as well as offer a broad range of safety services to the pharmaceutical industry.

Community outreach and education

Our Center continued to promote healthy drug-free lifestyles to youth, parents and communities. Our staff includes prevention specialists, health educators, pharmacists, and other health care professionals working as positive role models. Last year, more than 27,000 people in Hamilton County benefitted from services including delinquency and violence prevention, positive life skills, health promotion and community engagement issues among African-American youth populations and other disparate populations. Our Center also was instrumental in the development of City Camp and the Cincinnati Police Department's latest youth intervention program: Hoops, Hope and Health (H3). As a founding partner, we also continue to support the People of Color Wellness Alliance Coalition and the Grassroots Urban Mobilization Benefitting Ohio initiatives to respond to health and wellness issues prevalent among disparate populations in Hamilton County. Through multiple newsletters, blogs and websites, our Center was active in lay and professional education about poison hazards.

EMERGENCY MEDICINE

Reducing costs while improving outcomes

We opened Urgent Care Burnet in the past year to reduce high-cost, unscheduled, low-acuity visits to the Emergency Department. This handled twice as many children as expected. The program, directed by Rima Rusnak, MD, and Tonya Ross, RN, also has reduced costs more than $700,000.

Julie Miller, APN, led a care coordination project that made flu shots available to more patients receiving emergency care as well as their family members. Nick Coorey, director, Clerical Staff, helped more patients connect with their medical homes or specialty needs by scheduling follow-up visits at the end of ED encounters.

Ben Kerrey, MD, led a team that designed interventions that markedly improved the safety and effectiveness of emergency placement of a breathing tube. Eileen Murtagh Kurowski, MD, led a team that improved the percentage of patients with high-risk conditions receiving timely, evidence-based care, according to our benchmarks.

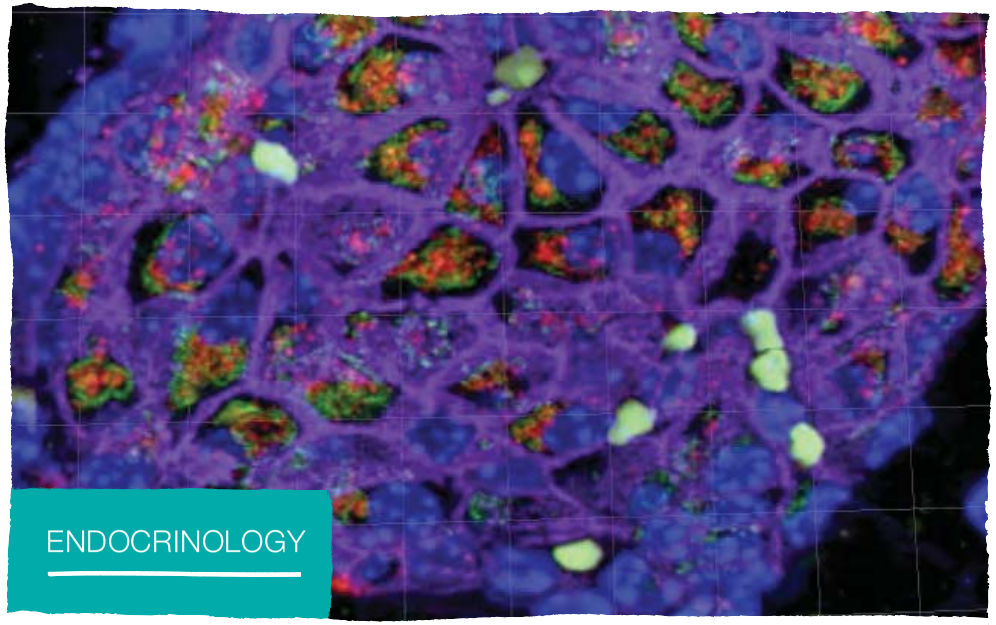
Emergency research

Our research director, Jackie Grupp-Phelan, MD, MPH, has led an effort to expand a study of a potential method for suicide risk screening from a single-site project into a multi-site project funded through the Pediatric Emergency Care Applied Research Network (PECARN).

Cincinnati Children's is one of 18 participants in PECARN, now in its 13th year. Important recent PECARN advances include using a decision support tool for reducing unnecessary head CT scans, creating a registry to benchmark ED quality measures involving seven hospitals, and the testing of a screening tool for alcohol use among teens developed by the Centers for Disease Control and Prevention. Jennifer Reed, MD, was awarded a grant from the NICHD to evaluate a method for linking teens to best practices in medical care for sexually transmitted disease. Todd Florin, MD, MSCE, is supported by a Gerber Foundation grant to characterize risk severity of pediatric pneumonia in partnership with colleagues in Hospital Medicine.

Making a difference in Malawi

A partnership between Cincinnati Children's and Kamuzu Central Hospital in Malawi has successfully completed year two. The partnership, led by Chuck Schubert, MD, seeks to build clinical capacity, improve Malawian medical education and explore collaborative research. Accomplishments with our partners include a 50 percent reduction in inpatient mortality and direct involvement as teachers for third-year medical students. Michelle Eckerle, MD, MPH, has been awarded a Fogarty Global Health Fellowship, which will allow her to spend 10 months there building research and supporting the partnership. So far, 20 residents, two Emergency Medicine Fellows, and three faculty members have completed rotations in Malawi.



ENDOCRINOLOGY

Disorders of Sex Development (DSD) Center joins Translational Research Network

Meilan Rutter, MD, Endocrinology, and the Disorders of Sex Development (DSD) Center at Cincinnati Children's have joined the national DSD Translational Research Network, the first network of its kind in North America. DSDs are congenital conditions in which development of chromosomal, gonadal or anatomic sex is atypical, resulting in severe consequences for behavioral health, fertility, cancer risk and quality of life. The new research network seeks to improve understanding of DSD, identify novel genetic mechanisms, deliver standardized clinical tools, and more. Our team already has started using the network's standardized forms in clinic and will soon be enrolling patients into a DSD registry.

Septo-Optic Dysplasia (SOD) clinic launched

The clinical needs of those with Septo-Optic Dysplasia (SOD) involve many subspecialties including Endocrinology, Ophthalmology, Genetics, and Behavioral Medicine. Patients also depend on occupational, physical, and speech therapists as well as resources from the Cincinnati Association for the Blind and Visually Impaired. Our SOD clinic, started in December 2013, was designed to incorporate all subspecialty patient needs into a centralized location. The new clinic also provides a base for expanded research for this under-studied population. Our team plans to work with colleagues at the University of Pennsylvania to identify genetic mutations associated with SOD.

EVERY CHILD SUCCEEDS

Launching Let's Talk Baby™

Every Child Succeeds (ECS) is taking its *Let's Talk Baby*™ Web app to the next level of testing thanks to the sponsorship of Procter & Gamble. This early language learning tool is designed to promote parent-child interaction and optimize development during the critical period of brain development: birth to age 3. The app delivers two weekly activities to a parent's email for viewing on a mobile device or computer. Procter & Gamble provided $50,000 to develop the prototype app, and the Center for Technology Commercialization at Cincinnati Children's provided support for developing the web platform. An invitation is being sent from Pampers first to 5,000 of its rewards members, then 10,000, and then 30,000 to test the app over a three-month period. Following the pilot test, the app will be updated with the potential to reach 4 million families who are subscribed to Pampers.com.

StartStrong initiative

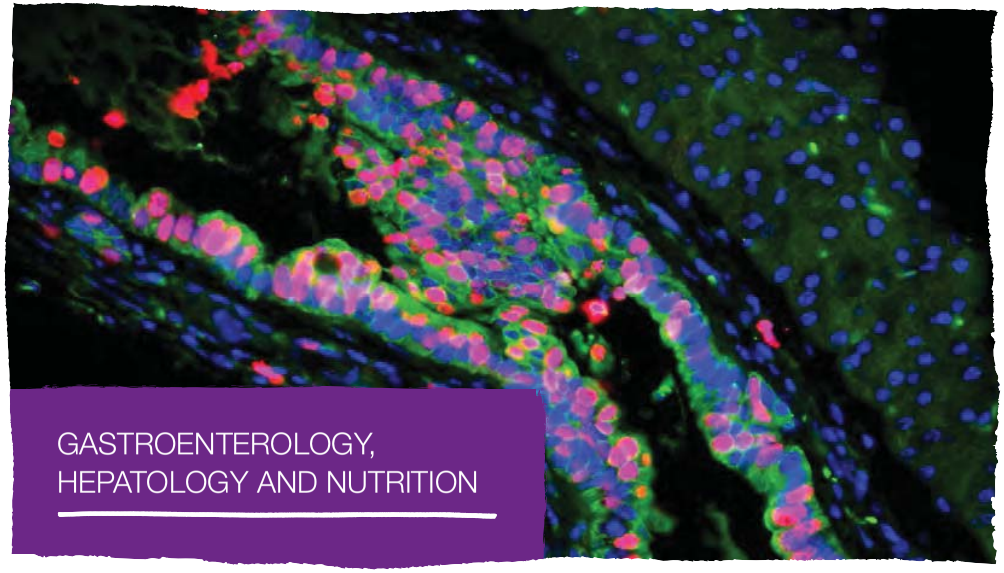
With three-year grant funding from Bethesda, Inc. and Cincinnati Children's, we are partnering with the Anderson Center and the Perinatal Institute to support the StartStrong Initiative. This community-wide project seeks to become a national model for reducing preterm births and inappropriate emergency department usage, starting with pilot projects in Avondale and Price Hill. The goal is to create a continuum of care, sensitive to the needs of high-risk pregnant women and their infant children. Through better use of heathcare resources, the initiative will improve the future for our community and all of our children. ECS will support the initiative through the use of trained home visitors, community health workers, moms group meetings, and other educational programs.

Community impact grows

Since its inception, Every Child Succeeds has served more than 22,000 families and provided nearly 500,000 home visits. Further accomplishments for Every Child Succeeds in the past year include:

- Expanding the role of our Transition Coordinators to increase the percent of children who attend quality preschool
- Engaging moms in four high-risk communities to support healthy child development and to address social issues
- Engaging community business leaders for funding and support
- Receiving a $324,000 Early Head Start grant to deliver home-based developmental services for 72 low-income families in Cincinnati
- Building linkages among families, home visitors and physicians' offices through our Medical Home initiati e
- Co-sponsoring, with the Pew Center on the States, the fourth annual National Summit on Quality in Home Visitation in Washington, D.C., in February. The Summit had its largest attendance ever, attracting more than 550 people.

> Our new Let's Talk Baby™ mobile app will help parents maximize the learning potential of their children.



GASTROENTEROLOGY, HEPATOLOGY AND NUTRITION

Digestive Health Center (DHC): a catalyst for research on digestive disease

The DHC is one of only 17 Silvio O. Conte Digestive Diseases Research Core Centers supported by the NIH, and the only one dedicated to pediatric diseases. With 101 investigators, the DHC contributes to the research goals of faculty from 21 divisions in the Department of Pediatrics and nine other Departments in the University of Cincinnati, College of Medicine. Our successful Pilot and Feasibility Program has distributed $1.3 million among 32 junior investigators since 2007. These investigators have since attracted $25.4 million in extramural grant funding.

Pediatric Liver Care Center (PLCC): new insights into biliary atresia

Despite the limited understanding of the pathogenesis of biliary atresia, steroids have been widely combined with surgery. To conclusively examine whether steroid therapy is an effective treatment, Jorge Bezerra, MD, led a multi-center study funded by the NIH. The study found that steroid treatment did not offer an advantage over placebo and the use of steroids was associated with an increased risk for post-operative complications *(Journal of the American Medical Association, 2014)*. In patients with biliary atresia, PLCC investigators found an unexpected increase in the cytokine interleukin-33 (IL-33). The administration of this cytokine into newborn mice with experimental biliary atresia healed the lining of injured ducts and allowed for growth of extrahepatic bile ducts *(Journal of Clinical Investigations, 2014)*. These findings have major implications for potential new therapies for biliary atresia and for the future engineering of bile ducts.

Schubert Martin Inflammatory Bowel Disease (IBD) Center: leading the way

This year, more than 700 IBD patients were seen in our center, including 100 newly diagnosed and 90 second-opinion patients from 25 states and abroad. The center is an integral and leading participant in collaborative consortia, i.e., ImproveCareNow, and Crohn's and Colitis Foundation's (CCFA's) PRO-KIDS. This role is reflected in superior outcomes for our patients with 80 percent of IBD patients in remission, 64 percent in sustained remission, and 84 percent having a good quality of life. These outcome measures are shared on the center's website. Our Annual IBD Family Education Day, co-hosted by CCFA, continues to be one of the largest educational events of its kind in the country.

GENERAL AND COMMUNITY PEDIATRICS

Proving walk-in care is a feasible alternative to emergency department use

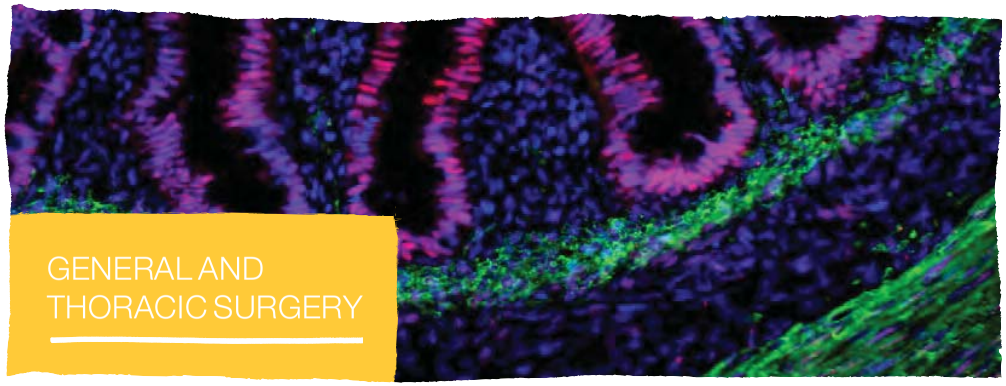
The Division of General and Community Pediatrics is on a journey to dramatically improve primary-care delivery, building a rigorously developed new model that can be shared nationally. This year, the Ill Care Improvement team, led by John Morehous, MD, and Steve Warrick, MD, successfully tested and developed a model for walk-in access for sick patients. The work began at the Pediatric Primary Care Center (PPC) in collaboration with the Anderson Center and Emergency Department. A separate care team and workflow stream for walk-ins were created. No patients are scheduled; patients are encouraged to walk in for care when it is convenient. The hours were initially limited, but have expanded to 8 am to 8 pm, fi e days a week. A significant shift has occurred: approximately 10 percent of ill visits have moved into the PPC from the hospital's ED and Urgent Care. This means more ill visits occur daily in the medical home, at greater convenience to families. This year was one for testing and the goal for the coming year is to accelerate this shift.

The model is being refined to address two important issues: missed preventive services and high acuity walk-ins. The team is testing delivery, during the walk-in visit, of immunizations, risk factor screening, lead screening, and developmental screening; this is one substantial advantage of visits in primary care over the ED. A severe acute illness protocol is also being developed, given the potential for a very sick patient to walk in suddenly. The redesign work has already led to two manuscript submissions and multiple presentations at national conferences.

Faculty awards for service and advocacy

This year, the Division of General and Community Pediatrics was home to two winners of the Cincinnati Children's Faculty Awards for Service and Advocacy. Robert Kahn, MD, MPH, and Andrew Beck, MD, MPH, were recognized for their innovative work in community health. Community health and advocacy are increasingly relevant given healthcare reform. The Division has been at the forefront of such work in clinical practice and research. Kahn is director of the Cincinnati Child Health-Law Partnership (Child HeLP), a partnership with the Legal Aid Society. This program has brought legal services related to public benefits, housing, and education to more than 2,000 families over the past fi e years. Beck directs two additional community partnerships. Collaborating to Lessen Environmental Asthma Risks (CLEAR) is a program that connects children hospitalized with asthma who have a home environmental risk with Cincinnati Health Department housing inspectors. The Keeping Infants Nourished and Developing (KIND) program is a partnership with the Freestore Foodbank to provide supplemental formula and other resources to food insecure households with infants.

The service and advocacy have been complemented by academic rigor and funding. Kahn and Beck, in collaboration with Melissa Klein, MD, MEd, Child HeLP program manager Adrienne Henize, and others, have published six papers on these partnerships. In addition to community partnerships, the work has spawned new collaborations across the University of Cincinnati.



GENERAL AND THORACIC SURGERY

Intestinal models pave the way for intestinal rehabilitation

Michael Helmrath, MD, Surgical Director of the Intestinal Rehabilitation Center, and his team focus on strategies to improve the outcomes of children with intestinal failure. Understanding the biology of intestinal stem cells is a key to unraveling the mechanism involved during the disease process. To that end, the Helmrath team developed *in vitro* culture techniques to maintain and expand individual human intestinal stem cells derived from human tissue samples.

Utilizing those techniques, the Helmrath lab is able to culture intestinal stem cells derived from a variety of diseased tissues. In association with colleagues in Pulmonary Medicine, we are using stem cells derived from patients with cystic fibrosis as a tool for evaluating promising drug compounds. In collaboration with investigators at the University of Cincinnati and in Gastroenterology, we also use intestinal stem cells to study intestinal infectious diseases.

The Helmrath lab, in collaboration with James Wells, PhD, Developmental Biology, and Noah Shroyer, PhD, Gastroenterology, also has developed a murine model of a vascularized and functional human intestine to study human intestinal physiology. These intestinal models will pave the way for understanding gastrointestinal related diseases and lead to the personalized treatment of patients.

Progress against congenital malformations

A team led by Jose Peiro, MD, Director of Endoscopic Fetal Surgery at the Cincinnati Fetal Center, is investigating the basic mechanisms of pediatric and fetal surgical congenital malformations, focusing especially upon fetal myelomeningocele (MMC), fetal congenital diaphragmatic hernia (CDH) and gastroschisis.

In MMC, Peiro's team is improving the fetoscopic approach for intrauterine repair by evaluating different patches and sealants in animal models, then translating these techniques for use in the human fetus. A new clinical trial will compare fetoscopic MMC repair in humans against the standardized open fetal surgery approach.

They are using a mouse model of neural tube defects to investigate how maternal immune status can influence incidence of congenital malformations. They are studying ways to use neural progenitor cells collected from the amniotic fluid of MMC patients as a potential form of neural regeneration (cell therapy).

In CDH, studies in animal models indicate that early fetal tracheal occlusion may induce faster and better fetal lung growth. A new animal model of CHAOS ligation of the fetal trachea early in gestation perfectly resembles the human histology of this condition. To continue this work, the team has begun studies to evaluate the metabolomics and proteomics of these tissues and fluids

They expect to start very soon with fetoscopic tracheal occlusion in human fetuses with severe CDH by detachable balloon insertion. This work will contribute to the ongoing multicenter TOTAL trial.

Can elective preterm delivery prevent gastroschisis?

In gastroschisis, we are leading an innovative international multicenter study designed to analyze elective preterm deliveries at 34 weeks' gestation instead of spontaneous delivery as an approach to avoid intestinal inflammation and obtain better neonatal outcomes.

GLOBAL CHILD HEALTH

Environment and diet shown to impact breastfeeding

Adekunle Dawodu, MBBS, and his group measured serum 25(OH)D levels in breastfeeding mothers and infants from Cincinnati, Shanghai, China and Mexico City to compare these populations enrolled in the Global Exploration of Human Milk (GEHM) Study. The study was designed to explore effects of different environments and diets on human milk composition, infant nutrition, and health. Maternal vitamin D deficiencies were more common in Shanghai and Mexico than Cincinnati mothers. In contrast, infant vitamin D deficiencies were more common in Cincinnati and Mexico than in Shanghai. The study provided data that vitamin D deficiency is common in breastfeeding mothers and infants worldwide, though the prevalence in diverse populations depends upon sun exposure and Vitamin D supplementation behaviors. Abstracts from this work were presented in May at the Pediatric Academic Societies annual meeting and in April at Experimental Biology 2014.

Study examines altered immune response to influenza immunization during pregnancy

After discovering that pregnant women have lower antibody responses to influenza vaccine compared to non-pregnant women, Elizabeth Schlaudecker, MD, MPH, collaborated with Fred Finkelman, MD, in the Division of Immunobiology to further evaluate this immune response. They found that the antibody isotypes associated with antibody-dependent killing of virus were more likely to be decreased in pregnant women, possibly inhibiting their ability to mount a response against influenza. Many pregnant women had a combination of low IgG1 and high IgG4 that was not seen in non-pregnant women and is likely to provide poor protection against influenza infection. This suggests a need to reconsider approaches for immunizing pregnant women against influenza.

Meningococcal vaccine appears safe for pregnant women in Africa

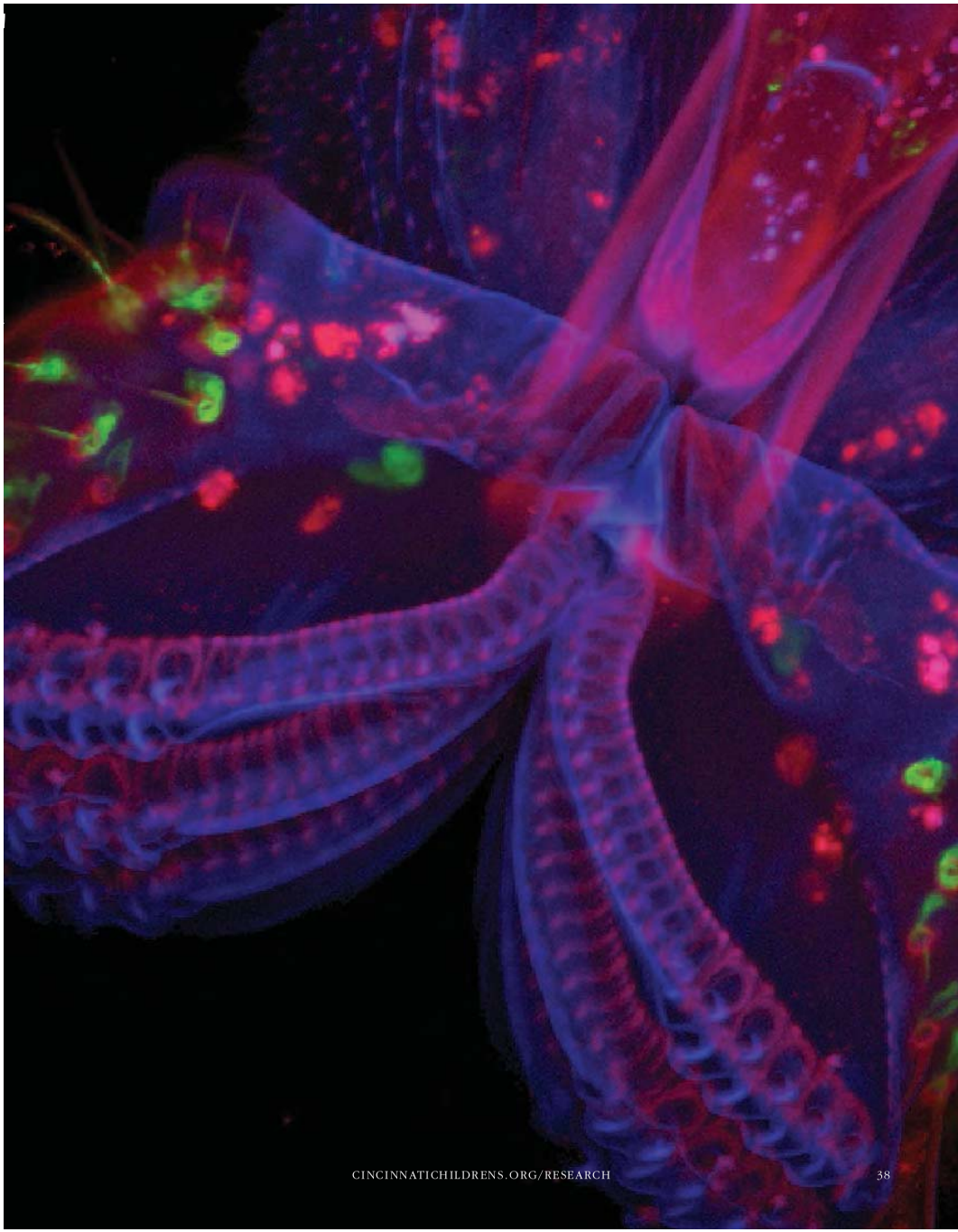
Steve Black, MD, has collaborated with WHO and the INDEPTH research center in Navrongo, Ghana, to conduct the first evaluation of the MenAfriVac conjugate meningococcal A vaccine in pregnant women. Meningococcus type A causes large and devastating epidemics in an African "meningitis belt" that includes northern Ghana. The MenAfriVac vaccine was developed specifically to address this issue, however no information was available about the vaccine's safety when given to pregnant women. Black compared the risk of adverse events in women who received the vaccine both to a historical control group and to pregnant women who elected not to receive this vaccine during the new program. Results presented to the WHO Global Advisory Committee on Vaccine Safety in June 2014 demonstrated that administering the vaccine was safe during pregnancy.

Neonatal outcomes study earns honor

The Bruce P. Squires Award for 2014 was conferred for our publication entitled, "Neonatal Outcomes after Influenza Immunization in Pregnancy," which first appeared in February 2012 in the journal *CMAJ*. This was the first report of the effect of increased neonatal weight and reduced prematurity related to maternal immunization with influenza vaccine. This unique evidence from a randomized controlled trial showing that prevention of influenza in the mother results in substantial benefits for the fetus and newborn has now been replicated in numerous reports.

Nurturing Children's Development program expands

This partnership between Cincinnati Children's and Procter & Gamble, which has supported research scholars and observers from China, Latin America, and Africa, was expanded this year to include one research scholar and four observers from India.



HEART INSTITUTE

Can the heart regenerate?

Worms can do it, tadpoles can do it; can humans? After a heart attack, large areas of heart muscle are lost and replaced with scar tissue. Not only does this tissue not effectively pump blood, it can actively interfere with the remaining, functional muscle tissue. Researchers have been working to replace this scar tissue with new, contracting muscle grown from stem cells. Data in animal models suggest that certain types of cardiac stem cells have the capacity to regenerate damaged heart muscle. However, clinical trials so far have been controversial and the results have been mixed.

Stem cells used in most human clinical trials have been identified by a certain type of protein they produce, known as "c-kit." Identifying stem cells for subsequent injection into humans on the basis of this marker has been widely used for the clinical trials. Jeffery Molkentin, PhD, and colleagues recently published a paper in the journal *Nature* that definitively shows that endogenous stem cells in the heart, expressing c-kit, are not a significant source for making new heart cells in the mouse. The Molkentin lab used sophisticated genetic tracing techniques to demonstrate that c-kit expressing stem cells have extremely limited capacity to make new cardiac myocytes and contribute to new, beating muscle in the heart, even after heart attack injury. These results suggest that any potential benefit of injecting c-kit cells into the hearts of human patients is unlikely to result from generation of new contracting heart tissue.

3D heart disease models help with surgery planning, educating families

During the past year, the Heart Institute developed the infrastructure and expertise to create patient-specific 3-dimensional (3D) complex congenital heart disease models. These 3D heart models have proven to be extremely valuable to our surgical team for both patient education and pre-surgical planning. In a recent case, a 3D-printed model of a patient with interrupted aortic arch was needed to help understand the basic anatomy prior to surgery. We delivered the model to the surgeon within six hours, and the resulting pre-surgical planning ultimately changed the surgeon's approach. The model also was used to educate the family about their child's heart condition, providing them with additional insight into the surgical approach. We have begun tracking the impact 3D heart modeling has upon surgical outcomes. If there is a proven benefit, this would represent the first evidence to support the paradigm shift of using 3D-printed heart models for routine surgical planning.

In a related project aimed at patients, parents, and trainees, we have created "Heartpedia," the first fully interactive 3D congenital heart disease mobile application. The initial version of this free app contains seven 3D heart models of the most common and complex congenital heart defects. Each defect also has an interactive model of the most commonly used surgical palliation. All the detailed information from the popular Heart Institute Encyclopedia website is contained within the app and it links to the recently updated Heart Encyclopedia animated videos. The primary aim of the Heartpedia app is to help patients and parents understand these defects. We hope it also helps parents share this complex information with relatives and friends. The Heartpedia app is being used clinically for counseling families about diagnoses and therapy options. It has received excellent initial reviews from parents and practitioners. The team responsible for both projects is headed by Michael Taylor, MD, and includes Peace Madueme, MD, (Cardiology faculty), Ryan Moore, MD, (Cardiology fellow), Ken Tegtmeyer, MD, (Critical Care faculty), and Jeff Cimprich (Critical Care Media Lab animator).

Community outreach: healthy kids

More than 40 percent of Norwood Public School children are overweight or obese. With this in mind, we have collaborated with the school system to create the Norwood Schools Center for Better Health and Nutrition Clinic, which opened in November 2013. The clinic delivers a comprehensive pediatric weight management program directly to the students of an entire city. The clinic features the services of a pediatrician, dietitian, exercise physiologist, nurse, and social worker. These complete services are offered twice a month at Norwood High School.

The Norwood clinic is the centerpiece of "Healthy Kids Norwood," a comprehensive initiative between Cincinnati Children's and the City of Norwood to lower obesity rates in children. This effort has several community-based interventions, including Fun2BFit, a youth exercise program offered at the Richard E. Lindner YMCA, and Norwood Grows, an augmentation of the Woven Oak Initiative's student gardening program. Efforts to improve nutrition and activity for Norwood Public School students include redesigning cafeteria serving strategies, cooking classes, student taste testing and 100-mile walking/running clubs. The clinic also issues a "Healthy Kids Norwood" newsletter with health information and activities for the entire community. To further these health efforts outside of school, the clinic has been working to increase the availability of fruits, vegetables and other healthy foods at the Zion Food Pantry and Lydia's House (a residential facility for single-parent families in distress). In August 2014, we also launched a pilot Norwood Farmer's Market. All of these initiatives will be monitored closely. Once we know what the most effective approaches are, we can scale those efforts up so that more children in our region are reached.

HOSPITAL MEDICINE

Hospital medicine complex care team

The care of patients with complex medical needs requires multidisciplinary care coordination due to frequent admissions, involvement of multiple subspecialties, and need for multiple medications. In July 2013, the complex care team (also known as the Yellow team) was created in partnership with the Division of General and Community Pediatrics and the Complex Care Center to provide comprehensive inpatient care to these medically fragile patients. Patients admitted to this inpatient team include those with developmental disabilities or technology dependence (e.g., require a feeding tube). In addition to a core group of Hospital Medicine attending and fellow physicians, this team also includes Complex Care Center physicians, social workers, pharmacists, care managers, residents, nurses, and advanced nurse practitioners. Goals of the team include providing safe, coordinated family-centered care, developing clinical expertise in the inpatient care of complex patients, and advancing the care of medically complex patients through research focused on their unique needs.

Hospital medicine adult care

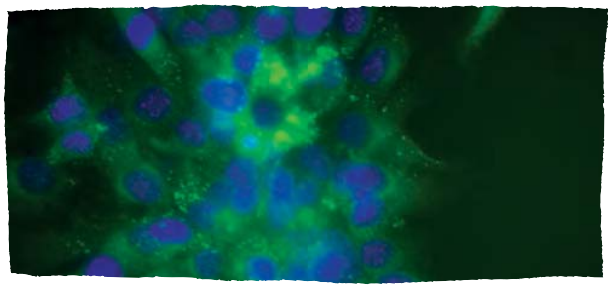
Survival into adulthood is now common for many diseases that were historically fatal in childhood, such as congenital heart disease, extreme prematurity, and childhood cancer. As adults, these patients require care from specialists with expertise in caring for their "pediatric" condition as well as those with expertise in adult medical issues. In July our division launched the Hospital Medicine Adult Care (HMAC) service to provide high quality consultative care to adult patients admitted to Cincinnati Children's. Physicians who have training and experience in the care of both hospitalized children and adults will staff this service. Under the leadership of Jennifer O'Toole, MD, MEd, four new faculty members (Erin Conway, MD, Brian Herbst, MD, Lori Herbst, MD, and Benjamin Kinnear, MD) will develop this service in partnership with Cincinnati Children's Adult Transition clinic faculty. The HMAC faculty members will also practice at the University of Cincinnati Medical Center and Cincinnati Children's to maintain exceptional skills in both internal medicine and pediatrics. Major goals for the HMAC service are to enhance clinical expertise in the care of this specialized population, improve patient experience, improve access to care, and improve safety for adult patients admitted to Cincinnati Children's, while establishing a reputation as national leaders in this area.

Partnership with community pediatricians to improve care

Timely and efficient transitions of care are important to ensure patient safety at the time of hospital discharge. Review of our data revealed that telephone calls to discuss hospital course and determine the follow-up plan of care occurred for only 52 percent of discharged patients. A multidisciplinary team implemented systematic improvements, including mandatory use of Physician Priority Link, tying signing of the discharge order with initiation of the call, and batching outgoing calls to minimize work disruption to primary care physicians. These improvements led to 96 percent of calls successfully completed.

At Cincinnati Children's, some community physicians admit and manage their own patients. Having those patients assigned to the correct attending physician and resident team is important to facilitate communication between the community physician and resident as well as to expedite the rounding process. Baseline data indicated that 50 percent of community physician patients were being incorrectly assigned. A multidisciplinary team, which included community physicians, implemented improvements and decreased incorrect service assignment to less than 5 percent.

HUMAN GENETICS



Ending the diagnostic odyssey through exome sequencing

The past year marked an expansion in exome sequencing to provide molecular diagnoses to individual families, both through research and as a clinically available test offered through the Molecular Diagnostic Laboratory. Led by Cindy Prows, MSN, CNS, and Kristen Sund, PhD, LGC, 24 families were enrolled and sequencing studies completed by the Cincinnati Children's DNA Sequencing and Genotyping Core. Analysis has been completed in 21 families. For seven families, a molecular diagnosis in a known gene fitting the phenotype was identified; and for an additional six families, a potentially novel gene was identified. Throughout this process, family preferences for return of results were investigated.

In July 2013, the Molecular Diagnostic Laboratory launched ExomeSeq for clinical exome sequencing. A multidisciplinary team of laboratory professionals, analysts, genetic counselors, and clinical geneticists completed 24 exome studies and were able to provide a molecular diagnosis to eight families for whom a genetic diagnosis had been elusive, some for more than 15 years.

Of mice and men

Rolf Stottmann, PhD, has received an NIH grant to study congenital brain defects in cortical circuits and structural development. Stottmann will use forward genetics in the mouse to efficiently generate and capture genetic mutations in genes important for cortical circuit formation and structural development, and will identify and validate causal mutations in novel mouse models of cortical circuit formation and structural brain defects. He also plans to apply next-generation sequencing approaches to identify mutations leading to human movement disorders and structural brain defects in children with brain malformations recruited from Cincinnati Children's. These studies will lead to the identification of several genes essential for mammalian forebrain structure and function. This work has the potential to implicate entirely new molecular pathways in neurological disease, which eventually could lead to development of novel therapeutic targets.

Bringing new options for individuals with rare disease

The work of genetics is not limited to diagnosis. Our Clinical Trials Unit, led by Laurie Bailey, MS, LGC, has helped 36 adults and children participate in seven interventional trials of new biologic approaches to disease management. A new trial to study the benefits of enzyme therapy for hypophosphatasia led by Howard Saal, MD, was launched. As preliminary results of this transformational therapy for a skeletal dysplasia became known, Cincinnati Children's quickly became a busy site, enrolling four patients from the U.S. and two children from the Middle East. Other diseases in which our physicians are participating in interventional trials include Pompe, Gaucher, Fabry, and cholesteryl ester storage disease. Progress in rare disease management depends on collaborative registries. The division has enrolled 281 individuals in seven rare disease registries, and several clinical faculty and counselors have been involved in registry boards that analyze the accruing data and make sure that worldwide experiences are translated into better patient outcomes.

Our Human Genetics team has enrolled 281 children in seven rare disease registries in the past year.

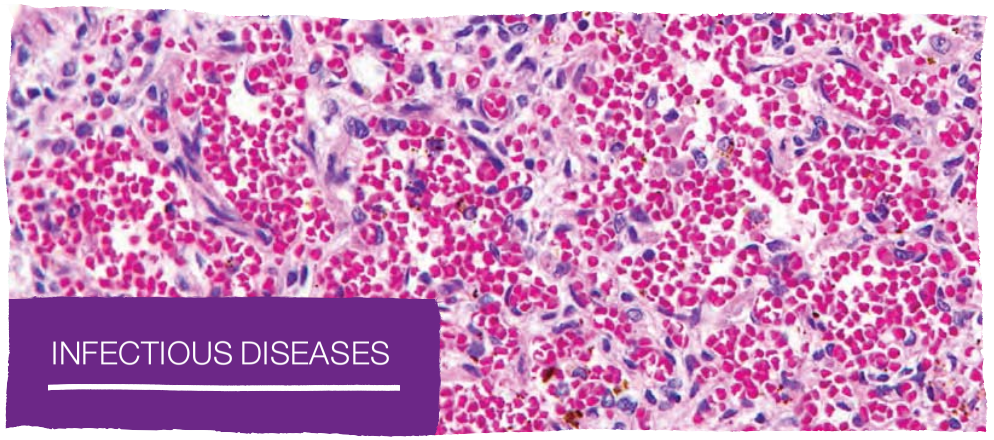
IMMUNOBIOLOGY

Studies suggest method for controlling inflammatory disorders in premature infants

The laboratory of Claire Chougnet, PhD, is focusing on the functioning of a critical subset of CD4+ T cells termed regulatory T cells (Tregs) in the context of preterm birth. Tregs are required both to establish and sustain immunological self-tolerance and to limit responses to foreign antigens such as those derived from beneficial commensal bacteria. Tregs arise at an early stage during the development of the human infant immune system. In a recent article published in *The Journal of Immunology*, Chougnet's laboratory showed that intra-amniotic inflammation induced by administration of IL-1β in Rhesus macaques, a particularly suitable model for humans, leads to fetal lung inflammation and rapidly alters the balance between regulatory T cells and IL-17-producing T cells in fetal lymphoid organs. These data have been extended to another model of prenatal inflammation Chougnet's laboratory is now studying the underlying molecular mechanisms. The loss of Tregs that is accompanied by the generation of IL-17-producing T cells may play a role in several debilitating diseases in prematurely born infants, including bronchopulmonary dysplasia and necrotizing enterocolitis. These findings suggest that boosting Treg cells and/or neutralizing IL-17 may provide new therapeutic interventions for uncontrolled inflammato y disorders in premature infants. The NIH and Burroughs-Wellcome fund are supporting this and related research initiatives in the Chougnet laboratory, some of which involve collaborations with Lou Muglia, MD, PhD, in the Perinatal Institute.

Research explores connection between obesity and liver disease

The research program of Senad Divanovic, PhD, is focused on cellular and molecular mechanisms underlying chronic inflammation in obesity and obesity-associated conditions such as non-alcoholic fatty liver disease (NAFLD), the most common chronic liver disease in the developed world. Divanovic recently published findings in the journal *Hepatology* that also were highlighted by an accompanying editorial. The observations that obesity is associated with increased activation of IL-17 signaling and that this molecular pathway can instigate liver damage in diverse contexts prompted Divanovic to explore the role of IL-17 signaling in the progression of NAFLD. His laboratory has demonstrated that loss or inhibition of IL-17 signaling significantly reduces obesity-driven hepatocellular damage in mice. This research formed the basis of an NIH RO1 application titled, "Immunopathogenesis of Non-alcoholic Fatty Liver Disease," which was funded on its first attempt, a remarkable achievement for a junior investigator in a period of constrained federal research funding.



INFECTIOUS DISEASES

Grant funding rises fast

With overall grant funding rising to $9.4 million, our division ranked first of all divisions at Cincinnati Children's for its increase in grant funding in 2012 and 2013. We received funding from the NIH, CDC, Burroughs-Wellcome, Bill and Melinda Gates Foundation, NASA, and industry, which supported research projects exploring the pathogenesis of CMV, HSV, norovirus/calicivirus, and *Candida* infections; vaccine response; macrophage biology; and normal and aberrant immune responses in pregnancy.

Transplant infectious diseases program expands

High demand for expertise from our transplant infectious diseases program, launched in 2012 under the direction of Lara Danziger-Isakov, MD, MPH, led to plans to expand the service in August. The division recruited a new faculty member, Grant Paulsen, MD, a med/peds fellow trained in both pediatric and adult infectious diseases at the University of Alabama-Birmingham. Other support to the service will be supplied by a nurse practitioner.

Antimicrobial Stewardship Program provides expert consulting

Our Antimicrobial Stewardship Program is directed by David Haslam, MD, who was recruited in September 2013 from Washington University in St. Louis. The other partner in the program is Joshua Courter, PharmD, from the Division of Pharmacy. With the use of VigiLanz software to monitor adverse drug events, antimicrobial usage, and targeted infections, the team has provided expert consultation to a number of services, including oncology, bone marrow transplant, general surgery, and pulmonary.

Vaccine technology and genetic discovery take steps forward

Division faculty members Jason Jiang, PhD, and Ming Tan, PhD, have licensed the technology for the norovirus P particle as a vaccine platform. Meanwhile, the Hostetter laboratory worked with the Center for Technology and Commercialization to submit a provisional patent application for genes contributing to disseminated staphylococcal infection after osteomyelitis.

Vaccine and Treatment Evaluation Unit renewed

Under the direction of David Bernstein, MD, MA, Cincinnati Children's successfully renewed the Vaccine and Treatment Evaluation Unit (VTEU) contract, a seven-year award with a cumulative budget of more than $35 million. Our medical center has been a VTEU site for nearly 20 years. The contract also provides access to cutting-edge vaccines and treatments for various infectious diseases with recent pathogens including novel H1N1 influenza and anthrax. The ongoing work of Bernstein and his group has brought significant recognition to Cincinnati Children's as a leader in infectious disease research.

MAYERSON CENTER FOR SAFE AND HEALTHY CHILDREN

Childhood trauma reduction collaborative

The Mayerson Center has received two major gifts from the Dornette and Schmidlapp Foundations to improve our community's recognition of and response to children exposed to trauma and adversity, otherwise known as toxic stress. Reducing childhood toxic stress exposure has become a public health priority and the subject of a national call to action. A child's exposure to toxic stress can cause brain and other developmental changes resulting in lifelong learning difficulties, behavior problems, social maladaptation, physical illness and mental health disorders. Through these gifts the Mayerson Center will develop a community collaboration to screen for toxic stress, including the increased risk for adverse experiences, and improve the medical and community responses to trauma.

Increased trauma-informed mental health services

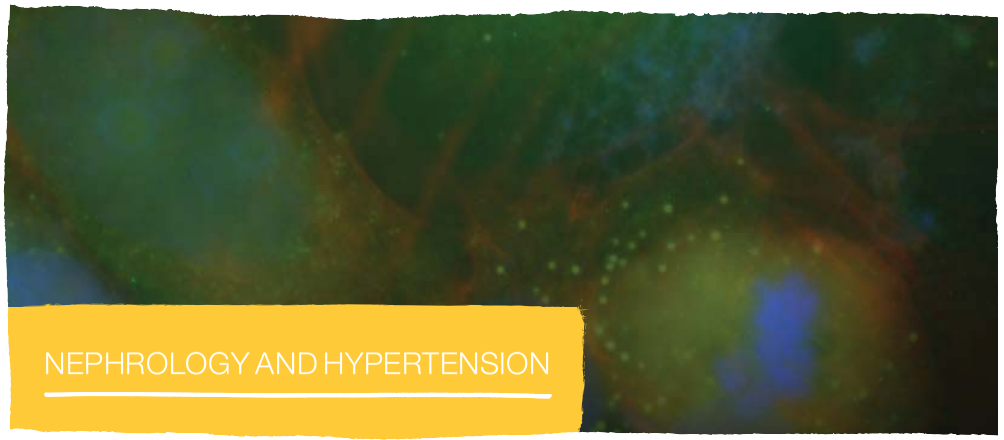
Increasing the mental health interventions for children and families who have been affected by child abuse has become a Mayerson Center priority. Expanding capabilities to provide trauma-informed treatment to more children and families through additional staff and new services has helped to accomplish this strategic initiative.

The Mayerson Center now offers a new acute, short-term mental health treatment called Child Family Traumatic Stress Intervention (CFTSI). April Barker-Casey, LISW, has joined the Mayerson Center to provide CFTSI, an intervention designed to help children and adolescents ages seven to 18 who have experienced potentially traumatic events such as sexual abuse, physical abuse, domestic violence, community violence, and accidents. The primary goals of CFTSI are to decrease post-traumatic symptoms and disorders and to identify individuals in need of more intensive treatment.

In a longstanding collaboration with Behavioral Medicine and Clinical Psychology, children exposed to traumatic events and children evaluated for abuse and neglect have access to trauma-informed mental health services through the Mayerson Center. This program has expanded by adding a third full-time staff psychologist, Julie Tiemeier, PsyD, who joins Heather Bensman, PsyD, and Erica Messer, PsyD, in providing these much needed services.

National/International training expert

This year we celebrate the success of Erica Messer, who was certified as a Level II Parent-Child Interaction Therapy (PCIT) trainer. PCIT is an evidence-based treatment supported by over 30 years of research and practice by PCIT providers throughout the U.S. and internationally (www.pcit.org). This therapy is useful for children ages 2 to 7 who have disruptive behavior disorders and for parents who are at-risk for or require rehabilitation for physically abusive parenting. PCIT is an assessment-driven, criteria-based therapy that focuses on improving positive child behaviors through a strong parent-child relationship. Messer, one of fewer than 10 Level II trainers worldwide, conducts PCIT training workshops for clinicians around the world.



NEPHROLOGY AND HYPERTENSION

New test panel revolutionizes diagnosis of thrombotic microangiopathy

A transformative advancement in diagnostic testing has further elevated the profile of Cincinnati Children's. Thrombotic microangiopathies are a group of disorders that cause damage to small blood vessels throughout the body, leading to organ damage and possibly death if not treated promptly. In the past, the required blood tests were available only piecemeal at different institutions. Through the efforts of Bradley Dixon, MD, in the Division of Nephrology and Hypertension, and his collaborators in the Cancer and Blood Diseases Institute and the Division of Human Genetics, all of these tests were brought under one roof at Cincinnati Children's. This platform of tests was made available for clinical use in September 2013, and has revolutionized the diagnostic testing of individuals with thrombotic microangiopathies. In recognition, Dixon received the Entrepreneurial Achievement Faculty Award in February.

Multidisciplinary Stone Center launched to meet soaring demand

More than 625 children were treated last year for kidney and urinary tract stones at Cincinnati Children's, double the number from fi e years ago and more than triple the figure over the last decade. In response to this growing epidemic, the Stone Center was launched. The Center's multidisciplinary team includes physicians, nurses, dieticians, genetic counselors, and social workers from seven specialties. Under the direction of Prasad Devarajan, MD, Nephrology Division Director, the Center provides families of children with kidney stones coordinated care, education, treatment, prevention and research. Children are seen by a nephrologist, urologist, dietician, and genetics counselor. Research in stone disease includes a data base, evaluation of the two-day versus one-day metabolic stone profile, stone risk before and after bariatric surgery, and development of a genetic chip to detect the common hereditary stone forming conditions. We are also one of the Coordinating Centers within the NIH-funded Rare Kidney Stone Consortium to test novel therapies for kidney stones.

Our Kidney Transplant Program is the busiest in the country

Our Kidney Transplant Program, spearheaded by nephrologists Jens Goebel, MD, and David Hooper, MD, MS, is one of the most experienced in the country at treating complex diseases of the kidney and urinary tract. We have excellent outcomes, with 100 percent one-year post-transplant patient and graft survival rates. Last year, we performed 34 kidney transplants, more than any other center in the U.S. In recognition of the achievements of the kidney transplant program, Hooper received the Clinical Care Achievement Faculty Award in February.

> Cincinnati Children's treated more than 625 children last year for kidney and urinary tract stones — twice as many as fi e years ago and more than triple the figure from a decade ago

NEUROLOGY

Tuberous Sclerosis

The division continues to grow, both in clinical care and research. In 2013, the clinicians in the Tuberous Sclerosis Clinic (TSC) evaluated more than 650 unique patients and welcomed fi e new specialists: Janet Boyle, MD, (Adult Nephrology), Stuart Goldstein, MD, (Pediatric Nephrology), Jens Goebel, MD, (Pediatric Nephrology), Elizabeth Gosnell, DMD, MS, (Pediatric Dentistry), and Jamie Capal, MD, (Pediatric Neurology and Neurodevelopmental Disabilities). The TSC continues to be the largest, most comprehensive clinic of its kind in the world. In research, Brian Siroky, PhD, joined the clinic team with a joint faculty appointment in Nephrology and Neurology. Results from the 2012 International TSC Consensus Conference, chaired by Darcy Krueger, MD, PhD, included one of 14 manuscripts published by the research team in 2013. Three new funded projects were added in 2013.

Movement disorder and Tourette Syndromes

The Movement Disorder and Tourette Syndrome Clinic sees children with tics, stereotypies, dystonia, tremor, chorea, ataxia, functional movement disorders, and drug-induced movement disorders at the base and several satellite locations. Our program has a national reputation and regularly gets referrals from other states for second opinions. The Dystonia and Complex Movement Disorder clinic provides pharmacological treatment, botulinum toxin, and deep brain stimulation. Pre- and post-operative management is multidisciplinary. Program highlights include publication of the first study of a novel agent for tic suppression in Tourette Syndrome and lead site for a phase 2 study in children and adolescents; and NIH funding for studies in Tourette genetics and ADHD brain physiology.

Neonatal neurology

The neonatal neurology team provides consultation services for the acute management of seizures and other neurological disorders in newborns at Cincinnati Children's, Good Samaritan Hospital and University Hospital of Cincinnati. We provide fetal consultations for brain disorders as part of a multidisciplinary team at the Fetal Care Center of Cincinnati. We continued to expand a combined neurology/neonatology follow-up clinic that treats children for their first several years of life. This outpatient care involves longitudinal identification of risk factors for poor neurologic development. The team is expanding services via telemedicine to Kettering, Ohio, and plans to add a faculty member to accommodate the growth.

Comprehensive epilepsy program

For the third consecutive year, clinical volume increased by 20 percent at the epilepsy surgery program. Ten peer-reviewed publications on Epilepsy surgery were published from several different first authors in the multidisciplinary group. Work continues on two institutional grants. The Epilepsy Advanced Therapies Clinic saw a greater than 50 percent increase in clinical volume for the third consecutive year.

NEUROSURGERY

Diverse, collaborative clinical and research activities

The surgical treatment of intractable epilepsy in children, and finding new ways to improve outcomes, remains our division's primary focus. Division Chief Francesco Mangano, DO, is co-principal investigator with Weihong Yuan, PhD, Department of Radiology, on a study of advanced MR imaging techniques in the field of hydrocephalus. Work from this multi-institutional study was published internationally.

Collaborating with physicians in medical neuro-oncology and radiation oncology, Charles Stevenson, MD, leads the division's brain tumor program. As a member institution of the Pediatric Brain Tumor Consortium (PBTC), Cincinnati Children's continues to innovate in clinical trials related to brain cancer. In one recent trial sponsored by the National Cancer Institute and PBTC, a special virus designed to kill tumor cells but not affect normal cells was injected into malignant brain tumors that defy chemotherapy and radiation therapy. Cincinnati Children's is the only pediatric hospital in the U.S. approved for this treatment.

Stevenson, with colleagues in Physical Medicine/Rehabilitation and Physical Therapy, launched a multi-disciplinary surgical spasticity clinic that focuses on early identification of patients with cerebral palsy and spinal cord injury. As part of the Fetal Care Center, Stevenson continues to perform *in utero* repair of myelomeningocele defects. Surgeons are investigating more minimally invasive procedures for both mother and child.

Karin Bierbrauer, MD, collaborates with other institutions to further our understanding of complex injuries and diseases, and is the site principal investigator for a national registry of children with Chiari I malformations and syringomyelia. She performs clinical research on spina bifida and neurologic conditions detected *in utero* and in 2014 co-authored a chapter about monitoring for dorsal rhizotomy and ablative spinal procedures in a textbook on intraoperative monitoring.

Sudhakar Vadivelu, DO, focuses on the surgical and endovascular treatment of children with vascular disorders of the brain and spine, complex craniocervical anomalies, and neurostimulation for children with movement disorders.

Focus on Hydrocephalus

Timothy Vogel, DO, heads a developmental neuroscience laboratory that studies primary and motile ciliary signaling related to hydrocephalus, a common neurological condition occurring in 1 in 1,000 children. The lab, along with collaborators Kenneth Campbell, PhD, and Masato Nakafuku, MD, PhD, is studying pathways related to ciliary signaling.

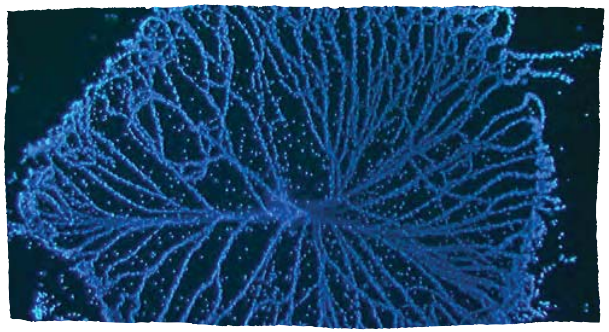
Instructor June Goto, PhD, collaborating in Mangano's lab, facilitates basic and translational research in hydrocephalus, cooperating with Yuan and Campbell to study molecular and cellular basis of hydrocephalus. In the past year, she performed brain surgeries, immunohistochemistry, and CRISPR-mediated gene targeting using rodent models of hydrocephalus.

Studying Neural Circuits

The laboratory of Steven Crone, PhD, studies motor circuits in the brain stem and spinal cord and how they are affected by disease or injury. In the past year he has developed several new mouse models in which specific populations of interneurons in the spinal cord are genetically targeted in order to determine their impact on disease. He has expanded his work on locomotor circuits to include therapies to prevent ventilator dependence in patients with neurodegenerative disease or spinal cord injury.

> Cincinnati Children's is the only pediatric hospital in the U.S. approved to use a virus designed to kill tumor cells in malignant brain tumors.

OPHTHALMOLOGY



Limited light exposure linked to retinopathy of prematurity

The Division of Pediatric Ophthalmology at the Abrahamson Pediatric Eye Institute has been investigating whether light exposure during pregnancy is a risk factor for severe retinopathy of prematurity (ROP), a potentially blinding vascular overgrowth in infants born prematurely. The project, led by Richard Lang, PhD, and Michael Yang, MD, is based on mouse studies of vascular development mechanisms and light response pathways. Yang has recently shown that there may be a critical threshold of light exposure during early gestation above which there is no further decrease in the risk for the subsequent development of severe ROP. This may have implications for the amount of light therapy needed to decrease the risk of severe ROP. Yang is now analyzing patient data in a multi-center database to confi m the results of the previous single center study.

Ocular genetics has an impact

The Eye Genetics Clinic completed its first full year of operations and evaluated patients with a wide array of genetic diseases linked to ocular problems. The clinic is a collaborative effort of Howard Saal, MD, Robert Hufnagel, MD, PhD, from Genetics and Constance West, MD, Virginia Utz, MD, Zubair Ahmed, PhD, and Patricia Cobb, MS, from Ophthalmology. Some novel disease genes will be considered for future reports.

Separately, Hufnagel, Ahmed, and lead author Robert Sisk, MD, a pediatric retina specialist, reported in *Ophthalmology* the case of an infant boy diagnosed with Norrie disease, which is characterized by postnatal retinal detachment and vision loss. When the child's mother became pregnant again, genetic testing showed that the male fetus also had the Norrie mutation. The infant was delivered preterm and treated with laser and anti-angiogenesis agents, which thus far have prevented blindness.

Reducing unnecessary screening for retinopathy of prematurity

Increased risk for ROP is associated with slow rate of weight gain after birth in premature infants, which reflects the infant's level of insulin-like growth factor 1, also important for retinal angiogenesis. Yang is the principal investigator in Cincinnati for the multi-center Growth in Retinopathy of Prematurity (G-ROP) study, which examines whether an infant's weight gain can help predict the severity of ROP. This could help determine which infants can be safely excluded from screening examinations. Cincinnati is one of the largest contributing centers, with more than 1,200 patients in the retrospective portion of the study.

ORTHOPAEDICS

Orthopaedic surgery leads quality, safety, value initiative

Over the past year, Orthopaedic Surgery has played a major role in the Pediatric Orthopaedic Society of North America's (POSNA) Quality, Safety, and Value Initiative (QSVI). This year, the Division of Orthopedic Surgery spearheaded contributions to QVSI, which provides a program for hospitals and practices to share best practices and ideas to improve quality of care, safety, and value. Quality work has been completed that improved utilization in the operating room resulting in millions of dollars of unrealized revenue and nearly 100 additional surgeries being performed using the same resources; creating surgical simulation programs to educate the next generation of surgeons; and completing and publishing a "compartment syndrome alert process" that has nearly eliminated the missed compartment releases.

Research suggests way to prevent contractures

Groundbreaking new basic science research tests the hypothesis that neonatal denervation, as occurs in brachial plexus injury, leads to impaired muscle growth and ultimate contractures. Understanding the molecular cross-talk between nerves and muscles during this critical postnatal development window will lead to novel treatments to preserve muscle growth while awaiting nerve healing. This has direct implications on the treatment of many other disorders, such as cerebral palsy and myelodysplasia. This work is funded by the Goldner Research Pioneer Award from the American Foundation for Surgery of the Hand and the Career Development Grant from the Orthopaedic Research and Education Foundation.

New research using flexible implants to treat early onset scoliosis

Scoliosis that begins at less than 5 years of age (Early Onset Scoliosis, or EOS) is much less common than adolescent idiopathic scoliosis. However, it has life-threatening consequences. Further, EOS is often a significant deformity and is therefore much more difficult to treat. The Crawford Spine Center provides comprehensive treatment options such as magnetically-activated "growing" rods and other guided growth techniques. New pilot research using flexible growing rods recently won an international award as an innovative approach to this devastating disorder.

OTOLARYNGOLOGY

Cotton receives 2014 Jacobson Innovation Award

Robin Cotton, MD, FACS, was awarded the American College of Surgeons (ACS) 2014 Jacobson Innovation Award for his life's work in the care and reconstruction of the pediatric stenotic airway. The prestigious award honors living surgeons who have developed a new technique in any field of surgery. ACS president Carlos Pellegrini said that, "Dr. Cotton embodies the meaning and spirit of this award. Until he developed his innovative approach to reconstruction of the stenotic airway, children were condemned to a lifetime of breathing through a tracheostomy."

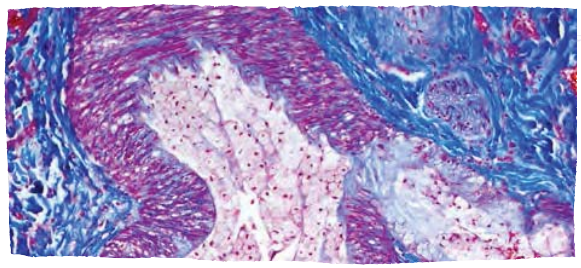
Molecular process behind a form of deafness also may damage other organs

An underlying molecular process that causes a genetic form of non-syndromic deafness also may put affected families at higher risk of damage to the heart, thyroid and salivary glands, according to findings led by scientists at Cincinnati Children's and published in August 2013 in the Journal of Clinical Investigation. The study focused on finding treatments for DFNB49 non-syndromic hearing loss, an inherited condition caused by mutations in the gene TRIC. But the mouse model developed for the research showed that TRIC mutations also can damage cell structures in other organs. "Understanding the function of a deafness-causing mutation and the mechanism of disease progression is an important first step towards finding a therapeutic solution. But our study on mice also suggests we should clinically evaluate affected individuals more thoroughly, as they may have some other and not very obvious clinical problems involving multiple organs," says Saima Riazuddin, PhD, division member and the study's senior investigator.

The deafness – virus link

Division Director Daniel Choo, MD, discussed sensorineural hearing loss caused by cytomegalovirus (CMV) during a panel session at the Annual Meeting of the Triological Society, held in May 2014. To be definiti e, testing for CMV hearing loss should be conducted within the first three eeks after a child is born.

PATHOLOGY AND LABORATORY MEDICINE



Investigating brain tumors

The Pediatric Brain Tumor Consortium is part of a national effort to improve the outcome for the nearly 4,000 new pediatric brain tumor cases diagnosed and managed each year in this country. Maryam Fouladi, MD, MSc, chairs the Consortium, which develops treatment protocols, central pathology review and banking of rare tissue specimens to benefit investigators in their research.

Lili Miles, MD, is responsible for central pathology review of tumor cases for multiple clinical studies in the consortium. Miles directs the tissue banking efforts for these cases from across the U.S.

Cincinnati Children's has also established the Diffuse Intrinsic Pontine Glioma (DIPG) study, led by Mariko DeWire, MD. DeWire has organized a multidisciplinary group to obtain these rare tumor specimens from autopsy and patient families now contribute to the effort to better understand these highly lethal tumors. Fifteen patients have contributed to the study and extensive investigations are underway.

Advances in metabolomics

Our division has made major investments in mass spectrometry to enhance research at Cincinnati Children's. We established a Mass Spectrometry Metabolomics Core facility to provide insight into how metabolic changes account for disease, to search for disease biomarkers, and to evaluate and monitor responses to therapy.

Using a state-of–the-art Waters Xevo G2S Q-TOF (triple quadrupole/time of flight) instrument capable of extremely fast scanning speeds (80,000 ions/sec), we can detect as many as 10,000 metabolites from a drop of urine, blood, plasma, tissue or cell extract. We can compare diseased and non-diseased states, pre- and post-treatment changes, or longitudinal changes that may occur with disease. Consequently, we have found novel metabolic changes of clinical significance Among them are perturbations in lipid metabolism in cell lines, animal models and patients with Fanconi Anemia; the mechanism behind patients with PFIC3 heterozygosity developing liver disease in early life; skin barrier development; modulating macrophage immune function during infections; and lipid metabolism in airway disease.

The Mass Spectrometry Metabolomics Core is complemented by the newly formed Nuclear Magnetic Resonance Metabolomics Core directed by Lindsey Romick-Rosendale, PhD, making a powerful platform for biomarker discovery.

Faculty teaching recognized

The Division of Pathology has a history of contributions to the University of Cincinnati College of Medicine medical student curriculum and educational training programs. In the past year, Keith Stringer, MD, Kathryn Wikenheiser-Brokamp, MD, PhD, and David Witte, MD, have received awards for their teaching contributions.

Anita Gupta, MD, was invited to lecture at the 2014 Indo-Global Healthcare Summit in Hyderabad, India, in recognition of her contributions to the understanding of liver tumors and vascular malformations and tumors in children.

PATIENT SERVICES RESEARCH

Mentoring for successful outcomes

Heather Tubbs Cooley, PhD, RN, is examining the role of missed nursing care as a mediator of the effect of nurse staffing levels on neonatal outcomes through a career development award with mentorship provided by Rita Pickler, PhD, RN, Professor and Scientific Director of Nursing. Tubbs Cooley completed post-doctoral training as a Quality Scholar in the Anderson Center (2013), received the inaugural Research Scholars in Patient Services (PS2) Award to study missed nursing care in neonatal intensive care units, analyzed data from Pickler's existing large data set (resulting in two presentations and two publications), and published several papers related to her emerging program of research. She received the 2014 Brilliant Young Scientist Award from the Council for the Advancement of Nursing Science, a highly prestigious award given to a young scholar who will have a remarkable impact on advancing nursing research and clinical care delivery.

Translational science and collaboration

Nancy Daraiseh, PhD, specializes in occupational safety and health, and the assessment of workload and work environment on health outcomes in healthcare personnel. She collaborates with individuals from the University of Cincinnati's Colleges of Nursing and Allied Health Sciences as well as with Maurizio Macaluso, MD, Division of Epidemiology and Biostatistics, on a study to examine injury under-reporting and near-misses among pediatric nursing personnel, and the impact of individual and organizational factors on these reports.

Additional collaborations include Drew Barzman, MD, Division of Psychiatry, on the use of motion sensors to monitor patients for early signs of aggression and violence; and Kathleen Walsh, MD, MSc, the James M. Anderson Center for Health Systems Excellence, on patient and family injury and error reporting. Daraiseh is working on testing an evaluative tool that determines proper personal protective equipment and behavioral plans in psychiatric units with the goals of reducing staff and patient injury and improving care. She has two funded projects related to these areas of research.

Our efforts in reading and literacy

Initially created as a research program, the Reading & Literacy Discovery Center (RLDC) has initiated a new program for children with reading disabilities. And the RLDC is piloting a new clinical evaluation program that will expand to meet the needs of the Cincinnati metropolitan area.

Longer-term plans include a literacy outreach arm and a treatment program for dyslexia. RLDC and its partners envision a center that will provide full intervention and assessment services for reading disabilities, with a fi m foundation in research. This will provide evidence for the most effective treatments. The RLDC advisory board of leaders from the Cincinnati community meets annually; a website will serve as an informational hub for reading difficulties The Center is transitioning from a reading research center to a clinical reading and literacy center thanks to the gifts of several generous donors.

PEDIATRIC AND ADOLESCENT GYNECOLOGY

New staff expands clinical access

This year we welcomed two new faculty members to expand our practice: Beth Schwartz, MD, and Gylynthia Trotman, MD. Under the leadership of Lesley Breech, MD, Division Director, we further improved access for our patients and families by adding nearly 10 percent more clinic visits at outpatient locations in Northern Kentucky and Green Township. We also increased the number of surgeries performed by more than 20 percent compared to last year.

Chronic care program improves

We continued to improve the diagnosis and treatment of heavy menstrual bleeding through our work in the Chronic Care and Outcomes program. We improved management of sexually transmitted infections with a project initiated by the Rapid Cycle Improvement Collaborative. We also continued to preserve future fertility in children, adolescents and young women treated for malignancies. Our progress in these areas and in other important research initiatives was presented at the 2014 North American Society of Pediatric and Adolescent Gynecology (NASPAG) Annual Clinical and Research Meeting. Notably, the Cincinnati Children's team made more presentations than any other pediatric adolescent gynecology program in North America.

Building the Oncofertility Program

Our division collaborated with the Division of Hematology/Oncology to build the Oncofertility Program at Cincinnati Children's. This program focuses on protecting future fertility for patients being treated with chemotherapy or radiation. We also are enrolling patients in an Ovarian Tissue Cryopreservation project launched in conjunction with the Oncofertility Consortium through Northwestern University.

Educational successes

Our mission to train and educate the next generation of specialists in Pediatric and Adolescent Gynecology continued this year with the graduation of two remarkable clinical fellows: Laura Kruger, MD, and Schwartz, who has joined our faculty.

PERINATAL INSTITUTE

Lung atlas to provide framework for understanding lung disease

Investigators in the Perinatal Institute and the Divisions of Neonatology, Perinatal and Pulmonary Biology, Developmental Biology, and Genetics were awarded a $4 million grant from the National Heart, Lung, and Blood Institute (NHLBI) to establish a consortium of investigators that will produce a detailed map of the cells, structures, and transcriptome comprising the human and murine lung.

Jeffrey Whitsett, MD, Co-Director of the Perinatal Institute, and Steven Potter, PhD, Developmental Biology, serve as co-principal investigators. Co-investigators from multiple divisions will conduct confocal microscopy, NexGen-RNA sequencing of the single cell transcriptome, and bioinformatic analyses to identify the multiple cell types, their interactions, and their changing structures during lung formation. Molecular imaging will be performed by the recently established Nikon Imaging Center, led by Matt Kofron, PhD.

The Cincinnati Children's team will work in a consortium with investigators from several institutions to produce a detailed molecular atlas of the lung during development, with an emphasis on the formation of alveoli, the tiny air sacs responsible for the exchange of oxygen and carbon dioxide. Understanding the normal processes of lung formation will provide the framework needed to understand bronchopulmonary dysplasia, respiratory distress syndrome, interstitial lung disease and other abnormalities in lung formation and growth that can lead to lifelong consequences.

Potential gene correction for Pulmonary Alveolar Proteinosis

Bruce Trapnell, MD, MS, and Takuji Suzuki, MD, PhD, have received an NIH grant to continue studying a gene therapy approach for correcting Pulmonary Alveolar Proteinosis (PAP), a rare lung disease caused by mutations in the GM-CSF receptor. Their recent publications show the ability to correct PAP in mice lacking GM-CSF receptor by transducing the alveolar macrophages with the normal receptor and placing the corrected cells into their lungs. Their work provides the groundwork for moving these remarkable findings into the clinical arena, by generating vectors and methodologies for transducing human bone marrow cells that will be used for future therapies of this life-threatening disorder.

Focusing on infant mortality and preterm birth

Our focus on crucial community health problems affecting our patients and families continues to gain momentum. Our new Familial Preterm Birth Clinic, led by Louis Muglia, MD, PhD, is providing research, innovation, and clinical care for women at risk for preterm delivery. In June 2013, we also established Cradle Cincinnati, a large collaborative that seeks to reduce infant mortality in Hamilton County.

The Perinatal Institute serves as the convening organization for Cradle Cincinnati, which also includes the City of Cincinnati, Hamilton County, the Cincinnati Health Department, the Hamilton County Health District, United Way, the Greater Cincinnati Foundation, Interact for Health, CareSource, Deskey Branding, UCMC, TriHealth, the Christ Hospital, the Mercy Regional Health System, and the Center for Closing the Health Gap. During its first year, Cradle Cincinnati formed a consensus around three key indicators of health relevant to infant mortality: Smoking, Safe Sleep, and Spacing (of pregnancies). We issued our first report to the community in February 2014, formed three community action networks to address these areas, and raised $1.3 million in new annual funding.

The Perinatal Institute also provides leadership for several other community-based applied research and improvement programs. StartStrong-Avondale, funded by the Bethesda Foundation and Cincinnati Children's, seeks to reduce preterm birth and inappropriate emergency department use in the Avondale neighborhood. This program is a joint partnership between Every Child Succeeds, the Anderson Center, and the Perinatal Institute. The Best Babies Zone program, funded in part by the Kellogg Foundation, supports community awareness and action to reduce preterm birth in the Lower Price Hill and East Price Hill neighborhoods through facilitation of moms' groups, a block captain program and community-focused micro grants.

NICU receiving more out-of-region referrals

Overall, Division of Neonatology physicians generated 117,290 encounters, up from 109,490 during the prior year. Our neonatal intensive care unit (NICU) also experienced its highest average daily census to date in FY14. The primary driver was a significant increase in out-of-region referrals for management of complex medical and surgical problems, including those managed by the Cincinnati Fetal Center.

The second phase of our NICU renovation was completed, which will optimize patient safety by providing state-of-the-art private rooms with superior visibility and access. Renovation continues through this year. The NICU team also significantly reduced the number of central line-associated blood stream infections in FY14 compared to the year before.

A $4M project will use single-cell 'NextGen' RNA sequencing to create the world's most detailed atlas of the developing lung.

PHYSICAL MEDICINE AND REHABILITATION

New funding for brain injury clinical trials

Our division received funding for three clinical trials in FY14. Shari Wade, PhD, received funding from the Patient-Centered Outcomes Research Institute (PCORI) to examine the comparative effectiveness of three family problem-solving therapies in reducing behavior problems and improving quality of life following adolescent brain injury. Brad Kurowski, MD, was awarded a K23 grant from NICHD to examine the efficacy of various dose levels of methylphenidate for attention problems following traumatic brain injury (TBI). Kurowski also obtained a grant from the Ohio Department of Public Safety and a Cincinnati Children's Trustee Award to study the efficac of an aerobic exercise intervention for persistent post-concussive symptoms. These interventions will expand the limited evidence base for treating both mild and severe TBI.

The Cerebral Palsy Clinic

The Cerebral Palsy Clinic led by Jilda Vargus-Adams, MD, MSc, is a team-based, multi-disciplinary clinic at the heart of our Cerebral Palsy Program. Our clinic provides individualized care plans and treatment for conditions ranging from surveillance for hip displacement to bone health. We have served more than 600 patients and families since 2011, and our clinic had a 34 percent increase in new visit team evaluations over the previous year.

The clinic team includes pediatric physiatrists, occupational and physical therapists, care coordinators, dietitians, nurses and staff from the Perlman Center and Divisions of OT/PT and Pediatric Rehabilitation. Clinics operate in an arena-style setting providing comprehensive, family-centered and coordinated care. We collaborate closely with James McCarthy, MD, in the Division of Orthopaedics in a monthly combined clinic for CP and with Charles Stevenson, MD, in the Division of Neurosurgery.

Our research initiatives include validation studies of PROMIS in CP (Patient Reported Outcome Measurement Information System) and therapy-based intervention with robotic gait training and functional electrical stimulation. Moreover, pilot work is ongoing to explore magnetoencephalography as an outcome measure in CP, and outcomes of combined transcranial magnetic stimulation and constraint induced movement therapy.

National honors and presentations

Kurowski was awarded the Association of Academic Physiatrists (AAP) Young Academician Award. At the same meeting, he and his student, Barynia Backeljauw, were recognized by the AAP with Best Paper Awards in faculty and student categories.

Kurowski and Wade together with collaborators in Emergency Medicine, Lynn Babcock, MD, Judith Dexheimer, PhD, and Nicole McClanahan, BA, presented "A 'SMART' Approach to Managing Concussion: Development and Pilot Trial of a Web-Based, Self-Monitoring Activity-Restriction and Relaxation Training (SMART) Program for Kids with Mild Traumatic Brain Injury" at the International Society for Research on Internet Interventions (ISRII) annual conference, May 2013 in Chicago.

Vargus-Adams presented "Tweet this! Social Media for the Medical Professional" and "Review of Neuropharmacology in Pediatric Brain Injury," at the Annual Assembly of the American Academy for Cerebral Palsy and Developmental Medicine, Milwaukee, October 2013.

Wade presented "Children from Disadvantaged Families Are More Likely to Benefit from Family-Centered Treatment for TBI" at the Tenth World Congress on Brain Injury, March 2014, San Francisco.

Wade also presented on "Individual, Social-Environmental, and Treatment-Related Influences on Long-Term Functional Outcomes of Early Childhood TBI: Implications for Intervention" at the International Neuropsychological Society Conference, 2014, Seattle.

PLASTIC SURGERY

The genetics of craniofacial development

Samantha Brugmann, PhD, was awarded a grant from the National Institute of Dental and Craniofacial Research for her work on the role primary cilia play in a mouse model of craniofacial development. With Rolf Stottmann, PhD, Human Genetics, Brugmann uses next-generation sequencing technology to identify genetic variants in three families being cared for at Cincinnati Children's. The research could significantly influence their care and lead to crucial discoveries in developmental biology.

Producing neurons and glial cells from iPSCs

Brugmann and James Wells, PhD, Developmental Biology, use pluripotent stem cells to generate neural crest cells that can differentiate into enteric neurons and glial cells. Their goal is to integrate a generated enteric nervous system into a human intestinal organoid and make it capable of intestinal contraction.

To understand the cellular mechanisms of palate development, Yu Lan, PhD, has established a mouse model for cleft palate research using ENU mutagenesis and exome sequencing approaches. Lan was awarded a grant from the National Institute of Dental and Craniofacial Research for her work with the role of Golgi function in cleft palate syndrome.

Lan and Rulang Jiang, PhD, Developmental Biology, explore molecular mechanisms involving odd-skipped family transcription factors in patterning mammalian dentition and tongue. They collaborate with Jing Hu, DDS, PhD, at Sichuan University in China, on the critical role of Smad7 in regulating cranial suture development.

Working with mouse mandibles, Donna Jones, PhD, has shown that muscle forces affect bone shape by altering bone deposition and resorption, particularly during early growth. She presented findings in September 2014 at the national meeting of the American Society for Bone and Mineral Research.

Research to improve reconstruction

Christopher Gordon, MD, Alessandro DeAlarcon, MD, and Michael Rutter, MD, have produced a tissue-engineered neotrachea. The grafts appear fully mucosalized with ciliated respiratory epithelium, crucial to translating this technology to a human model. Gordon also is pursuing tissue-engineered mandible reconstruction as an alternative to microsurgical reconstruction.

Using shape analysis from 3D photographs, Jones characterizes growth curves of craniofacial shape in children. Analyzing ear position and symmetry demonstrates that ear placement alters through growth, and developmental constraint of the ears is less than that of the midface, providing important guidelines for surgical planning.

Ann Schwentker, MD, Brian Pan, MD, and Bruce Aronow, PhD, are investigating the impact of autologous and cultured adipocyte injections in a porcine model of hypertrophic burn scarring.

Skin Sciences Program

Marty Visscher, MD, studies premature infants who lack *vernix caseosa* and are predisposed to infection. She studies the ontogeny of *stratum corneum* barrier in premature infants, measuring barrier integrity, hydration, pH, and collecting skin surface samples to determine lipid composition, structural proteins and specific c tokines.

Visscher collaborates with researchers from Johns Hopkins University to study the effect of topical oils on neonatal skin integrity. Using high-resolution color imaging, thermal imaging and three-dimensional surface scans, she characterizes the disease and healing processes of skin conditions, including hemangiomas, pressure ulcers, contact dermatitis and burn scars.

> Tissue engineering advances developed here are changing the outcome for children who need trachea and jaw reconstruction.

PSYCHIATRY

Lessening the impact of post-traumatic stress

Rich Gilman, PhD, is Director of Clinical Care and Training at the newly established University of Cincinnati (UC) Health Stress Center Program. The center brings together clinicians from UC Health, Cincinnati Children's and the Cincinnati Veterans Administration Medical Center. They care for families living with post-traumatic stress disorder (PTSD), with the goal of alleviating the impact of PTSD and resuming a healthy life. Established in part by seed money from the Joey Votto Foundation, several clinical trials are underway, including projects funded by the Eunice Kennedy Shriver National Institute of Child Health and Human Development.

Lowering the risk of self-injury

Children and adolescents struggling with acute psychiatric disorders frequently pose a serious risk to themselves from self-injury or suicide attempts. Inpatient psychiatric units are high-risk sites for such behaviors. Division-wide efforts to improve safe management of these patients, led by Michael Sorter, MD, Dan Vogel, MD, and Adam Hill, MSN, RN-BC, have decreased significant self-injury events from near-monthly to no occurrences in more than 700 days and more than 5,000 inpatient admissions. Through performance improvement methodology, they developed better assessment and risk prediction tools to improve care and achieve safe outcomes for patients.

OCD research recognized

Obsessive Compulsive Disorder (OCD) is a neuropsychiatric condition that affects two percent of children worldwide. First-line treatment with cognitive behavior therapy plus medication only leads to remission in half of the children treated. Elana Harris, MD, PhD, has initiated a research program to look for a neurophysiological marker that will predict treatment response in children with OCD, thereby eliminating the need for a trial-and-error approach in the choice of treatment and tailor the treatment to what is best suited for each individual. In recognition of her efforts, the National Institute of Mental Health awarded Harris a Mentored Patient-Oriented Research Career Development Award (K23) that protects her time so that she can hone her skills in magnetoencephalography.

PULMONARY MEDICINE

High national ranking continues

For the fourth year in a row, our division was ranked the No. 2 pediatric pulmonary program in the nation by *U.S. News & World Report.*

New ways to treat complex and difficul asthma

This year we developed The Asthma Complex Care Center (ACCC) for children with complex and difficul to treat asthma. Specialists including otolaryngologists (ENT), pulmonologists, allergists, gastroenterologists, bronchoscopists, nutritionists, and sleep and adherence specialists collaborate in a single location to care for each child. They meet weekly to review each child's case and care plan. The ACCC focuses on children with asthma who are prone to sleep difficult , eczema, gastroesophageal reflux eosinophilic esophagitis, allergies and food allergies.

The program allows children to spend up to eight hours in a patient unit as outpatients in order to complete treatment that would otherwise take several trips to the hospital to accomplish. For those who require multiple days of treatment, the ACCC allows families to return home or stay at the nearby Ronald McDonald House if they live out-of-town.

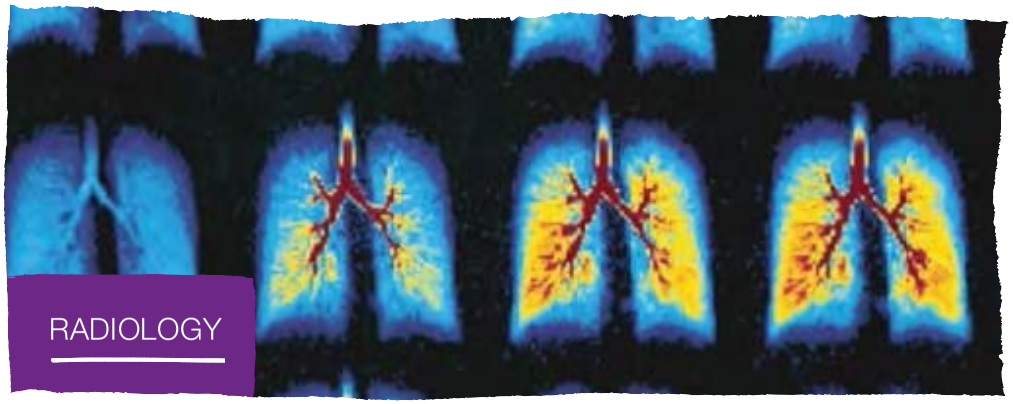
New lung transplant program

Our new Lung Transplant program began in January 2014. We have had 23 referrals or inquiries into the program and completed several evaluations. So far, planning has focused on processes, patient flow, space needs, key personnel, education, and establishing collaborative relationships throughout the hospital.

Quality metrics and data collection processes are in place; research efforts are underway to collect and store tissue and fluid to advance research in pediatric lung disease. In the coming year, the Lung Transplant program will continue to build collaborations among the Division of Pulmonary Medicine, the Heart Institute, and other disciplines within the hospital. We will continue to evaluate patients for transplant, attain proof of concept for storage of tissue, and refine processes

A collaborative chronic care network (C3N) for Cystic Fibrosis

Leaders and faculty from Pulmonary Medicine and the Anderson Center collaborated with the Cystic Fibrosis (CF) Foundation and the Dartmouth Institute to develop a Collaborative Chronic Care Network (C3N) for CF. A C3N is a peer-produced Learning Health System in which patients, families, providers, and researchers collaborate to learn, conduct research, and implement the findings We envision this will become the CF care model of the future: ensuring that patients get the right treatment at the right time, every time. The design of the network began in July 2014 and will continue for one year; the team will then conduct a pilot within the CF Foundation's Learning and Leadership Collaborative at select CF Care Centers. The CF Foundation will award Pulmonary Medicine $776,373 for this project.



RADIOLOGY

Leadership in patient safety

The Department of Radiology continues to lead efforts in quality improvement and operational excellence. Our "Right Patient, Right Exam" initiative prevented more than 490 patient care errors in 2014, achieving 5-sigma process reliability.

In radiography and fluorosco y, doses have been reduced as much as 75 percent from standard practices. Our interventional radiology team, physicists, and industry partners have created techniques that reduce radiation exposure up to 95 percent during complex and lengthy interventional radiology cases, while obtaining high-quality images.

Patients with scoliosis often need repeat whole spine radiographs. We have recently installed a specialized digital slot scanning system that allows image acquisition with up to a 90 percent reduction in radiation exposure for these patients.

Expanding capabilities in imaging technology

This year, with the Imaging Research Center (IRC), we invested in infrastructure and capabilities to ensure that researchers throughout the medical center have access to the latest technologies.

We installed a 1.5 Tesla MR system used by the interventional laboratory for research into multi-modality interventions. The system's Sonalleve™ high-intensity focused ultrasound (HIFU) system is the only one in a preclinical research facility in the country. Our 7 Tesla MR imaging system was upgraded to enable faster scanning with new imaging capabilities.

On the clinical side, we added a new 3T system in Radiology and a new 1.5T system for cardiac imaging in the Heart Institute. Both systems allow state-of-the-art clinical research and advances in imaging evaluation for our patients.

Expanding our Imaging Research Center (IRC)

We expanded the breadth and depth of research by installing a 1.5T Philips MRI and hyperpolarizers for 3He and 129Xe MR imaging, and upgrading our 7T system. The IRC won a "Taking on Tomorrow Award" from Boston Children's Hospital for our NICU MRI, to continue our work in making this modality accessible to our most fragile patients.

Our NICU MRI capabilities, our hyperpolarized gas capabilities, and the collaborative relationships between Radiology, Pulmonology, the Perinatal Institute, and Developmental Biology resulted in an abstract entitled "Pulmonary MRI in Neonatal Medicine." The project was recognized as one of the most significant abstracts at an international radiology meeting this year.

Zackary Cleveland, PhD, joined the faculty in Radiology and Pulmonary Medicine as an assistant professor; his knowledge of hyperpolarized gas imaging adds significant expertise to our growing pulmonary MR imaging program.

Pediatric Neuroimaging Research Consortium (PNRC)

C-MIND (Cincinnati MR Imaging of NeuroDevelopment) is an NICHD-sponsored project, led by the PNRC, to provide a database of brain structural, functional, and perfusion MRI. The database includes structural and functional neuroimaging data and neurocognitive assessments for nearly 200 healthy, normally developing children from infancy to 18 years. The database was recently released for public use, and is available for download at *https://research.cchmc.org/c-mind/*.

REPRODUCTIVE SCIENCES

Awards to our graduate students

Jeeyeon Cha, PhD, who works in the laboratory of S.K. Dey, PhD, received a Scholar Award from the Philanthropic Educational Organization in May 2014, a one-time competitive national-level award that celebrates the advancement of women in research. The award comes with partial monetary support for her research; Cha is pursuing an MD within the MD/PhD MSTP program at the University of Cincinnati (UC). She is currently supported by an National Institutes of Health/National Institute of Aging F30 Research Fellowship Award titled, "Premature Uterine Aging and Preterm Delivery," which was also renewed for the fourth year. Thus far, she has published four papers related to work on this grant.

Success of junior faculty

Tony DeFalco, PhD, has obtained funding from a competitive March of Dimes Basil O'Conner Starter Scholar Award ($150,000 over two years) titled, "Macrophage regulation of fetal testis vascularization and morphogenesis." DeFalco also received a CancerFree KIDS Research Grant of $22,000 for one year titled, "The role of macrophages in the testicular cancer microenvironment."

Our student research achievements

Megan Shroder, a student in the laboratory of Satoshi Namekawa, PhD, was accepted to the UC College of Medicine Research, Observation, Service, and Education (ROSE) program. The program involves early acceptance, internship, and mentoring. As a member of the Namekawa lab, Shroder worked to elucidate the mechanisms underlying epigenetic regulation of meiotic sex chromosomes. She found that the mixed lineage of the leukemia gene Mll1 — also known as a histone methyltransferase that mediates H3K4me2—is involved in sex chromosome regulation. Furthermore, she provided evidence that Mll1 is established on meiotic sex chromosomes.

Kris Alavattam, a student and research assistant II in the Namekawa lab since May 2012, was accepted into the UC College of Medicine Graduate Program in Cancer and Cell Biology. His work examining the genetic function of the breast cancer susceptibility gene, BRCA1, during meiosis was reported in his co-first authored paper, published in the *Journal of Cell Biology* in June 2014.

RHEUMATOLOGY

Clinical trials lead to a new medication for Juvenile Idiopathic Arthritis (JIA)

Daniel Lovell, MD, MPH, and Division Director Hermine Brunner, MD, MSc, lead the Pediatric Rheumatology Collaborative Study Group (PRCSG), a large research network that coordinates international clinical trials. A recent PRCSG study resulted in the regulatory approval of the interleukin-6 inhibitor, tocilizumab, for the treatment of moderately to severely active JIA by the U.S. Food and Drug Administration as well as the European Medicines Agency. The successful completion of this trial and subsequent regulatory approval markedly increases the types of medications available to achieve inactive disease status and lessens the likelihood of longstanding disability from JIA.

Progress in detecting mechanisms leading to juvenile arthritis and its complications

Alexei Grom, MD, in collaboration with the Novartis Institutes for Biomedical Research based in Switzerland, and Center for Autoimmune Genomics and Etiology (CAGE) performed whole-exome sequencing of patients with systemic juvenile arthritis (SJIA). These patients often develop macrophage activation syndrome (MAS), a severe complication of SJIA. *De novo* mutations were identified that support the hypothesis that SJIA/MAS is due to alterations in genes affecting cellular assembly, morphology and function as well as cellular stress.

In collaboration with Experimental Hematology, Sherry Thornton, PhD, utilized animal models of arthritis to assess the role hemostatic factors play in the pathogenesis of arthritis. These studies identified plasminogen (and its interaction with other hemostatic factors) as a part of a mechanism explaining why joint inflammation is restricted to only some but not all joints of a patient with arthritis. This research also suggests that interventions at the level of hemostatic factors can be novel drug targets of inflammato y arthritic diseases.

Advances in the diagnosis of neuropsychiatric lupus

Our Lupus Research Team co-developed and validated Pediatric Automated Neurocognitive Assessment Metrics, a PC-based software program, to serve as a screening tool for neuropsychiatric involvement in children with lupus. This research is complementary to Brunner's innovative MRI-based imaging studies performed together with the Pediatric Neuroimaging Research Center. The investigators demonstrated gray and white matter degenerative changes in children with lupus. Such neurodegeneration is especially pronounced among children with overt cognitive impairment but is also present, albeit to a lesser degree, in children with systemic lupus erythematosus who have normal cognitive function based on clinical assessment.

A national research network coordinated by Cincinnati Children's conducted the clinical trials that led to approval of tocilizumab, the first n w treatment in years for moderate to severe JIA.

SPORTS MEDICINE

Concussion research earns award

Catherine Quatman-Yates, PT, DPT, PhD, received the American Physical Therapy Association Sports Section Excellence in 2014 Research Award for her study of "A Postural Sway Complexity Protocol for Detection of Post-Concussion Deficits in Youth."

Paul Gubanich, MD, MPH, joined the division in December 2013 as an associate professor. Gubanich practices at our Liberty Campus, where he focuses on concussion management and musculoskeletal injuries in athletes. He has served as medical provider for sports teams including the Cleveland Browns, Cleveland Indians and the Ohio State University. Gubanich also has taken over the role of Fellowship Director and welcomed two new fellows: James Hahn, MD and Gregg Kottyan, MD.

Outreach program debuts

We completed the first full year of our Sports Medicine Outreach Program, which provides athletic training coverage and services to local high schools, clubs, organizations and tournaments. In the past year, we worked with seven high school programs and provided training and injury prevention services to the Warren County Soccer Club, Thunder United Futbol Club, Kolping Soccer Club, the Cincinnati Gymnastics Academy, and other organizations.

UROLOGY

Top-ranked clinical services

Our division was ranked fourth in the nation among all pediatric urology programs ranked by *U.S. News and World Report*. Our national reputation is linked to institutional and divisional strategic goals for clinical expansion. The Center for Disorders of Sex Development (DSD) provides specialized care for children with congenital chromosomal, gonadal or anatomical variations of sex development. We also are part of the NIH-funded Translational Research Network (TRN) with six other hospitals who offer DSD services.

Our Urogenital Center cares for children with highly complex genitourinary conditions involving abnormalities of the bladder, urethra, vagina, and anorectum. The Stone Center began clinical operations this year. The Stone Center offers comprehensive, cost effective, and coordinated care management of patients with stone disease of the urinary system. We are also working with the Cancer and Blood Diseases Institute and Gynecology to support oncofertility efforts for male oncology patients. We continued outcomes improvement work, sustaining renal function for all patients with posterior urethral valve. We kicked off a Rapid Cycle Improvement Collaborative (RCIC) team with the Division of Nephrology, aimed at providing nephrotoxic drug education to parents of children with chronic kidney disease (CKD). These important patient safety efforts will expand in FY 2015.

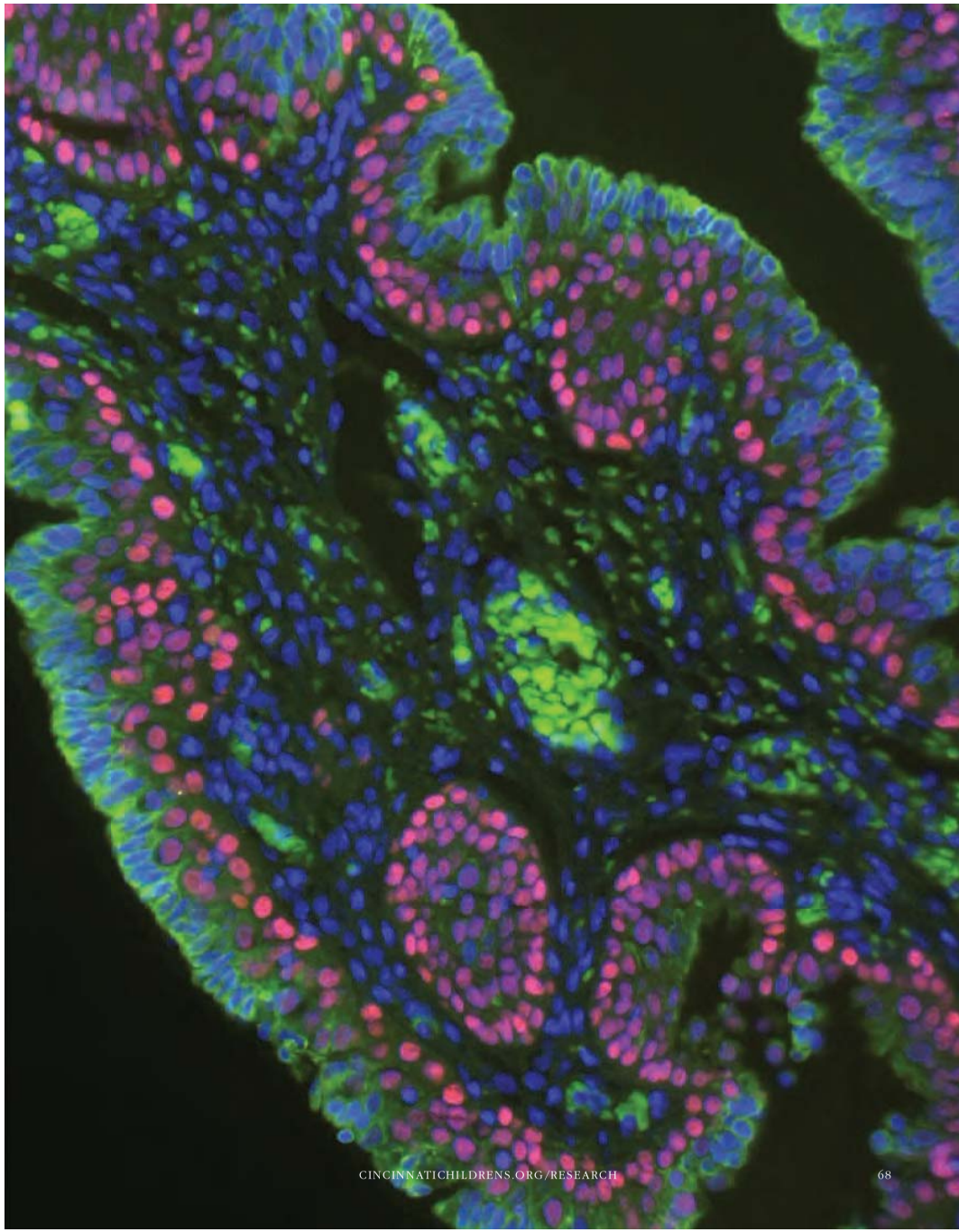
Surgeons share expertise overseas

Partnering with Global Health, Pramod Reddy, MD, traveled to India and Eugene Minevich, MD, traveled to Israel to perform complex urological surgeries. Several faculty members also were invited to present at international pediatric urological conferences: W. Robert DeFoor, Jr., MD, MPH, in Germany; Minevich in Germany, Dubai, and India; Paul Noh, MD, in Germany; Reddy in Germany and India; and Brian VanderBrink, MD, in Germany.

Leadership and recognition

Joo-Seop Park, PhD, received an NIH grant for his study on cell fate regulation of nephron progenitors. The goal of this study is to determine the roles of Six2 and Hox proteins in Notch 2-mediated transcriptional activation in nephrogenesis. The leaders of the North Central Section of the American Leadership Association (AUA) selected DeFoor to participate in the 2014-2015 AUA Leadership Program. The program selects urologists who have demonstrated effective leadership skills within organized medicine or the community. Minevich served as the co-chair of the pediatric urology portion of the Friends of Israel Urological Symposium in Israel. Minevich also served as the chairperson of the "Fall Congress," the annual meeting of the Society of Pediatric Urology, in Las Vegas.

> Our Center for Disorders of Sex Development provides specialized care for children with variations of sex development.

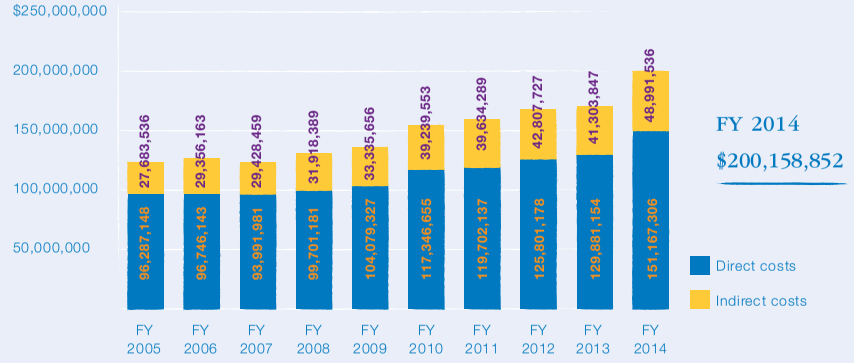


BY THE NUMBERS

Fiscal Year 2014

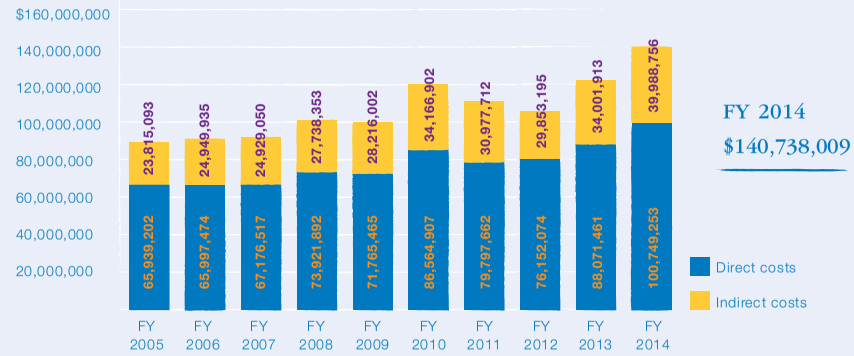
AWARDS AND FUNDING

Sponsored program awards
total costs (prime and sub-awards)



FY 2014
$200,158,852

National Institutes of Health awards
(direct and indirect costs)



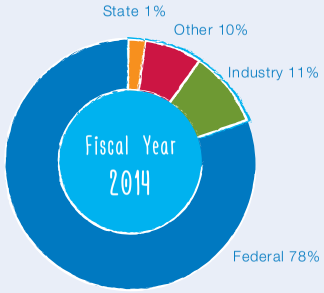
FY 2014
$140,738,009

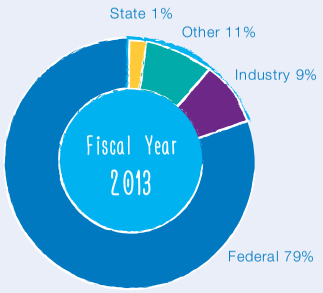
Approximately $6.8 million of American Recovery and Reinvestment Act (ARRA) awards received in FY10 were awarded for a two-year period. All are shown in FY10.

Approximately $13.7 million of ARRA awards received in FY11 were awarded for a three-year period. All are shown in FY11.

EXTERNAL FUNDING

Sources of external funding





Sources of federal funding 2014

National Institutes of Health (NIH)	$140,738,009
Department of Health and Human Services (DHHS)	3,349,528
Health Resources & Services Administration (HRSA)	2,798,755
Centers for Disease Control (CDC)	2,145,034
Department of Defense Army (DOD)	1,981,125
Agency for Healthcare Research and Quality (AHRQ)	1,663,587
U.S. Department of Education	999,623
Center for Medicare/Medicaid Services	844,761
Food & Drug Administration (FDA)	415,018
National Aeronautics and Space Administration (NASA)	318,325
U.S. Department of Agriculture	226,954
National Science Foundation (NSF)	179,159
Department of Labor	126,576
Department of Veteran Affairs	113,440
Department of Justice	56,087
Total	**155,955,981**

State and other foundation/agency awards 2014

March of Dimes	$4,001,581
Ohio Department of Health	1,663,315
Patient-Centered Outcome Research Institute	1,290,050
American Heart Association	1,045,999
The Leukemia & Lymphoma Society	710,000
Miscellaneous other (119)	13,717,165
Total	**22,428,110**

OUR FACULTY

Pediatrics: 741
651 full time, 90 part time

Surgery: 104
104 full time

Anesthesiology: 56
42 full time, 14 part time

Radiology: 49
42 full time, 7 part time

Patient Services: 3
3 full time

RESEARCH & PUBLICATIONS

Peer-reviewed articles:	1,783
Non-peer-reviewed articles:	81
Books (edited or authored):	9
Chapters of books:	129
Online site contributions:	15
Total	**2017**

TRAINING

Students

Junior medical students in the pediatric clerkship	167
Senior medical students entered pediatric training	14
Senior medical students entered medicine/pediatric training	3
Pediatrics/Neurology	1
Total	**185**

Residents

Pediatrics	118
Medicine/Pediatrics	27
Pediatric Physical Medicine and Rehabilitation (PM&R)	6
Dental	10
Psychology	6
Psychiatry/Child Psychiatry/Pediatrics	13
Human Genetics/Pediatrics	6
Neuro/Pediatrics	20
Dermatology	6 rotating
Anesthesia	12
Surgery*	137
Radiology	34 rotating
Total	**395**

** (includes General Surgery, Pediatric Adolescent Gynecology, Cardiothoracic, Neurosurgery, Otolaryngology, Ophthalmology, Plastic, Orthopedic & Urology)*

Pediatric house staff recruitment

Pediatric candidates interviewed	290
Medicine/Pediatric candidates interviewed	70
PM&R candidates interviewed	6
Psychiatry/Child Psychiatry/ Pediatrics interviewed	20
Human Genetics/Pediatrics interviewed	6
Neuro/Pediatrics interviewed	32
Total	**424**

SUMMER RESEARCH PROGRAMS

High school interns	24
Undergraduate students	148
Medical students	21

FELLOWS

Adolescent Medicine	3
-Transition Medicine	0
Allergy/Immunology	5
Anesthesia	12
-ABA Alternate PathwayHG	1
-Advanced Fellowship in Quality Improvement & Safety	1
-Advanced Pediatric Anesthesia Fellowship in Education	1
-Intraoperative Neurophysiological Monitoring	1
-Pediatric & Congenital Cardiac Anesthesia	1
Cardiology	12
-Adult & Adolescent Congenital Heart Disease	1
-Cardiac Electrophysiology	1
-Cardiac Imaging	1
-Cardiac Intensive Care	2
-Fetal Cardiology	1
-Heart Failure, Cardiomyopathy & Transplant	3
-Interventional Cardiac Cath	1
Child Abuse	2
Congenital Cardiac Surgery	1
Critical Care	14
Developmental Behavioral Pediatrics	4
Emergency Medicine	12
Endocrinology	10
Gastroenterology	12
-Pediatric Transplant Hepatology	1
Division of General Pediatrics	
-Pediatric Master Educator	3
-Pediatric Primary Care Research	5
Hematology/Oncology	13
-Bone Marrow Transplant	2
-Clinical Immunodeficiency	1
-Neuro-Oncology	1
-Sickle Cell Disease	1
Hospice & Palliative Care	1
Hospital Medicine	6
Infectious Disease	4
Medical Genetics	0
-Clinical Biochemical Genetics	0
-Clinical Cytogenetics	1
-Clinical Molecular Genetics	2
Neonatology	13
Nephrology	5
-Acute Care Nephrology & Dialysis	1
Neurology	
-Clinical Neurophysiology	1
-Clinical Neurosciences	1
-Pediatric Epilepsy	1
-Pediatric Neuromuscular	1
Neurosurgery	1
Ophthalmology	1
Orthopaedics	2
-Hand & Upper Extremity Surgery	1
-Surgery of the Spine	1
Otolaryngology	6
Pain Medicine	1
Pathology	2
Plastic Surgery	1
Psychiatry	6
Psychology	12
Pulmonary	6
Radiology	8
-Body MRI	0
-Interventional Radiology	2
-Pediatric Neuroradiology	2
Rehabilitation Medicine	2
Rheumatology	5
Sleep Disorder Medicine	2
Sports Medicine	2
Surgery	2
-Pediatric & Adolescent Gynecology	3
-Colorectal Surgery	2
-ECMO	0
-Fetal Surgery	1
-Pediatric International Surgical Fellow	1
-Trauma Surgery	1
-Vascular Anomalies	0
Urology	2
-International Pediatric Urology Fellow	2
Total, clinical fellows	**243**
Total, research postdoctoral fellows	**183**

PROCTER SCHOLARS

This program supports the development of highly skilled faculty members from the Departments of Pediatrics, Surgery, Radiology, and Anesthesia with strong interest in pursuing academic research careers.

3rd Year

Stephanie Merhar, MD
Neonatology

Safety, tolerability and efficacy of Levetiracetam as initial monotherapy for the treatment of neonatal seizures

Elizabeth Schlaudecker, MD
Infectious Diseases (6 mos. funding)

Influenza infection and immunization in pregnancy

2nd Year

Jonathan Howell, MD, PhD
Endocrinology (6 mos. funding)

Investigating the regulatory pathways that control endocrine cell function within the pancreas and intestine

Benjamin Mizukawa, MD
Oncology

Targeting Cdc42 in leukemia stem cells

Amy Shah, MD, MS
Endocrinology

Exploring HDL's *in vitro* functions in youth with type 2 diabetes

Andrew Beck, MD, MPH
General and Community Pediatrics

Bringing neighborhood phenotypes and geomarkers to the bedside for children with asthma

Brian Varisco, MD
Critical Care Medicine

Chymotrypsin-like Elastase-1 regulates pulmonary vascular morphogenesis

1st Year

Jennifer Davis, DO
Oncology

ETV2 role in embryonic and tumor induced lymphangiogenesis

Andrew Lindsley, MD, PhD
Allergy and Immunology

ORMDL3-driven airway inflammation triggers pediatric asthma

Jeffrey Tenney, MD, PhD
Neurology

Seizure generator location and neurocognitive deficits in CAE

Patrick McGann, MD
Hematology (6 mos. funding)

A phase I/II study of hydroxyurea for children with sickle cell anemia in Angola

PHILANTHROPY

As a nonprofit hospital and research center, Cincinnati Children's relies on the support of generous friends and partners like you, to improve the health of children in our community and beyond. Together, we advance scientific discovery, improve care and help children in our community – and beyond – reach their optimal health.

When you give to Cincinnati Children's, you are investing in the future of child health. You are investing in the future of children.

We are profoundly grateful to those who have chosen to partner with Cincinnati Children's. You have a tremendous impact on our work.

Together, we save lives and advance discovery. Together, we provide hope. Together, we *Change the Outcome.*

Of $56 million in gifts
to Cincinnati Children's in the past year,

$28 million - Patient Care and Support
$13 million - Research
$11 million - Areas of Greatest Need
$4 million - Community Outreach and Prevention

Gifts of every size make a difference.

Please visit www.cincinnatichildrens.org/campaign to view our Honor Roll of generous donors.