2018 ANNUAL REPORT

THE ROBERTS INDIVIDUALIZED MEDICAL GENETICS CENTER

Children's Hospital of Philadelphia®

Cover: Sadie, 13, found the cause of her leg pain at the Roberts IMGC.

At right: Grady, 6, and his family are still searching for a genetic cause for his symptoms.

RIMGC MISSION

To facilitate access to state-of-the-art individualized genetic testing and management for children, families and clinicians and to promote integration of phenotypic and genomic information into the diagnostic and research efforts at CHOP.

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LETTER FROM THE DIRECTORS

It has been another whirlwind year for the Roberts Individualized Medical Genetics Center (RIMGC), as we increased the number of patient visits and served new populations, initiated new research projects and expanded boundaries. As the Directors of this unique and evolving Center, we are humbled by the dramatic advances happening in genomics and amazed as our talented team of physicians, genetic counselors, research coordinators, bioinformaticians, laboratory technicians and administrators nimbly adapt and incorporate these advances into research breakthroughs and improved care for our patients and their families. As evidenced by the descriptions of the RIMGC's new clinical and programmatic initiatives, research advances and family stories in this report, it has been a year of innovative delivery of care to an ever-growing, diverse patient population.

Now with more than 3,500 patient visits, the RIMGC has become an established resource for clinicians across all divisions and programs at CHOP and a destination for patients and families from the region, the nation and around the world. As a result, our team continues to expand, and in the last year we welcomed several new genetic counselors: Christopher Gray, MS, LCGC; Tiffiney Hartman, MS, CGC, PhD; and Ellen Xu, MS, CGC.

This past year has seen remarkable clinical growth and expansion of our programs in genomics of hearing loss, differences of sexual development, genetics of retinal disorders and immune deficiencies. The RIMGC has spearheaded collaborative studies in evaluating novel technologies, such as rapid genome sequencing in vulnerable critically ill newborn populations, and has been involved in cutting-edge therapeutics such as gene therapy for a genetic form of blindness. The RIMGC has hosted internationally recognized leaders in pediatric genomics as invited speakers at CHOP and led numerous educational initiatives as well as hosting rare disease family meetings and awareness events.

This report provides a glimpse into some of our team's activities with highlights ranging from broad conceptual projects to individual personal stories — all anchored by our mission to facilitate access to state-of-the-art individualized genetic testing and management for children, families and clinicians and to promote integration of clinical and genomic information into the diagnostic and research efforts at Children's Hospital of Philadelphia.

Ian Krantz, MD
Co-director

Līvija Medne, MS, LCGC
Co-director

OUR TEAM

Ian Krantz, MD
Co-director
Attending physician, scientist

Līvija Medne, MS, LCGC
Co-director
Genetic counselor

Priyanka Adusumalli, MBA
Business administrator

Emma Bedoukian, MS, LCGC
Genetic counselor

Donna Berrodin, BS
Research database developer and manager

Sawona Biswas, MS, LCGC
Genetic counselor

Brandon Calderon, MBA
Administrative director

Matthew Deardorff, MD, PhD
Attending physician, scientist

Batsal Devkota, PhD
Bioinformatics scientist

Sierra Fortunato, BS
Clinical and research coordinator

Christopher Gray, MS, LCGC
Genetic counselor

Ann Tokay Harrington, PT, DPT, PhD, PCS*
Physical therapist

Tiffiney Hartman, MS, CGC, PhD
Genetic counselor

Kosuke Izumi, MD, PhD
Attending physician, scientist

Maninder Kaur, MS
Research laboratory manager

Jacqueline Leonard, MSc, MS, LCGC
Genetic counselor

Kathleen M. Loomes, MD*
Attending physician, Gastroenterology

Deborah McEldrew, BS
Research associate

Jasmine Montgomery
Office administrator

Mary Pipan, MD*
Attending physician
Developmental & Behavioral Pediatrics

Louisa Pyle, MD, PhD
Attending physician, scientist

Sarah Raible, MS, LCGC
Genetic counselor

Cara Skraban, MD
Attending physician

Jamila Weatherly, MS
Clinical research assistant

Tyrah Williams
Office coordinator

Ellen Xu, MS, CGC
Genetic counselor

**Member of the Center for Cornelia de Lange Syndrome and Related Diagnoses clinic team*

First row, from left: *Līvija Medne, Ian Krantz, Emma Bedoukian, Louisa Pyle and Kosuke Izumi.* Second row: *Christopher Gray, Cara Skraban, Jasmine Montgomery and Jacqueline Leonard.* Third row: *Ellen Xu, Tyrah Williams and Tiffiney Hartman.* Top row: *Jamila Weatherly, Batsal Devkota and Sierra Fortunato.*

MAKING FAMILIES FEEL WELCOME

Jasmine Montgomery and Tyrah Williams are the clinical and office coordinators for the RIMGC, overseeing all administrative and patient care operations for the Center. Jasmine and Tyrah are the primary contact for families, serving as resources before, during and after visits. They help families navigate insurance barriers, collect pertinent medical information, coordinate appointments and manage all of the Center's administrative duties. Their dedication is clearly evident as they are committed to ensure each and every family has the best experience possible. Jasmine and Tyrah are essential to the Center's day-to-day operations and have contributed to every aspect of our mission.

Nothing means more to us than providing our families with the care they deserve. That's why we do our best to provide that quality care to each family that comes to the RIMGC.

It can be scary for families to hear someone over the phone say, "I'm calling from the Roberts Individualized Medical Genetics Center regarding your child." However, this is what Jasmine and I do every day when we reach out to families that are referred to the Center. We understand that hearing the word "genetics" can be terrifying for families, which is why we work hard to ease any tensions a family may be experiencing about their child having genetic testing.

We believe it is our responsibility to let families know, from the outset, that we will walk them through the entire process. The RIMGC provides a number of resources and tools for families. Our online educational modules, for example, provide an idea of what genetic testing is and how our team hopes to help families understand their child's diagnostic process.

Genetic testing can be costly, and each insurance policy has its own nuances. We aim to make information about these things clear. When a family is referred to us for genetic testing and counseling, we help navigate the insurance authorization process. We want to alleviate stress and support families. We are there with them through the entire time leading up to their child's first appointment.

Jasmine and I have been with Children's Hospital of Philadelphia for a combined 21 years. We have dedicated ourselves to the families we care for. In bringing our values to the RIMGC, we contribute to our team's mission by providing families with our support, compassion and knowledge. ■

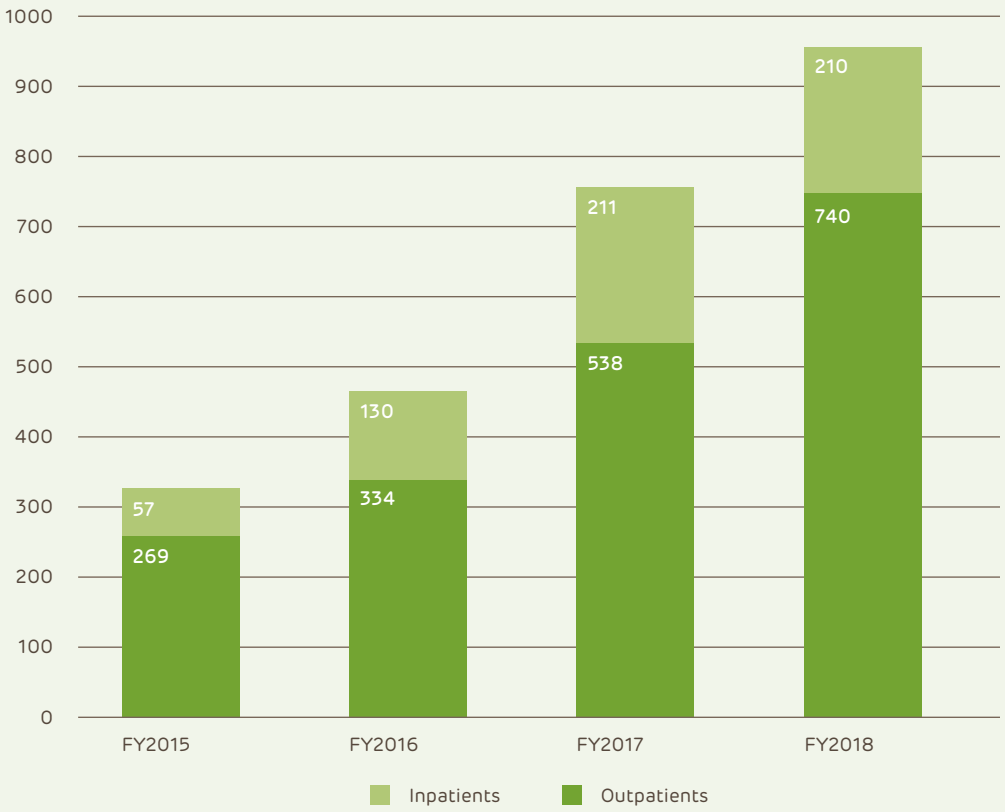
– Tyrah Williams

Tyrah Williams (left) and Jasmine Montgomery are families' first point of contact when they reach out to the Roberts IMGC for help.

BY THE NUMBERS

As word of the services and care the Roberts IMGC provides has grown, more patients have come to Philadelphia for our help. We have nearly tripled our patient encounters in four years. We also see adult patients, providing diagnoses to families that have often waited decades for answers. In concert with the Division of Genomic Diagnostics, we offer additional tests for specific conditions, leading to personalized treatments.

PATIENT ENCOUNTERS



PATIENT SPOTLIGHT

MEET SADIE

FINALLY, FIVE-PLUS YEARS LATER: AN ANSWER

Sadie Stahl's short-term but severe leg pain didn't change over the 5½ years she and her family searched for a diagnosis. But the world of genetics did. A new test, facilitated by the Roberts Individualized Medicine Genetics Center at Children's Hospital of Philadelphia, was the key to unlocking the mystery.

Her health odyssey started when Sadie was 7. She had brief periods when her legs hurt, especially during or after activities like soccer or skiing. The pain didn't last long and went away as quickly as it started. She continued to be active and enjoyed being a big sister to her new brother, Cameron.

Right before Christmas break, the school nurse called Sadie's parents, Melissa and Kevin Stahl, to say Sadie had complained of severe groin pain. Sadie's pediatrician ordered a blood test.

The test revealed Sadie's creatine kinase (CK) level was sky-high at 31,000 units per liter. A normal CK range for a child is up to 250 U/L. Creatine kinase, an enzyme in the heart, brain and skeletal muscles, leaks into the bloodstream when muscle tissue is damaged or undergoes stress. The results so surprised their pediatrician he suggested re-doing the blood work. The second test's results: 34,000 U/L.

OFF TO CHOP NEUROLOGY

He told the Stahls that Sadie needed to see a pediatric neurologist ASAP. Her family chose Children's Hospital of Philadelphia, even though it was three hours from their Lycoming County home.

"I had always heard wonderful things about CHOP," Melissa says, "and we knew that was where we wanted to take Sadie."

It was Dec. 27, 2012, when Sadie saw Brenda Banwell, MD, Chief of the Division of Neurology, and other members of CHOP's Neuromusclar Program for the first time. Given Sadie's symptoms, Dr. Banwell ordered extensive blood work to check for the leading causes of high CK levels: muscle disease, genetic metabolic disorders or viruses. Everything came back normal.

"Over the next six months, Sadie's symptoms increased in frequency and intensity," Melissa says. "Most days, she had pain. Sometimes it was severe, but it never lasted more than an hour. It usually occurred in one leg at a time and didn't favor one leg or specific area."

DETERMINING WHAT IT WAS NOT

Sadie made more trips to CHOP to make sure the high CK levels weren't disrupting her heart and kidney functions. She had an electromyography/nerve conduction velocity test to look for muscle or nerve damage. She had two muscle biopsies to see what was going on at the cellular level. Normal all around.

"We were ruling out a lot of 'bad' diagnoses," Kevin says, "but we still didn't know why Sadie was having these episodes."

Carsten G. Bönnemann, MD, a former CHOP physician now at the National Institutes of Health who returns to consult on

tough cases in the Undiagnosed Neuromuscular Disease Clinic, was stumped as targeted genetic tests were negative.

To help relieve the symptoms, Sadie, then 8, started on prednisone, a steroid that did help with the pain but caused GI problems, weight gain and affected her mood. "It was a lot for anyone to deal with, let alone an 8-year-old girl," Melissa says.

THE HUNT CONTINUED, WITH AN AMPS DETOUR

Since prednisone helped, it pointed to inflammation. Perhaps her pain was triggered by some sort of autoimmune disease? Rheumatologist Melissa Lerman, MD, PhD, MSCE, joined Sadie's team.

"We tried many different meds — immunosuppressants, infusions of IVIG and Rituxan — hoping that we could get her off steroids, but nothing seemed to work," Sadie's mother says.

Normally an upbeat kid, Sadie was getting discouraged. "As the years passed, I felt scared and frustrated," she says. "Even though I had great doctors and nurses, I was scared that I wouldn't be able to walk because of the pain. I worried I would never get a diagnosis."

Then, she started having severe and constant pain in her stomach that got worse when she ate. She missed 52 days of sixth grade and lost 12 pounds in five weeks because she only ate soup. Nothing helped; she was miserable. The complete GI workup at CHOP came back — what else? — normal.

But this time, Drs. Lerman and Banwell suspected a cause: amplified musculoskeletal pain syndrome, or AMPS, a medical condition that causes intense episodes of pain. Of the several causes for AMPS — stress, illness, injury, age and genetics — Sadie checked the box on a few. David D. Sherry, MD, who started the Center for AMPS at CHOP, outlined the intense treatment program of occupational and physical therapy Sadie would need to do to "break" the pain cycle.

She accepted the challenge, diligently did her exercises at home — with her family doing them along with her for motivation — and her AMPS gut pain went away.

Her leg pain persisted, however. It was time to look again for a genetic cause.

LOOKING TO GENETICS FOR ANSWERS

Because Sadie was adopted from China, it wasn't possible for doctors to review a typical family medical history for clues. Genetic counselor Līvija Medne, MS, LCGC, Co-director of the Roberts IMGC, who first met Sadie in 2012, explained that a broad-scale approach with an exome sequencing test — a more recently available test where all the approximately 20,000 human genes are analyzed at once — might provide an answer for Sadie's unique symptoms.

The RIMGC team cleared several hurdles to help the family obtain insurance coverage for exome sequencing. Sadie gave more blood; then they waited.

"Dr. Banwell called on the Saturday of Labor Day weekend and asked if we could come Tuesday to meet with her and Liv," Melissa says. "Could we meet with them? Of course!"

Sadie had a rare genetic muscle condition the neuromuscular community was just starting to learn about. It is caused by two identical mutations in the *MLIP* gene, expressed in the cardiac and skeletal muscle. Sadie is the first person on record in the United States with this disorder and the third recorded patient in the world; the others are in United Arab Emirates (diagnosed through the RIMGC) and Japan.

The condition is so rare, it doesn't have a clever name yet, and information on it is very limited. The two other patients are faring well; the muscle symptoms aren't progressing. Banwell recommended Sadie abstain from strenuous, endurance sports, like soccer, and stay well hydrated. She continues on a low dose of prednisone for now, and it's helping.

"Once I got my diagnosis, I felt pretty lucky," says Sadie, now 13. "I have so many people who care about me and want to help me. Now that we know what's causing my pain, I hope they can find a cure. And if they do, I hope that I can play soccer again!" ■

Newly available genetic tests led to a rare genetic diagnosis for Sadie, 13, much to the relief of her parents, Melissa and Kevin, and brother, Cameron.

TRAINING THE NEXT GENERATION

The Educational Core of the Roberts IMGC, led by Emma Bedoukian, MS, LCGC, strives to optimize the learning experience for students. Each year the Center accepts genetic counseling students, clinical fellows and postdoctoral laboratory fellows to train under our RIMGC clinical and research team.

Trainees gain vast exposure to different areas of pediatric genetic medicine through this program. Students not only gain experience with facilitation and interpretation of complex testing, such as exome sequencing, but also rotate in specialty clinics such as hearing loss, ocular genetics, differences of sex development, CdLS and related diagnoses, and disorders of immune dysregulation.

Over the past few years, more than 15 genetic counselors, eight clinical genetics fellows and five laboratory fellows have been trained by our esteemed team.

CHOP, in particular, partners with the University of Pennsylvania's Master of Science in Genetic Counseling program (formerly at Arcadia University) to train the future generation of genetic counselors. In addition to the clinical training the RIMGC provides, three Arcadia students completed their master's thesis project with the Center this past year.

Genetic counseling students Marlise Combe, Marisa Chamness and Caitlin Menello completed their master's thesis projects at the Roberts IMGC.

Marlise Combe (Arcadia MS '19), under the direction of Jacqueline Leonard, MSc, MS, LCGC, studied the patient experience of individuals with a difference of sex development (DSD) in order to further understand their experience in medical and genetic care. As this is a population whose differences intersect the cultural areas of gender and sex, classically this population has experienced hardships in receiving a timely diagnosis and appropriate care. Combe interviewed eight adults with a diagnosed DSD and investigated their journey to getting their diagnosis. This included a focus on their patient experience, what type of care was helpful, where care could have been improved, the stressors associated with their diagnosis or the process of receiving their diagnosis, and their experience surrounding genetic counseling. The purpose was to provide recommendations for genetic counseling best "practice guidelines for informed and compassionate care for individuals with a DSD.

Marissa Chamness (Arcadia MS '19) worked with supervisor Sarah Raible, MS, LCGC, on a project to further understand the transition process from pediatric to adult healthcare for children with Cornelia de Lange syndrome (CdLS). Once children with CdLS reach adolescence, a plan to transition into adult care is necessary. Limited resources are available to guide this process in teens with CdLS. The objective of this study was to assess the current climate of the transition process in families of children with CdLS. Parents/guardians were invited to participate in a small focus group that examined caregiver attitudes, ages of transition and services available.

The goal of this project is to aid in the development of best practices for the transition to adult care in this population. Findings may be extrapolated to other rare multisystemic diagnoses, as many challenges faced by families are not specific to CdLS.

Caitlin Menello (Arcadia MS '19) is the 2018 recipient of the Center for CdLS and Related Diagnoses Marie Barr Genetic Counseling Award. The mission of the award is to promote the development of expertise in genetic counseling issues related to rare developmental diagnoses. The program, initiated in 2014, annually awards a tuition scholarship to a first-year graduate student in the genetic counseling master's program at Arcadia University (now at Penn). Students work with members of the Center for CdLS to gain an understanding of the molecular etiology, clinical complexities and targeted management of individuals with CdLS and related diagnoses. Under the direction of the center team, award recipients develop a master's thesis project focused on CdLS or a related diagnosis.

Menello's thesis project investigated gastrointestinal dysmotility and other GI complications in individuals with CdLS. These complications range from gastroesophageal reflux disease (GERD) to gastrointestinal volvulus/obstruction (GIVO) and are responsible for 19% of deaths in the CdLS population. As of now, there is limited understanding regarding the frequency and severity of the gastrointestinal complications seen in affected individuals.

In collaboration with CHOP gastroenterologist Robert Heuckeroth, MD, PhD, this research aimed to identify what gastrointestinal issues are most frequent in the CdLS population and determine how these medical issues impact the quality of life for affected individuals and their caregivers. ■

RIMGC ANNUAL LECTURESHIP HITS SECOND YEAR

We were happy to host Fowzan Alkuraya, MD *(at right)*, for the Second Annual Clinical Genomics Lectureship as part of CHOP's Pediatric Grand Rounds series. He joined us from Riyadh, Saudi Arabia, where he is a professor of Human Genetics at Alfaisal University and a senior consultant and principal clinical scientist at King Faisal Specialist Hospital and Research Centre. Dr. Alkuraya and his lab have made numerous seminal contributions to the field of human genetics.

Dr. Alkuraya's Grand Rounds lecture highlighted how pervasive genetics is in pediatric medicine. His talk, titled "The Deconvolution Resolution of Clinical Genomics: Pediatrics Reimagined," illustrated the gap that still remains in proper diagnosis and thus, management of pediatric genetic disorders. He provided examples of how state-of-the-art genomics can help address this gap.

Later, Dr. Alkuraya also presented to the broader audience of genetics professionals across the Penn

campus. His talk, "What Does it Mean to Lose a Gene? Lessons from Human Knockouts," provided examples of gene discovery in a population where consanguinity rates are high. He is in a unique position to better the region's public health by means of gene discovery, awareness and prevention. He was able to highlight various differences and similarities between working in genetics in the United States versus Saudi Arabia.

We were extremely pleased to have Dr. Alkuraya in Philadelphia this year. ■

CENTER FOR CdLS NOW UNDER RARE DIAGNOSES PROGRAM

Among several new Roberts IMGC initiatives last year was the establishment of the Rare Diagnoses Program. Led by Sarah Raible, MS, LCGC, the program meets a long-term need at CHOP to provide a medical and research home with centralized resources for children and families with rare diagnoses. The first step of creating a broader rare diagnosis focus was to integrate the Center for Cornelia de Lange Syndrome (CdLS) and Related Diagnoses into the RIMGC.

CHOP's Center for CdLS and Related Diagnoses, which was launched in 2009, exists to provide clinical care and to improve the lives of children and adults with CdLS and related diagnoses. The center has an internationally recognized team that draws patients from all over the country *(meet one of our CdLS patients on Page 12)* and the world. To provide the best medical care, we collaborate across many specialties and with primary care providers and families so every patient has a personalized care plan that optimizes development and quality of life.

Though CdLS is the most common diagnosis we care for, we also focus on providing medical care to children with Pallister-Killian syndrome (PKS), CHOPS syndrome and chromosomal abnormalities such as Kleefstra syndrome. In fact, PKS is the second most common diagnosis we care for *(meet one of our PKS patients on Page 20)*. The Center for CdLS is also committed to serving local, national and international families. The center has evaluated more than 1,000 individuals with CdLS and related diagnoses, making it the largest program of its kind in the world. Patients travel from all over the country and the globe to attend the monthly multidisciplinary clinics to receive expert advice from our specialists.

The center is also an international leader in research. Not only are we committed to further understanding the mechanisms involved with these diagnoses, but we're also focused on therapeutics. The center offers the opportunity to translate clinical and basic science research into improved management and treatment for individuals with these complex diagnoses in a setting where they can receive comprehensive care and coordinated services.

With the Center for CdLS now a part of the RIMGC Rare Diagnoses Program, the ultimate goal is to continue to develop and grow the center within the RIMGC and expand this model to other rare diagnoses requiring similar care and infrastructure support. We're excited to facilitate this growth. ■

CdLS CONSULTING TEAM

In addition to the RIMGC team listed on Page 3, these physicians also treat Rare Diagnoses Program patients.

Richard S. Davidson, MD
Division of Orthopaedic Surgery

Deborah A. Driscoll, MD
Chair, Department of Obstetrics and Gynecology, Penn Medicine, CHOP Attending Physician

John A. Germiller, MD, PhD
Division of Otolaryngology

Elizabeth Goldmuntz, MD
Division of Cardiology

Soma Jyonouchi, MD
Division of Allergy and Immunology

Andrea Kelly, MD, MSCE
Division of Endocrinology

Sudha Kessler, MD
Division of Neurology

Rochelle Lindemeyer, DMD
Division of Dentistry

Monte Mills, MD; James A. Katowitz, MD
Division of Ophthalmology

Kevin Myers, MBBCh
Division of Nephrology

Stephen Zderic, MD
Division of Urology

GRANT BRINGS DENTAL CARE TO CHILDREN WITH RARE DIAGNOSES

A new dental program allows patients like Luca Borgia, 4, to receive dental care from Dental Resident Allison Brand, DDS, without anesthesia.

A grant awarded to the RIMGC Rare Diagnoses Program and Penn Dental is helping to create a new program focusing on providing dental care to children and adults with rare genetic diagnoses. The $30,000 Access to Care grant, awarded by Delta Dental, is supporting a program within CHOP's Center for CdLS to provide dental care for children and adults with CdLS and similar diagnoses. We can support families for routine dental health services, obtain specialized equipment and develop educational materials for families and clinicians.

So far, the grant funding has allowed us to formally establish dental evaluations as a component of our monthly multidisciplinary clinic for children and adults with CdLS and related diagnoses. We have a dentist now available during clinics to provide evaluations and education to all families attending the clinic. Grant money has also been used to purchase equipment, including a portable X-ray machine. The portable X-ray has many advantages, such as taking radiographs nearly twice as fast as a conventional X-ray system, making it ideal for children and patients with special needs — many of whom would otherwise require sedation.

This program has been incredibly valuable to the families we care for as many struggle to find dentists who are comfortable treating their children and also understand their diagnosis. Many patients have not received routine dental care or even had routine teeth cleaning in years given their behavioral complexities and need for sedation in some cases.

We are also identifying children who need to return for more detailed examinations and even need treatment under anesthesia. The funding allows us to offset some of families' direct medical costs. We also plan to develop materials to help educate our patients on oral health conditions, dental procedures and proper oral hygiene techniques.

The center's consulting dentist, Rochelle G. Lindemeyer, DMD, associate professor emeritus of Pediatric Dentistry at Penn Dental Medicine and CHOP, is the grant's principal investigator. Co-investigators on the project are Ian D. Krantz, MD, Director of the Center for CdLS and Related Diagnoses, and Sarah E. Raible, MS, LCGC, genetic counselor and Clinical Director of the center. ■

PATIENT SPOTLIGHT

MEET OLIVER

A SPECIFIC PLAN FOR A SPECIFIC CHILD

Molly Hesse is a proactive parent. When a prenatal test showed an increased risk of Down syndrome, she had an amniocentesis, which was negative for Down's.

When baby Oliver, who was born at 5 pounds, 15 ounces, was still small at 6 months, she and husband, Andrew, had Oliver tested for cardiac and GI issues. The only thing that came back was mild reflux. Even though he was developing fairly normally (he was a little unsteady sitting up), when Oliver was 8 months old, they took him for a genetics consultation at Lurie Children's Hospital near their Chicago-area home.

Inside knowledge of CdLS

Geneticist Mindy Li, MD, who just happened to have trained as a resident at Children's Hospital of Philadelphia and spent time in its Center for Cornelia de Lange (CdLS) and Related Diagnoses, spotted subtle signs their pediatrician and other specialists had not. "She told us, 'I can't know anything definitively until genetic tests come back, but I suspect he has a mild case of CdLS.' We had never heard of it," says Molly.

Molly immediately began researching CdLS and, once she learned a bit about it, "I could really see it," she says. "While, luckily, none of his issues are very serious, it just explained everything."

The more Molly researched, especially with the help of the Cornelia de Lange Syndrome Foundation and by connecting with families on the Facebook CdLS Discussion Board, the more proactive she became.

She didn't wait for genetic testing, "which was a good thing because it ended up being 10 months before our insurance company approved it."

She quickly arranged for an evaluation by her county's Early Intervention Unit, which resulted in physical therapy for Oliver right away. A sedated auditory brainstem response (ABR) hearing test indicated mild hearing loss, so he received hearing aids and treatment from a developmental hearing therapist. After discovering how important speech development was, Molly insisted on adding speech therapy to his treatments. "I am beyond grateful for the CdLS families we have connected with online and in person. We would not be where we are today without their knowledge and support," she says.

Oliver was already excelling in his therapies by the time the CdLS diagnosis was official, via genetic test results, when he was 18 months old.

CHOP's focus on individualized care

Another key thing Molly learned from the CdLS community was about CHOP's Center for CdLS, located within the Rare Diagnoses Program of the RIMGC. "When I looked it up, I was impressed with its focus on life-long treatment," Molly says. "Because every kid with CdLS is so different, I wanted to get a plan especially for him and what he needed."

Oliver's appointment in the CdLS Clinic was in July 2018. He stayed in one exam room while physical therapist Ann T. Harrington, PT, DPT, PhD, PCS; gastroenterologist Kathleen M. Loomes, MD; developmental pediatrician Mary Pipan, MD; center Director Ian Krantz, MD; and Clinical Director Sarah E. Raible, MS, LCGC, came in to perform their evaluations. Krantz and Raible then presented an overall plan.

"It's every parent's dream to get that specific information for your specific child," says Molly. "It was great to meet the CdLS experts. Our medical team in Chicago is amazing, but they do not always have answers to CdLS-specific questions. At CHOP, they know."

For example, Molly and Andrew had contemplated starting Oliver in kindergarten at age 6, not 5. Dr. Pipan wholeheartedly agreed. "We came home with concrete steps to take to keep Oliver's development moving forward. I loved that the CHOP doctors gave me that level of expertise."

A phone call away

The Hesses appreciate that they can contact CHOP's CdLS team by phone or email if a question comes up. "When some of Oliver's immune levels came back low, I wanted a second opinion about what to do," Molly says. "Sarah told me it was OK to watch and retest, and now they're up. We're so grateful the experts are just a phone call away."

One way they showed their gratitude was to designate gifts "in lieu of flowers" from Molly's father's funeral to CdLS research at CHOP. Oliver's grandfather, Steve Doran, was an oral surgeon and acted as the Hesses' "medical partner" with Oliver's diagnosis and treatment options. Doran had come to Philadelphia with Molly and Oliver for their clinic appointment. "He was so incredibly touched by meeting the CdLS doctors," Molly says.

Oliver, now 3, with parents Molly and Andrew and big brother Isaac, came from Chicago to receive a care plan from the Center for CdLS.

Family's 'mischief maker'

"Oliver is just a joy. He has a smile that draws people in. When we're out, people always comment on his eyes, his eyelashes, his smile. He loves that and gives them a high five or blows them a kiss," Andrew says.

He actively plays with his older brother — and best friend — Isaac, 5, and he loves dancing and music. *Wheels on the Bus* is the current favorite. Taking after Andrew, Oliver has become the family "mischief maker." "He always walks his therapists to the door, and then he'll put their shoes on his feet — looking for the laugh," Molly says.

He's always been a social butterfly, interacting with anyone and everyone. That's one reason Molly and Andrew decided to be proactive again, openly talking about his CdLS diagnosis.

If someone asks about his small size or long eyelashes, Molly might explain, "Oliver has a mild form of a genetic syndrome. Depending on their reaction or the circumstance, I'll gladly provide more information. I treat it like you would talk about any topic concerning any child," she says.

Next up is school. Oliver qualifies for school district provided preschool, which will include his various therapies and incorporates typical children, too.

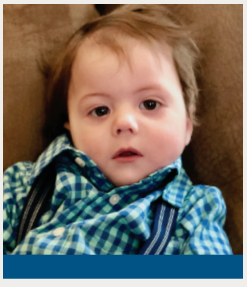
"Oliver will have challenges just like any kid; it's just that some of his challenges have a name," Molly says. "We won't always be able to control how the rest of the world sees him, but, by sharing our experiences, we hope to build awareness about the beautiful diversity and the shared experiences that we all have." ■

SHARING RESEARCH RESOURCES

The research core of the Roberts IMGC has been led by Sawona Biswas, MS, LCGC. This year, Tiffiney Hartman, MS, CGC, PhD; Melissa Gilbert, PhD, and Batsal Devkota, PhD, will join the team.

Pediatric Genomic Sequencing in Health and Disease: Our group has successfully enrolled 1,504 participants in a broad Institutional Review Board (IRB) approved protocol that allows for the collection, banking and sharing of de-identified data and biospecimens. Through this effort, we aim to create an open data and sample resource for all CHOP physicians and investigators. This will facilitate gene discoveries, aid in the development of novel therapeutics and ultimately improve patient care. Toward this end, we have developed a research portal that connects data from different sources into one platform. This portal is accessible to all CHOP clinicians and researchers, allowing them to easily perform searches by patient phenotype(s), genotype(s) or sample availability. Clinicians and researchers can quickly request data for conducting focused research studies or identify cohorts for clinical trials. The RIMGC research portal, along with electronic recruitment tools, will help CHOP researchers reduce project initiation time and facilitate collaboration and discovery.

A PARENT'S PERSPECTIVE: PARTICIPATING IN RESEARCH



My name is Kayla and I am the proud mom of a little boy named Carter. When Carter was born, we knew something was different, but it seemed we were unable to get any answers. They told us genetic testing could take weeks, even months, and every moment that went by Carter's prognosis became more and more unclear. We were transferred to CHOP when Carter was 4 days old. Immediately upon arriving, we were welcomed by a team of nurses and doctors, including those from Genetics.

They began ordering tests we'd hoped would give us some hints or leads to what we were dealing with. During that time, we were asked if we'd like to participate in a research study called NICUSeq since Carter fit the qualifications. This would also include blood samples from my husband and me. The process was explained and consents were signed. We both eagerly checked "yes" in that little box that basically says: "If we find other things, would you like to know?" We wanted to know it all, we wanted to find out what was happening with our little boy. That box turned out to be much more important than we had ever expected.

When Carter was 9 days old, the preliminary karyotype came back with the result of tetrasomy 18p. Although it was a shock, we were given so much support and guidance from the RIMGC team at CHOP. For the first time since he was born, we felt like he would be OK. At 45 days old, Carter was discharged

Genomics Research and Innovation Network:

The RIMGC is facilitating CHOP's continued contribution to the Genomics Research and Innovation Network (GRIN). GRIN is a collaboration between three premier pediatric academic medical institutions (CHOP, Boston Children's Hospital and Cincinnati Children's Hospital) to share clinical, genomic and sample metadata to accelerate genomic discovery and foster a culture of collaboration and data sharing. We have successfully submitted several National Institutes of Health grants to support these efforts and are in conversation with industry partners to conduct focused research projects that will benefit children and families with rare disorders. More information can be found at **www.grinnetwork.org**.

NICUSeq:

NICUSeq is a multi-institutional industry-sponsored trial (Illumina) where we are evaluating the clinical utility of rapid whole genome sequencing compared to standard-of-care testing in acutely ill infants in CHOP intensive care units who are suspected to have a genetic condition. We have enrolled 85 families in this study since last year. Several families have benefited from early molecular diagnoses that have led to a change in medical management. Enrollment in this study has recently ended, and outcomes will be analyzed and published in the upcoming year. ■

home. He was happy, healthy and eager to join his big sister and extended family. We settled in and began living our new normal.

A week or so later, I received a call from the RIMGC research team to discuss results of the NICUSeq study. Carter's and my husband's results came out as expected, Carter's tetrasomy 18p was confirmed. It was a huge relief to know everything else looked to be of no significance at this time.

My results however, were not as uneventful. It was discovered through this test that I was positive for *BRCA1* mutation, indicating a high risk for breast cancer. This was explained in detail and I was very surprised, especially since no family member has had any form of cancer. I did not expect this result; it was a complete shock. I was immediately referred for appropriate testing and confirmation. I met with genetic counselors and we began to look for where I inherited it from.

My mother and sister were tested, which confirmed both have the same *BRCA1* mutation. My mother underwent a prophylactic mastectomy and hysterectomy five months after receiving her results. My sister and I will follow in a few years.

Testing we received from this study has provided invaluable information for our family. We are so thankful for the opportunity to participate and for the support we received through the process and beyond. ■ ”

CHOPS SYNDROME: WHAT'S IN A NAME?

ORIGINAL THREE PATIENTS JOINED BY 12 MORE WORLDWIDE

Kosuke Izumi, MD, PhD, and Sarah Raible, MS, LCGC, with one of the first three CHOPS patients, Leta Moseley

CHOPS syndrome is a multisystemic developmental diagnosis caused by missense mutations in the *AFF4* gene. The acronym "CHOPS" describes the shared clinical characteristics of the diagnosis: **C**ognitive impairment and coarse facial features, **H**eart defects, **O**besity, **P**ulmonary involvement, **S**hort stature and skeletal dysplasia.

In 2015, the first three individuals with CHOPS syndrome were reported by Kosuke Izumi, MD, PhD, and Ian Krantz, MD. All three individuals had been referred to the Center for CdLS and Related Diagnoses at Children's Hospital for a suspected diagnosis of CdLS. While these three children's features (intellectual disability, short stature and craniofacial dysmorphisms) overlapped with CdLS, they demonstrated clinically distinct medical and physical features, establishing CHOPS syndrome as a novel recognizable diagnostic entity *(Izumi, et al., 2015)*.

Since the first described patients were identified in 2015, more than 15 individuals with CHOPS syndrome have been identified to our knowledge, and our group, led by the efforts of Dr. Izumi, recently published a manuscript further describing the clinical manifestations of the diagnosis *(Raible, et al. 2019)*.

While children with CHOPS syndrome share characteristics with CdLS patients (such as small head circumference, developmental delay, intellectual disability, heart defects and hearing loss), they have distinguishing features: obesity, pulmonary involvement, skeletal findings and distinct craniofacial features. Though all individuals with CHOPS syndrome identified thus far have short stature (which is observed in CdLS), all CHOPS patients also are overweight for their stature and many were noted to exhibit food-seeking behaviors.

Dr. Izumi, in collaboration with Dr. Krantz, has been focused on using cellular and animal models to understand the function of the *AFF4* gene. *AFF4* is known to control gene expression and therefore, as a result of an *AFF4* gene change, one might expect to see gene expression differences in CHOPS syndrome. Utilizing skin samples donated by children with CHOPS syndrome, Dr. Izumi observed gene expression changes unique to children with CHOPS syndrome. In addition, an *AFF4* mouse model interestingly showed obesity and lung differences, which are some of the main clinical symptoms in CHOPS. Dr. Izumi and collaborators continue to investigate the mechanism and function of *AFF4*.

In July 2019, the RIMGC Rare Diagnoses program, in collaboration with Lainey Moseley, mother of 21-year-old Leta Moseley, one of the first children diagnosed with CHOPS syndrome, is hosting the first-ever CHOPS family meeting. Families from all over the country and the world are traveling to Children's Hospital to meet our clinicians and researchers and network with other families who have children with the same diagnosis. ■

RARE DIAGNOSES PROGRAM RECEIVES GRANT TO STUDY GENETIC CAUSES OF CdLS

Developmental diagnoses are a major cause of suffering for the affected children and their families. Congenital anomalies are identified in approximately 3% of term births, 10% of stillbirths and in as many as 50% of first trimester spontaneous abortuses. While most, if not all, human structural birth defects have a significant genetic component, identification of genetic causes of isolated structural birth defects has been complicated by the complex nature of their underlying etiologies. These likely involve disruption of regulatory elements that can act in a temporal and tissue-specific manner, with multigene, epigenetic and gene-environment interactions.

The National Institutes of Health (NIH) Gabriella Miller Kids First Pediatric Research Program (Kids First), launched in 2015, is a large-scale data resource program to help researchers uncover new insights into the biology of childhood cancer and structural birth defects.

The RIMGC Rare Diagnoses Program was awarded funding through Kids First to sequence 400 genomes of individuals with Cornelia de Lange Syndrome (CdLS) and CdLS-like phenotypes for which a molecular etiology has not yet been established.

CdLS is a developmental disorder characterized by development delays, cognitive impairment, short stature, hearing loss, specific facial features and structural birth defects, such as differences of the limbs, heart, kidneys and GI tract.

Our approach to tease out genetic contributions to birth defects has been to identify the underlying causes of syndromic birth defects, which are often Mendelian in nature and therefore lend themselves more readily to genetic causal identification. Once identified, these genetic causes of syndromic forms of birth defects can be leveraged to understand the genetic contributions to isolated birth defects seen in constellation in syndromes such as CdLS. This work will lead to the identification of genes critical in human embryonic development, provide novel insights into transcriptional regulation, and help identify genetic causes and candidate genes for isolated birth defects seen in constellation in similar diagnoses.

As structural birth defects have lifelong effects on not only the children but also their families, the Kids First program aims to promote research into these areas, discover shared genetic pathways, and ultimately provide improved diagnostics, counseling, management and therapeutic interventions for affected individuals and their families.

Data generated from sequencing our 400 genomes will be publicly available through the NIH dbGaP (the database used to archive and distribute data from genotype/phenotype studies in humans) and the Kids First Data Resource Portal. ■

Congenital anomalies are identified in approximately 3% of term births, 10% of stillbirths and in as many as 50% of first trimester spontaneous abortuses.

SHARING OUR EXPERTISE

Selected talks:

Emma Bedoukian, MS LCGC (moderator). *Seeing into the Future: Gene Therapy Has Arrived.* Annual Clinical Genetics Meeting. Seattle, Wash.

Ian Krantz, MD, Maninder Kaur, MS, and Sarah Raible, MS, LCGC. *Mosaicism in Cornelia de Lange Syndrome.* Biennial CdLS National Foundation Scientific and Educational Symposium. Minneapolis, Minn.

Sarah Raible, MS, LCGC; Ian Krantz, MD; and others (Bettale C, Kaur M, Benedict M, Mills JA, Dorsett D). *Investigating Indomethacin and Acemetacin Efficacy in Normalizing Expression Levels of Known Cornelia de Lange Syndrome Dysregulated Genes in Human-derived Fibroblasts.* Biennial CdLS National Foundation Scientific and Educational Symposium. Minneapolis, Minn.

Kosuke Izumi, MD, PhD; Sarah Raible, MS, LCGC; Ian D. Krantz, MD, and others (Salzano E, Kaur M, Wilkens A, Sperti G, Tilton RK, Bettini LR, Rocca A, Cocchi G, Selicorni A, Conlin LK, McEldrew D, Gupta R, Thakur S). *Prenatal Profile of Pallister-Killian Syndrome: Retrospective Analysis of 114 Pregnancies, Literature Review and Approach to Prenatal Diagnosis.* David W. Smith Workshop on Malformations and Morphogenesis. Banff, Canada.

Kosuke Izumi, MD, PhD; Sarah Raible, MS, LCGC; Ian D. Krantz, MD, and others (Mehta D, Bettale C, Fiordaliso S, Rio M, Haan E, White SM, Cusmano Ozog K, Nishi E, Okamoto N, Miyake N, Matsumoto N). *Clinical and Molecular Spectrum of CHOPS Syndrome.* American College of Medical Genetics. Seattle, Wash.

Cara Skraban, MD. *Genetics for the Primary Care Physician.* 2019 Pediatric Conference Presented by Pennsylvania Chapter, American Academy of Pediatrics. Grantville, Pa.

Olivia Katz, Ian Krantz, MD, Yaning Wu, PhD. *A Drug Rescue Study of Neurological Deficits in a Drosophila Model of Cornelia de Lange Syndrome.* Biennial CdLS National Foundation Scientific and Educational Symposium. Minneapolis, Minn.

Kosuke Izumi, MD, PhD; Sarah Raible, MS, LCGC; Maninder Kaur, MS; Matthew Deardorff, MD, PhD; Ian Krantz, MD. *Molecular Update on the Cohesinopathies and Disorders of Transcriptional Regulation (DTRs) – A Growing Group of Disorders with Implications for Understanding Cornelia de Lange Syndrome.* Biennial CdLS National Foundation Scientific and Educational Symposium. Minneapolis, Minn.

Selected publications:

Rapid and accurate interpretation of clinical exomes using Phenoxome: a computational phenotype-driven approach. Wu C, Devkota B, Evans P, Zhao X, Baker SW, Niazi R, Cao K, Gonzalez MA, Jayaraman P, Conlin LK, Krock BL, Deardorff MA, Spinner NB, Krantz ID, Santani AB, Tayoun ANA, Sarmady M. Eur *J Hum Genet.* 2019;27(4):612-620.

Novel findings with reassessment of exome data: implications for validation testing and interpretation of genomic data. Gibson KM, Nesbitt A, Cao K, Yu Z, Denenberg E, DeChene E, Guan Q, Bhoj E, Zhou X, Zhang B, Wu C, Dubbs H, Wilkens A, Medne L, Bedoukian E, White PS, Pennington J, Lou M, Conlin L, Monos D, Sarmady M, Marsh E, Zackai E, Spinner N, Krantz I, Deardorff M, Santani A. *Genet Med.* 2018;20(10):1298.

Anticipated responses of early adopter genetic specialists and nongenetic specialists to unsolicited genomic secondary findings. Christensen KD, Bernhardt BA, Jarvik GP, Hindorff LA, Ou J, Biswas S, Powell BC, Grundmeier RW, Machini K, Karavite DJ, Pennington JW, Krantz ID, Berg JS, Goddard KAB. *Genet Med.* 2018;20(10):1186-1195.

Prenatal profile of Pallister Killian syndrome: retrospective analysis of 114 pregnancies, literature review and approach to prenatal diagnosis. Salzano E, Raible SE, Kaur M, Wilkens A, Sperti G, Tilton RK, Bettini LR, Rocca A, Cocchi G, Selicorni A, Conlin LK, McEldrew D, Gupta R, Thakur S, Izumi K, Krantz ID. *Am J Med Genet.* 2018;176(12):2575-2586.

AUDIOME: a tiered exome sequencing-based comprehensive gene panel for the diagnosis of heterogeneous nonsyndromic sensorineural hearing loss. Guan Q, Balciuniene J, Cao K, Fan Z, Biswas S, Wilkens A, Gallo DJ, Bedoukian E, Tarpinian J, Jayaraman P, Sarmady M, Dulik M, Santani A, Spinner N, Abou Tayoun AN, Krantz ID, Conlin LK, Luo M. *Genet Med.* 2018;20(12):1600-1608.

Utility and limitations of exome sequencing as a genetic diagnostic tool for children with hearing loss. Sheppard S, Biswas S, Li MH, Jayaraman V, Slack I, Romasko EJ, Sasson A, Brunton J, Rajagopalan R, Sarmady M, Abrudan JL, Jairam S, DeChene ET, Ying X, Choi J, Wilkens A, Raible SE, Scarano MI, Santani A, Pennington JW, Luo M, Conlin LK, Devkota B, Dulik MC, Spinner NB, Krantz ID. *Genet Med.* 2018;20(12):1663-1676.

Cornelia de Lange syndrome in diverse populations. Dowsett L, Porras AR, Kruszka P, Davis B, Hu T, Honey E, Badoe E, Thong MK, Leon E, Girisha KM, Shukla A, Nayak SS, Shotelersuk V, Megarbane A, Phadke S, Sirisena ND, Dissanayake VHW, Ferreira CR, Kisling MS, Tanpaiboon P, Uwineza A, Mutesa L, Tekendo-Ngongang C, Wonkam A, Fieggen K, Batista LC, Moretti-Ferreira D, Stevenson RE, Prijoles EJ, Everman D, Clarkson K, Worthington J, Kimonis V, Hisama F, Crowe C, Wong P, Johnson K, Clark RD, Bird L, Masser-Frye D, McDonald M, Willems P, Roeder E, Saitta S, Anyane-Yeoba K, Demmer L, Hamajima N, Stark Z, Gillies G, Hudgins L, Dave U, Shalev S, Siu V, Ades A, Dubbs H, Raible S, Kaur M, Salzano E, Jackson L, Deardorff M, Kline A, Summar M, Muenke M, Linguraru MG, Krantz ID. *Am J Med Genet A.* 2019;179(2):150-158.

Clinical manifestations of Xia-Gibbs syndrome: findings of consecutively identified cases at a single children's hospital. Ritter AL, Mcdougall C, Skraban C, Medne L, Bedoukian EC, Asher SB, Balciuniene J, Campbell CD, Baker SW, Denenberg EH, Mazzola S, Fiordaliso SK, Krantz ID, Kaplan P, Ierardi-Curto L, Santani AB, Zackai EH, Izumi K. *Am J Med Genet.* 2018;176(9):1890-1896.

Genotype-phenotype specificity in Menke-Hennekam syndrome caused by missense variants in exon 30 or 31 of CREBBP. Banka S, Sayer R, Breen C, Barton S, Pavaine J, Sheppard SE, Bedoukian E, Skraban C, Cuddapah VA, Clayton-Smith J. *Am J Med Genet A.* 2019;179(6):1058-1062.

Bohring-Opitz syndrome caused by an *ASXL1* mutation inherited from a germline mosaic mother. Bedoukian E, Coopenheaver D, Bale S, and Deardorff M. *Am J Med Genet A.*2018;176(5):1249-1252.

NFIB haploinsufficiency is associated with intellectual disability and macrocephaly. Schanze I, Bunt J, Boppudi S, Lim JWC, Schanze D, Dean JR, Alders M, Blanchet P, Attié-Bitach T, Berland S, Boogert S, Bridges CJ, Cho MT, Dobyns WB, Donnai D, Douglas J, Earl DL, Edwards TJ, Faivre L, Fregeau B, Genevieve D, Gérard M, Gatinois V, Holder-Espinasse M, Huth SF, Izumi K, Kerr B, Lacaze E, Lakeman P, Mahida S, Mirzaa GM, Morgan S, Nowak C, Peeters H, Petit F, Pilz DT, Puechberty J, Reinstein E, Rivière J-B, Santani AB, Schneider A, Sherr EH, Smith- Hicks C, Wieland I, Zackai E, Zhao X, Gronostajski RM, Zenker M, Richards LJ. *Am J Hum Genet.* 2018;103(5):w752-768.

De novo variants in myelin regulatory factor (MYRF) as candidates of a new syndrome of cardiac and urogenital anomalies. Pinz H, Pyle LC, Li D, Izumi K, Skraban C, Tarpinian J, Braddock SR, Telegrafi A, Monaghan KG, Zackai E, Bhoj EJ. *Am J Med Genet A.* 2018;176(4):969-972.

WDR26-Related Intellectual Disability. Skraban CM, Grand KL, Deardorff MA. In: Adam MP, Ardinger HH, Pagon RA, et al., editors. *GeneReviews®* [Internet]. Seattle (WA): University of Washington, Seattle; 1993-2019.

PATIENT SPOTLIGHT

MEET VIOLET

Violet, 2, with her father, Bobby Valenziano

MOVING CLOSER TO THE PKS EXPERTS

The Valenzianos would go to the ends of the earth to get their daughter Violet the care she needs.

They didn't need to go that far. But they did move from the Chicago area to Philadelphia so Violet, who has Pallister-Killian syndrome (PKS), could be treated by many pediatric specialists at Children's Hospital of Philadelphia.

The decision to uproot their lives and leave their close-knit family and friends was an easy one to make, for both practical and inspirational reasons.

"When we came to CHOP for the clinic visit, it was the first time since Violet was born that we were given hope," says Bobby Valenziano. "They gave us a plan for Violet's future. It was amazing to hear something so hopeful."

Something wrong, but what?

Violet spent the better part of her first year in three different Illinois hospitals. Because her tailbone was exposed at birth, doctors knew something was amiss — they just didn't know the full extent.

"It seemed like they found something else wrong every day," says Amber Valenziano. "She wasn't eating well. She didn't nurse like her sister had."

Doctors determined Violet had a high arched palate and was aspirating, making it difficult for her to latch on, so a gastrostomy tube was placed for feeding. Her gut anatomy was abnormal, a condition called intestinal malrotation, so she underwent a Ladd surgery to put things in their proper place. In time, other anomalies came to light, such as her congenital diaphragmatic hernia, sparse hair pattern, anorectal malformation, hypotonia and craniofacial differences. Eventually, she underwent genetic testing.

"They met with us to inform us she had PKS," Amber remembers. "They gave us a website and a couple of articles on the condition. That was it. She was the first patient with PKS the hospital had ever had."

Through the **PKSkids.net** website, the Valenzianos learned about CHOP and the research that RIMGC physician-scientists Kosuke Izumi MD, Ian Krantz, MD, and others were doing in PKS. That prompted the clinic visit in April 2018 that changed their lives.

Expertise in Pallister-Killian syndrome

"In Chicago, we were the ones telling the doctors about PKS, from what we had learned, but at CHOP, doctors gave us information on her diagnosis," Bobby says. "We went from a very negative outlook on Violet's quality of life to learning that, while she'll never be fully capable, she can live a long, happy life."

Amber says, "They knew so much about PKS and were treating several other PKS patients, so we knew right away that this is where we wanted to be. Philadelphia was where Violet would get the best care possible."

With family and friends pitching in, they put their house on the market, Bobby's employer transferred him to its Swedesboro, N.J., facility and the family — including Azalea, now 4 — was in their Delaware County, Pa., home by July. Amber's mother, Kim Raymond, who's a nurse, moved as well.

"The house sold in one day," says Amber. "The way everything fell into place, it was meant to be."

Amazing care coordination

Given that Violet sees 15 different specialty practices at CHOP *(see below)* — in addition to her primary care pediatrician in the CHOP Care Network Haverford practice — keeping track of when she is due for follow-up appointments and making sure all her doctors know what is happening could have been a daunting chore.

Instead, Violet qualified for CHOP's Compass Care Program for children with complex healthcare needs, and her Compass Care physician, Annique Hogan, MD, has become the glue that holds all the pieces of Violet's care together.

"It's such a weight lifted off our shoulders, words can't express it," Bobby says. "Dr. Hogan knows who Violet needs to see in the current moment and who she needs to see in the future. We've been able to breathe."

"I sing the praises of Children's Hospital and Compass Care," says Amber. "They've been wonderful. I also love, love, love MyCHOP," the hospital's electronic medical record that families can access online. "It helps me keep track of appointments, medicines, everything."

Pennsylvania services: a big help

The level of services provided by the state of Pennsylvania also far outperforms what is available in Illinois. For example, Amber has been able to return to her career as a middle school social studies teacher because Pennsylvania provides day and night home nursing care. "I hadn't thought it would be possible," Amber says.

To make things even better, Violet's grandmother, the nurse, was named as her daytime care provider. "She calls it her dream job," Amber says.

Children with disabilities in Pennsylvania are automatically eligible for Medicaid as a supplemental insurance, which is a big help with co-pays and deductibles.

Violet also receives physical, occupational, vision, speech and audiology therapies from the Delaware County Early Intervention Unit, along with social work services, which provides services for families with a child who has developmental and physical delays.

Seeing progress

With Violet's many physical challenges in the capable hands of CHOP clinicians, her personality is starting to blossom.

"She's our wiggle worm," says Amber. "She's working on rolling over."

"She's beginning to vocalize more and more," Bobby says. "She's letting us know her likes and dislikes."

Likes: being tickled, lights, music and, especially, her big sister. Dislikes: a delay in feeding time.

"It's amazing that she knows, to the minute, when it's time for her feeding," Amber says, "and she lets us know if we're even a tiny bit late."

The biggest thing the Valenzianos have learned from Violet is patience. "Milestones that most parents take for granted, we celebrate each and every one. We're her biggest cheerleaders." ■

IT TAKES A VILLAGE

Key members of the CHOP team that cares for Violet:

Primary Care Pediatrician (Haverford): *Jessica Chi, MD*

Compass Care Program: *Annique Hogan, MD*

Audiology: *Lyndsey Spencer, AuD, CCC-A; Christina Le, AuD, CCC-A*

Cardiology: *Elizabeth Goldmuntz, MD*

Developmental Pediatrics: *Mary Pipan, MD*

ENT: *Luv Javia, MD; John Germiller, MD, PhD*

Genetics: *Ian Krantz, MD; Sarah Raible, MS, LCGC; Sierra Fortunato, BS*

GI: *Kathleen Loomes, MD; Susan N. Peck, MSN, CRNP*

Immunology: *Melanie Ruffner, MD, PhD*

Neonatal Follow-up Program: *Susan Friedman, MD*

Neurology: *Lori Billinghurst, MD, MSc; Thornton Mason, MD, PhD, MSCE*

Neurosurgery: *Gregory Heuer, MD, PhD*

Nutrition: *Colleen Vicente, RD, LD, CNSC*

Ophthalmology: *Monte Mills, MD*

Pulmonary: *Howard Panitch, MD*

Rehabilitation: *Christopher Keenan, DO*

Surgery: *Myron Allukian, MD*

RIMGC KEY TO FINDING CAUSES OF IMMUNE DYSREGULATION

Christopher Gray, MS, LCGC, is a genetic counselor with the Roberts IMGC and Immune Dysregulation Program.

For most children, the immune system helps fight illness. For children with immune dysregulation disorders, however, the immune system malfunctions, affecting multiple systems of the body. An overactive immune system attacks the body, causing dangerous inflammation and organ damage. An underactive immune system leaves a child vulnerable to infection.

Immune dysregulation disorders are rare, complex and often difficult to diagnose. Many of these disorders have a known genetic cause, or may have a genetic cause that has yet to be discovered. If diagnosed quickly and accurately, children can be treated — and in some cases, cured. However, due to the complex nature of immune dysregulation, many children remain undiagnosed and without an individualized treatment plan.

In mid-2018, genetics specialists from the Roberts IMGC were approached by clinicians and researchers from multiple CHOP subspecialties who wanted to address this problem. Their goal: develop a novel, multidisciplinary program to diagnose patients with suspected immune dysregulation and individualize their medical management. The RIMGC was thrilled to rise to the challenge.

Since a dysregulated immune system can affect any organ, diagnosis and management of these conditions demand the careful attention of many subspecialties, according to Edward Behrens, MD, Chief, Division of Rheumatology, and a founder of the Immune Dysregulation Program.

"The clinical presentations of immune dysregulation cut across the spectrum of medical subspecialties, requiring more knowledge than any one clinician could ever hope to deal with," Behrens says. "At the same time, the ever-increasing array of targeted immune suppressing and modulating drugs available means that with the right knowledge, dramatic improvements in outcomes are possible."

Recognizing the challenges and rewards in diagnosing and treating such complex conditions, the new program brings together subspecialists that span virtually every organ system, each with expertise in immune function. The team is poised to diagnose known immune syndromes and discover new syndromes where traditional diagnostic techniques have failed.

The Immune Dysregulation Program brings together CHOP specialists from: Blood and Marrow Transplant Program, divisions of Hematology, Infectious Diseases, Rheumatology, Oncology/Cancer Center, Global Patient Services, hemophagocytic lymphohistiocytosis (HLH) treatment team, immunology laboratory, Immunology Program and the Roberts IMGC.

RIMGC'S COLLABORATION WITH DGD PRODUCES NEW TESTS, COST SAVINGS FOR FAMILIES

The RIMGC works with the Division of Genomic Diagnostics (DGD) to augment its genetic test offerings. Together, the RIMGC and DGD continue to work with genetic champions from across the institution. Such collaborative efforts are essential to the development of new tests in specialized areas of medicine.

For example, the DGD has expanded its cancer predisposition testing to include targeted TP53 testing for Li-Fraumeni syndrome (LFS) and a Fanconi anemia (FA) FISH panel. Exome-based testing has also been expanded to include options for mitogenome sequencing for patients with complex phenotypes requiring both exome and mitochondrial testing and exome reanalysis, allowing for the diagnosis of patients with an evolving clinical presentation without repeating time consuming and costly sequencing steps.

One particularly fortified effort the last year was working with the Immune Dysregulation Program. The DGD worked with the program to design a rapid next generation sequencing panel for hemophagocytic lymphohistiocytosis (HLH). This will allow for expedited diagnosis of patients with HLH, a life-threatening condition. Rapid and accurate diagnosis will guide management, for example bone marrow transplants, a potentially life-saving intervention. With a two-week turnaround time, this will be a significant improvement to currently available commercial testing.

The DGD is also working with the Immune Dysregulation Program to develop an exome-based gene panel. This test will not only aid in diagnostic sensitivity and specificity, but will serve as an important tool in identifying candidate genes, which can then be further explored by researchers.

The DGD continues to work with multiple divisions across CHOP to provide the best diagnostic options for our patients. Next year, the DGD will continue to expand its mitochondrial testing and cancer testing with development of paired tumor/normal analysis for solid tumors along with transcriptome sequencing. ■

By leveraging genetic information with functional testing to characterize immune syndromes, the team pushes the diagnostic process and treatment to the cutting edge of science. The team is dedicated to finding answers for patients struggling with symptoms related to immune dysregulation, with hopes of improving their lives through accurate diagnosis and individualized, targeted therapeutic approaches.

"The Immune Dysregulation Program at CHOP exemplifies a shared vision of the future of genomic medicine in the context of the diagnosis and treatment of patients with immune dysregulation," explains Christopher Gray, MS, LCGC, genetic counselor with the Roberts IMGC and the Immune Dysregulation Program.

"The clinic's architecture brings together multiple specialists from across CHOP, all working together in real time to effectively diagnose, treat and counsel our patients and families. The Roberts IMGC is excited to continue to play an important role by facilitating genetic testing and genetic counseling."

Since the program's inaugural clinic in October 2018, the team has already identified genetic diagnoses of immune dysfunction for several patients coming from near and far, directly resulting in changes to their medical management. The program looks forward to continuing to help patients and families in search of answers.

For patients who would benefit from an evaluation with the Immune Dysregulation Program, external referring clinicians can call the Immune Dysregulation Program at 215-590-6706. CHOP clinicians can place a ***Consult to Immune Dysregulation Program*** *order in Epic.* ■

PARTNERSHIPS WITH DIVISIONS ENHANCE CLINICAL PROGRAMS ACROSS CHOP

The RIMGC clinical care mission is the cornerstone of our program. With our expansion over the last five years, we have formed a Clinical Core within our Center, led by Cara Skraban, MD.

It is integral to our mission to facilitate access to genetic testing across the vast pediatric specialties at CHOP. One way we have ensured this is to enable RIMGC's genetic counselors to develop subspecialty expertise in unique areas by working with divisions and programs that do not already have a full-time genetic counselor.

Emma Bedoukian, MS, LCGC, specializes in ophthalmic genetics. She works directly with Bart Leroy, MD, PhD, and Tomas Aleman, MD, in Ophthalmology, providing a broad array of genetic counseling services, including coordinating the first Food and Drug Administration-approved gene therapy treatment for eligible patients affected with *RPE65*- related retinal dystrophy. Other genetic testing for Ophthalmology patients' is facilitated through the RIMGC, and the patients are seen by Bedoukian and a RIMGC physician geneticist.

Bedoukian and Christopher Gray, MS, LCGC, have developed expertise in the genetics of hearing loss. The Genetics of Hearing Loss Clinic was the first subspecialty clinic developed by the RIMGC. It was started by Ian Krantz, MD, based on his long-standing clinical and research interests and work with this patient population. Patients referred from Audiology and Otolaryngology are evaluated for genetic etiologies of nonsyndromic and syndromic hearing loss. Care for these patients has recently shifted with the recommendation of a "genetics first" approach after the clinical diagnosis of hearing loss, as establishing a specific genetic etiology guides the life-long clinical management for these children.

Jacqueline Leonard, MS, LCGC, specializes in the genetic basis of various endocrine disorders, with a particular interest in differences of sex development patients. This subspecialty clinic, led by Louisa Pyle, MD, PhD, was established two years ago and continues to grow. The team evaluates, coordinates care and provides genetic testing services while working together with the divisions of Urology and Endocrinology.

Gray joined the Immune Dysregulation Program that started in fall 2018 as a CHOP-supported Frontier Program *(see related story on Page 22)*.

We are working to develop relationships with all divisions and programs in order to enhance access to genetic and genomic testing at CHOP and improve patient experience during this process. ■

It is integral to our mission to facilitate access to genetic testing across the vast pediatric specialties at CHOP.

Honorary chairman former Eagle's Coach Dick Vermeil at last year's Concours d'Elegance

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The children, adults and families cared for by the Roberts IMGC are counting on you to support and further our mission with the common goal of providing help and hope to individuals with complex genetic diagnoses. Funds generated from the endowment support costs for patient care, family programs, personnel, education and outreach, as well as translational research.

Thanks to our many generous families and donors who continue to support our work. This past year, there have been many generous efforts. James and his family hosted a golf tournament, Julia's mother chose RIMGC as a charity for their family's holiday event, and Oliver's family honored his grandfather's memory with donations to RIMGC, to name a few.

In addition, the Roberts IMGC has been supported by outside organizations. For example, Cool Cars for Kids (CCfK) is a nonprofit organization founded in 2016 that exists to increase awareness of the issues faced by children and families affected by rare developmental disorders and to raise funds to support research into better treatments.

CCfK hosts an annual event, the Philadelphia Concours d'Elegance, which is a classic and antique car show at the Simeone Foundation Automotive Museum in Philadelphia. This two-day event, that falls over Father's Day weekend, consists of an evening preview gala with dinner and dancing followed by a day-long showcase of numerous American and European classic automobiles, motorcycles and racecars. Our RIMGC's Rare Diagnoses Program is the main beneficiary of this event. Over the past two years, CCfK has raised $75,000 for the Center. On June 14 and 15, 2019, CCfK is hosting its third annual Concours d'Elegance. This year's event celebrates the Bentley centenary as its featured marque, and honorary chairman former Eagle's Coach Dick Vermeil will be in attendance.

It is through your generous support and donations, large and small, that we are able to not only develop new initiatives within the RIMGC but also expand our current activities in support of the Center's mission of providing specialized clinical care and advancing medical research. For more information about supporting the RIMGC, please visit **chop.edu/giving** to make an online donation or contact Shanna Hocking at 267-426-6483 or **hockings1@email.chop.edu.** ■

Sarah Hubley, 13,
a patient of the RIMGC.

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