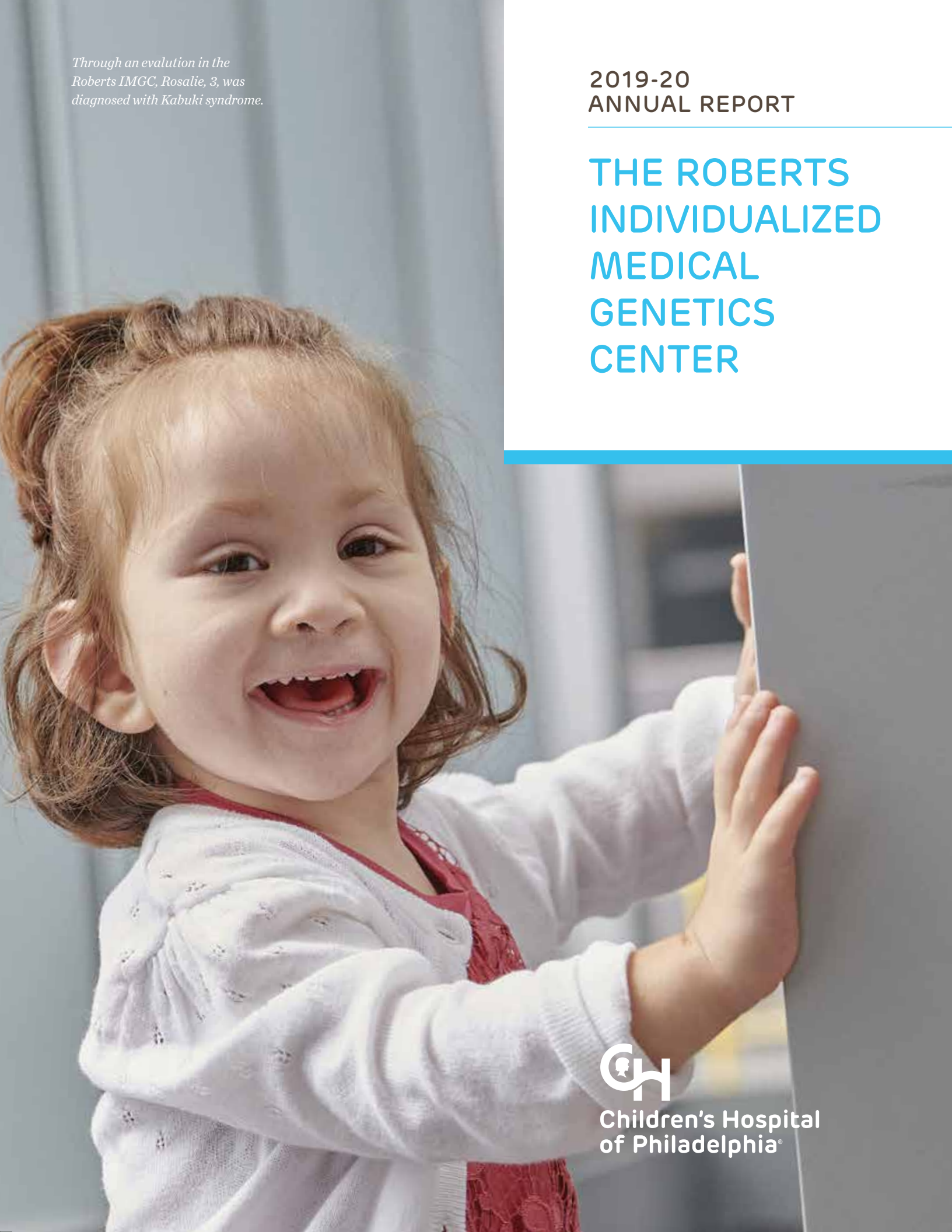


Through an evalution in the Roberts IMGC, Rosalie, 3, was diagnosed with Kabuki syndrome.

2019-20
ANNUAL REPORT

THE ROBERTS INDIVIDUALIZED MEDICAL GENETICS CENTER

Children's Hospital of Philadelphia®

LETTER FROM THE DIRECTORS

This has been quite a year — filled with both exciting accomplishments and exceptional challenges. Growing and expanding the work of the Roberts Individualized Medical Genetics Center (RIMGC) in response to our mission — while rising to the medical and humanitarian challenges posed by the COVID-19 pandemic — have truly demonstrated the depth, dedication and ingenuity of our faculty and staff. Working with our talented physicians, genetic counselors, investigators, administrative and research staff, as well as trainees and students, has been truly inspirational. This admiration goes well beyond the RIMGC. It extends not only to the broader Children's Hospital of Philadelphia, University of Pennsylvania and healthcare communities, but also to the children and families we treat and care for in their response to the myriad challenges the pandemic has presented.

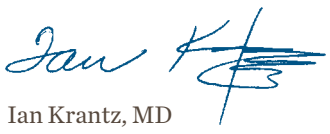
The RIMGC has been at the forefront of developing programs to integrate telemedicine into the routine care of our families. We initially started video visits several years ago to provide increased access to genomic medicine to families in a timely and convenient manner, as well as allowing face-to-face interactions for families unable to come to CHOP in person, and it proved prescient in the face of COVID-19-mandated stay-home orders. The RIMGC was able to nimbly scale up and transition almost all noncritical patient visits and interactions to telemedicine visits. The RIMGC telemedicine efforts are highlighted in more detail in this report.

We are also incredibly proud of the way the RIMGC was able to leverage its research network and pipeline to participate and contribute to a global study documenting the impact and clinical implications of COVID-19. We hope to continue to leverage that data to further understand the genomic aspects that contribute to some of the more severe clinical presentations in children infected with the novel coronavirus.

While the pandemic has affected almost all aspects of our lives — clinically, academically and personally — the RIMGC achieved additional milestones and accomplishments of which we are extremely proud.

Now with more than 3,500 total patient visits, the RIMGC has become an established resource for CHOP clinicians across all divisions and programs and a destination for families from the region, nation and around the world. We had a seminal paper published in the leading journal *Pediatrics* highlighting our experience over the past five years and outlining a roadmap for other institutions to develop and provide similar services to their pediatric populations. In addition to expanding established clinics and services, we were excited to initiate new services, including a Genomics of Vestibular and Balance Disorders Clinic, a Kabuki Syndrome Clinic and a partnership with the Center for Fetal Diagnosis and Treatment to study the genomics of congenital of diaphragmatic hernia. The RIMGC is working closely with the Division of Genomic Diagnostics in Pathology to develop a novel genome sequencing test that will revolutionize genomic diagnostics at CHOP. It will create a single platform with the potential to identify copy number variants, complex chromosomal rearrangements, trinucleotide repeat expansions and sequence alterations in a single test that can be performed more rapidly than our current testing allows.

This report provides a glimpse into our past year and highlights the diversity of efforts and the ability of our phenomenal team to overcome adversity and still push the boundaries of clinical care and discovery. It is a story of collegiality, perseverance and innovation we are proud to be a part of. We are humbled by the efforts of our entire team and the broader CHOP family, which has given us the support and encouragement to thrive.



Ian Krantz, MD
Co-director

Livija Medne, MS, CGC
Co-director

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 phenotypic and genomic information into the diagnostic and research efforts at CHOP.

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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

Brandon Calderon, MBA
Administrative director

Batsal Devkota, PhD
Bioinformatics scientist

Sierra Fortunato, BS
Clinical and research coordinator

Melissa Gilbert, PhD
Manager, Translational Research

Christopher Gray, MS, LCGC
Genetic counselor

Tiffiney Hartman, MS, LCGC, PhD
Genetic counselor

Kosuke Izumi, MD, PhD
Attending physician, scientist

Maninder Kaur, MS
Research laboratory manager

Jacqueline Leonard, MSc, MS, LCGC
Genetic counselor

Deborah McEldrew, BS
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Jasmine Montgomery
Office administrator

Louisa Pyle, MD, PhD
Attending physician, scientist

Sarah Raible, MS, LCGC
Genetic counselor

Emma Schindler, BA
Research technician

Cara Skraban, MD
Attending physician

Jamila Weatherly, MS
Clinical research assistant

Tyrah Williams
Office coordinator

Ellen Xu, MS, LCGC
Genetic counselor

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.*

TRAINING THE NEXT GENERATION

The RIMGC's educational goals and activities have persisted throughout the 2019-2020 year. We have supervised three genetic counseling students, two laboratory fellows and six Genetics residents for their rotations.

Cara Skraban, MD, as Associate Program Director for the Medical Genetics residency training program, has continued her leadership role in training residents and fellows. As part of this training, the RIMGC has formalized a continuity clinic. Skraban is the supervising attending for fourth-year resident Ian Campbell, MD. This aims to fulfill the training requirement of longitudinal outpatient experience in a continuity clinic. In the clinic, residents serve as primary care providers for children with genetic and metabolic disorders. It fosters maturation of clinical judgment by involving residents in medical decision-making surrounding testing, result disclosure and patient management.

RIMGC genetic counselors also supervise genetic counseling students in clinic and welcome observers who may be interested in the genetic counseling profession. Beyond clinical supervision, RIMGC members have helped with multiple thesis projects for Arcadia University and University of Pennsylvania masters of science in genetic counseling (MSGC) students.

Kaitlin Smith was the 2019 recipient of the Center for CdLS and Related Diagnoses Marie Barr Genetic Counseling Award. The mission of this 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. Sarah Raible, MS, LCGC, Ian Krantz, MD, and Laura Conway, PhD, advised Smith's project "Not alone anymore: Parent and sibling experiences finding support with an ultra-rare diagnosis."

Other advising roles included:

- Raible, Krantz, Tiffiney Hartman, PhD, and Laura Conway, PhD, advised Arcadia student Briana Feirstein in her project "Parental perceptions of genetic testing for hearing loss: Value and impact." This project is ongoing and transitioning to a UPenn MSGC student for the upcoming academic year.
- Christopher Gray, MS, served on the committee for Emory University student Smriti Singh's project "Family perceptions of genetic counseling services in the evaluation of pediatric immunodeficiencies."
- Jacqueline Leonard, MS, served on the committee for two students at the University of South Carolina School of Medicine: Christine Maccia's "Experiences with and knowledge of genetics in families affected by congenital adrenal hyperplasia: The parent perspective" and Sarah Burnzynski's "Parental questions about sex chromosome aneuploidies regarding sex, gender, and sexual orientation in a prenatal setting."
- The RIMGC team has also been involved with Arcadia and UPMSGC through course direction, committee involvement and lectureships.

RIMGC remained dedicated to education and clinical training during the COVID19 pandemic. Many courses and lectures were transitioned to online platforms. In addition, new educational opportunities were created, like weekly case conferences. By June, we were able to successfully incorporate genetic counseling students, medical students, residents, and fellows into the telemedicine platform.

The invited speaker, Ken Jones, MD, for the Third Annual Clinical Genomics Lectureship as part of CHOP Pediatric Grand Rounds series, was rescheduled to Oct. 14, 2020. ■

PATIENT SPOTLIGHT

MEET ATHAN

GENETIC TESTING BROUGHT ANSWERS, TARGETED TREATMENT AND NOW, HEALTH

When Athan was an infant, his mother would carry him to the window of the Newborn/Infant Intensive Care Unit (N/IICU) at Children's Hospital of Philadelphia and show him the view. "I would tell him that one day we would take him outside where he can touch the trees," Kristen remembers.

But the first-time mom didn't know when, or if, that would ever happen. Athan was gravely ill when he arrived at CHOP at 2 days old in February 2019, and doctors were searching for an answer.

A very sick baby

While Kristen's pregnancy was typical, her labor wasn't. The baby's heart rate dropped with each contraction and when Athan was born, his pale skin had a bluish tinge. His blood sugar tested abnormally low, even after breastfeeding, so the newborn was transferred to the central New Jersey hospital's neonatal intensive care unit for monitoring. Late that night, a doctor woke Kristen and her husband, John. Their baby's heel wouldn't stop bleeding when they drew blood to test his sugar level. Athan would need a blood platelet transfusion. "It was stressful. It was not what we planned for at all," Kristen says.

The next morning, Athan was rushed by ambulance to CHOP after an ultrasound showed a blood clot in his liver. Tests there ruled out a virus or infection. Specialists across the hospital were brought in, but each diagnostic test result came back inconclusive. "They reached out to every department possible. They kept testing for rarer and rarer things," Kristen says.

Over the next two weeks, she and John watched helplessly as their son's condition deteriorated. Athan had fevers, diarrhea, rectal bleeding, rashes and vomiting. He couldn't tolerate food, so was fed intravenously. He needed a machine to breathe. Despite many platelet and red blood cell transfusions — 36 in all — Athan's platelet level dropped to 3 per microliter of blood, putting him at tremendous risk of bleeding. The normal range for blood platelets is 150,000 to 450,000.

An autoimmune disorder is suspected

Edward Behrens, MD, Chief, Division of Rheumatology at CHOP, was called in. Dr. Behrens heads up the Immune Dysregulation Program, which sees patients with complex immune disorders that are difficult to diagnose. It appeared that Athan had an autoimmune disorder, in which the immune system mistakenly attacks the body.

Because genetic mutations are at the root of many immune disorders, the program works closely with the Roberts Individualized Medical Genetics Center (RIMGC) to facilitate state-of-the-art testing that might help with treatment, particularly with rare conditions.

"If you can find the gene that's causing the patient's problem, there's very likely to be a specific, hand-tailored drug that can treat that patient's condition," Dr. Behrens says. Otherwise, doctors are forced to rely on a "sledgehammer" approach, tamping down the symptoms with steroids and immune modulating drugs.

In Athan's case, Dr. Behrens had an idea of what was behind the infant's overactive immune system. He thought the Roberts IMGC could confirm his suspicion.

Familiar symptoms

Five years earlier Dr. Behrens had teamed up with the RIMGC to diagnose a baby girl with a mutation in the gene *NLRC4*, which regulates the body's inflammatory response to foreign invaders. The gene error, which had been discovered just a year earlier, puts the immune system into overdrive, attacking the organs and causing overwhelming inflammation. The RIMGC facilitated exome sequencing, a comprehensive test that reads the genetic code of about 20,000 genes, for the infant. The results showed she had the mutation.

"Finding the mutations that are meaningful is a collaborative effort between us, the diagnostic lab and clinicians describing the symptoms," says Livija Medne, MS, LCGC, co-director of the RIMGC and a senior genetic counselor.

Hopeful, Kristen and John sat down in a conference room with Medne and Cara Skraban, MD, an attending physician and RIMGC geneticist. They recommended rapid exome sequencing, a test that returns results in roughly two weeks. The couple agreed to proceed. Blood samples were taken from Athan as well as both parents.

Nine days later, they had their results. Dr. Behrens was correct: Athan had a mutation in the *NLRC4* gene. It occurred spontaneously; he did not inherit it from either parent.

A targeted treatment

After a patient of his was diagnosed with the *NLRC4* mutation in 2015, Dr. Behrens located a drug that blocks the molecules responsible for the overactive inflammatory response. He arranged for compassionate use permission to treat the baby girl with the drug. This is a special dispensation to use a medication when it has not yet been approved by the FDA. She responded so well that Dr. Behrens set up a clinical trial at CHOP.

Athan's parents enrolled their son in the clinical trial. Six days after his first treatment with the drug, Athan was breathing on his own. A week after that, he pulled out his feeding tube. "We would sit there every morning with the doctors going over his numbers and everything was improving," Kristen says. "His skin color started getting better, he was becoming more active, he started smiling. We got his first smile on camera."

Without the RIMGC on site to facilitate the rapid exome sequencing that identified the gene mutation responsible for Athan's illness, doctors would still be searching for answers and Athan would still be very sick. "Athan was the youngest patient ever to be enrolled in the clinical trial. And the reason why is because the Roberts IMGC allowed us to make this diagnosis so quickly," Dr. Behrens says. "This is a profound example of how knowing the genetics makes a big difference."

A new beginning

Athan was 3 months old when he was strong enough to go home to New Jersey. Spring was promising a new beginning and his parents couldn't wait to show their baby boy the trees up close.

"The first thing we did was put him in a stroller and take him to the park," Kristen says.

Today, Athan is a happy 18-month-old who wants to walk everywhere, says "momma" and "yum," and is "100% boy," according to his mom. Every other day, she gives him injections of the drug that put him on the road to good health — a treatment that wouldn't have been possible without the early diagnosis available through the RIMGC.

"In this case, the power of the exome sequencing was truly life altering," Medne says. "Having an answer in nine days is really a technological breakthrough." ■

Genetic testing revealed the cause of and potential treatment for Athan's illness.

PIONEERING RIMGC OUTLINES FRAMEWORK FOR CENTRALIZED APPROACH TO GENETIC AND GENOMIC TESTING

The Roberts IMGC launched in 2014 as a first-of-its-kind system to help pediatric patients and their families navigate the complex process of genetic and genomic testing and standardize how genetic testing is performed across different clinical disciplines.

In a special report published in February in the journal *Pediatrics*, RIMGC researchers, physicians, and genetic and financial counselors describe the success of the model, their plans to build on that success for the future, and the important lessons learned from their first four years in operation. As a trailblazer in the development of a center dedicated to genetic and genomic testing, the team also provides a framework for making such a center work, as other hospital systems around the country look to replicate the first-of-its kind model.

Whole genome sequencing has the potential to revolutionize the practice of medicine by allowing for the development of highly-targeted therapies and more nuanced treatment strategies. The practice will also accelerate research into difficult-to-treat conditions and help clinicians diagnose new diseases that would have otherwise remained a mystery. As the technology becomes more widely available, the cost to patients and the healthcare system has decreased significantly while demand has broadened across all specialties.

Despite these benefits, genome sequencing is relatively new to the field of medicine, and for all the issues the technology solves, new issues have arisen, such as developing the infrastructure to support this growing field, working with health insurance companies to impart its necessity, and educating families about the importance of this information to their health.

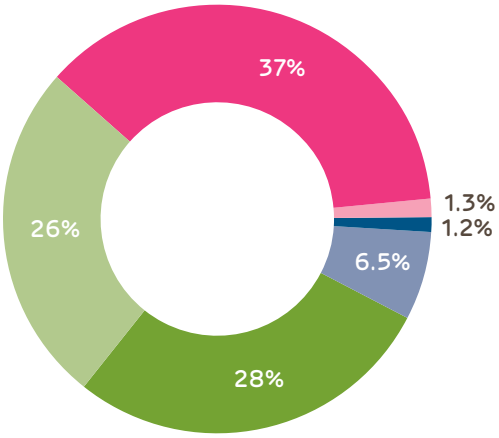
"We saw a need to standardize our hospital's approach to genetic and genomic testing, and we believe we have succeeded tremendously in this endeavor, especially since no other hospital had attempted a model like the one we established prior to the founding of the RIMGC," says Ian Krantz, MD, Co-director of the RIMGC and Director of the Center for Cornelia de Lange Syndrome and Related Diagnoses, and senior author of the report.

"As this report outlines, even in a relatively short time, our center has grown in response to clinical and research demands," Krantz adds. "We thought it was important to share what we've learned as more hospitals look to the model we've created to establish similar centers."

During its first four years, of the 1,172 genomic (exome) sequencing tests ordered by RIMGC clinicians, 26% yielded a positive diagnosis, 37% yielded an uncertain diagnosis and 28% yielded a negative diagnosis, while 6.5% yielded a diagnosis for a candidate gene — meaning a novel gene not previously associated with a known disease or diagnosis — and 1.2% yielded a dual diagnosis, meaning that two genes were identified as being responsible for symptoms.

To illustrate the complexity of the cases reviewed by the RIMCG, the report includes five examples of patients with medical conditions that were properly diagnosed thanks to the resources provided by the team. These examples highlight a small number of the cases seen at the center, including:

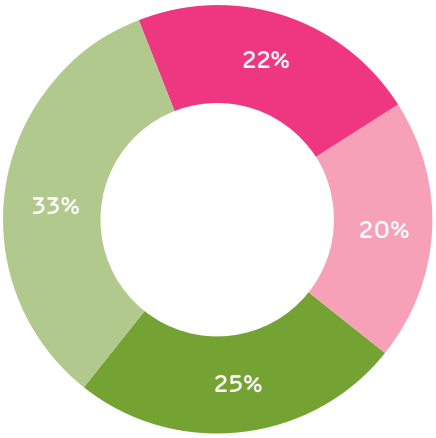
- An infant experiencing severe cardiac issues who received a life-saving cardiac transplant because exome sequencing results revealed two genetic mutations.
- A 34-month-old who had previously tested negative for cystic fibrosis but exhibited symptoms and was revealed to have a gene that increased the risk of the disease thanks to more robust and precise genetic testing facilitated by the RIMGC.
- An 11-year-old who received the diagnosis of Brown-Vialetto-Van Leare syndrome, a progressive hearing loss disorder that can lead to other issues such as vision loss, severe neurologic impairment and early death, which led to treatment that stopped the condition's progression.



EXOME SEQUENCING 2014-2019

1,172 total

- uncertain diagnosis
- other
- dual diagnosis
- candidate gene
- negative diagnosis
- positive diagnosis



REFERRED PATIENTS NOT SEEN 2014-2019

994 total

- unreachable parents
- patient/parents decline consult
- other reason
- insurance denials

However, the report highlights hurdles that still exist, such as the amount of time spent working with insurance companies to justify genetic testing and a lack of understanding among parents and patients. For example, of the 3,483 referrals to the RIMGC, 994 were not seen for a variety of reasons, including insurance denials (324), unreachable parents (217), or patient or parents declining consultation (196).

Since its launch, the RIMGC has more than quadrupled its full-time staff, and consistent assessment of the center's clinical load has led to an expansion of services. In spite of this rapid growth, the team says the RIMGC presents a cost-saving model by centralizing these services and avoiding dozens of individual clinical departments having to hire their own genetic counselors and specialized administrative and medical support staff.

"Since the center opened, we have seen how the demand for genetic and genomic services will require a different approach beyond what traditional divisions and departments specializing in this field are able to provide," says Livija Medne, MS, LCGC, Roberts IMGC Co-director and co-first author of the paper. "Our experience shows how a model like this allows for those growing needs to be properly met and sufficiently supported."

"We are deeply thankful to the Roberts family, whose generous support has pioneered the cutting-edge work we are doing in the RIMGC," Krantz says. "Their philanthropic commitment has enabled us to help thousands of patients and establish diagnoses of rare diseases that may have otherwise been missed, in turn allowing for improved management and treatment. Collectively, this experience will play a pivotal role in advancing our understanding of the impact that genetic and genomic testing will have in the years to come." ■

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COLLABORATIVE RESEARCH ENROLLMENT REDUCES REDUNDANCY, PROMOTES EFFICIENCY

One goal of the RIMGC is to enroll patients interested in participating in research to promote the integration of phenotypic (observable characteristics) and genomic information into research efforts at CHOP. To maximize collaboration and discovery, the RIMGC has created a shared resource and infrastructure for all CHOP researchers. This includes a database of de-identified information (names and personal information of patients removed) with a searchable portal where CHOP investigators can identify cohorts of interest.

In discussions about sharing this resource with departments across CHOP, it became apparent there are multiple teams with similar short- and long-term goals of enrolling patients into research studies to facilitate sharing of de-identified genomic, phenotypic and biosample data. Unfortunately, this means that often families are approached to enroll in more than one research study that have similar aims, which is burdensome for families and redundant for research.

In March, the RIMGC, in collaboration with cardiac surgeon William Gaynor, MD, and his team, hosted a mini symposium with multiple research groups at CHOP. The goal: design a study aimed at sharing de-identified phenotypic and genomic data using IRB-approved language to broadly consent patients to minimize the burden on the patients and their families and maximize the data available for sharing with all investigators at CHOP.

Shortly thereafter, RIMGC began participating in a research study that may act as a model for future enrollment and consent processes that utilize IRB-approved language for broad sharing of de-identified data in a collaboration with endocrinologist Adda Grimberg, MD. The study, "Uncovering the genetic basis of growth disorders," aims to study the genetic causes of abnormal growth in children where an underlying cause has not been identified by extensive and expensive clinical and biochemical evaluations.

Investigators will use detailed phenotype, genotype and biosample data to explore the underlying mechanisms leading to growth disorders in children and their families. As many of these genetic causes might be quite rare, sharing of de-identified information with investigators at CHOP and beyond — specifically with Boston Children's Hospital, Cincinnati Children's Hospital Medical Center and Children's National Medical Center in Washington, D.C. The highly collaborative research initiative is anticipated to have a higher yield than any smaller study performed alone at any individual research center.

We hope the success of this study will serve as a launching point for future collaborative studies between research teams with similar goals. CHOP research staff can access the searchable database at **rimgc.research.chop.edu/rimgc/public**. ■

STUDY AIMS TO UNCOVER GENETIC LINK FOR CONGENITAL DIAPHRAGMATIC HERNIA

In February 2019, the Fore Hadley Foundation provided a $55,000 grant in support of a congenital diaphragmatic hernia (CDH) study being performed by the RIMGC. This project is a collaboration between the teams of Ian Krantz, MD, and surgeon William Peranteau, MD.

CDH occurs when the diaphragm muscle — the muscle that separates the chest from the abdomen — fails to close during prenatal development, and the abdominal organs (stomach, intestines and/or liver) move up into the chest through this hole. When the abdominal organs are in the chest, there is limited room for the lungs to grow. This prevents the lungs from developing normally, resulting in pulmonary hypoplasia (or underdeveloped lungs). This can cause reduced blood flow to the lungs and pulmonary hypertension (high blood pressure in the pulmonary circulation), as well as asthma, gastrointestinal reflux, feeding disorders and developmental delays.

CDH is a relatively common birth defect, occurring in approximately 1 in 2,500 live births, yet our current understanding of its causes and treatment options are disproportionately lacking. Despite many lines of evidence suggesting a genetic etiology for CDH, genetic causes have only been identified in approximately 30% of cases.

Currently, CHOP's Center for Fetal Diagnosis and Treatment (CFDT) treats the largest number of CDH patients of any U.S. hospital. Holly Hedrick, MD, who heads the CDH Frontier Program, and her team are close collaborators on this project. This puts our team in an optimal position to enroll affected families and collect samples on a sizable cohort of patients. Our goal is to enroll families to establish and expand a clinical database and sample biorepository of babies with CDH. The research team contacts referred families and enrolls those interested in research before the infant undergoes CDH repair by the surgical team. This gives us the unique opportunity to evaluate the diaphragm, skin and blood of these patients without disrupting their routine clinical care.

K. Taylor Wild, MD, a fellow physician in Neonatology and Human Genetics, is using these resources to try to identify the genetic differences that cause CDH. She has designated time to pursue this research and spearhead the direction of data analysis with hope of improved diagnostics, counseling and management for families with a diagnosis of CDH.

Looking forward, we anticipate that everyone's contribution will prove to be invaluable as we continue to piece together the genetic causes of CDH, provide much needed answers to families, and work toward developing future risk assessment and therapies for this population. *(Meet a family enrolled in the trial on Page 12.)* ■

Jamila Weatherly, MS,

has been a clinical research coordinator for the RIMGC since completing a Master of Biomedical Sciences at Geisinger Commonwealth School of Medicine in Scranton, Pa., in October 2017. She works alongside lab personnel and clinical team members to enroll patients into the many different research opportunities available through the RIMGC. Her role includes enrolling referred patients, coordinating sample collection, database management and overseeing many administrative tasks for multiple research projects. Weatherly's project management responsibilities include the RIMGC Biorepository, the NICUSeq Illumina Collaboration and the CDH collaboration with Neonatology.

"Being at CHOP, working with everyone at RIMGC for the last three years, has been quite the ride," says Weatherly, who will leave CHOP in the fall to start medical school. "Working under Dr. Krantz and Livija Medne's leadership proved to be an exciting, innovative experience combining both clinical and research endeavors that are essential to modern patient care. I'll undoubtedly be taking these memories and experiences with me in my next step to become a physician."

Batsal Devkota, PhD,

was a bioinformatics scientist at Vela Diagnostics, where he analyzed and interpreted oncology and viral next generation sequencing (NGS) data and developed targeted and whole exome sequencing diagnostic panels, prior to joining CHOP. Earlier in his career, he worked at Reproductive Medicine Associates of New Jersey and RCSB Protein Databank at Rutgers, where he used a variety of different applications and pipelines. Devkota received his PhD in computational biology from Georgia Tech and his BS in biochemistry and molecular biology from University of New Hampshire.

Devkota joined CHOP and the Department of Biomedical and Health Informatics genome analysis group in 2014 as a bioinformatics scientist and has been working in the Krantz Lab since May 2015. He was involved with the Pediatric Genetic Sequencing Project (PediSeq). PediSeq was part of the Clinical Sequencing Exploratory Research consortium, a multi-institutional project created to bring genomic sequencing data into the clinical setting.

Devkota has been involved with various projects in the RIMGC. Soon, he will analyze whole genome sequencing data from a cohort of individuals with Cornelia de Lange syndrome, a project funded by the Gabriella Miller Kids First Program. The project will sequence and analyze samples do not have a known molecular diagnosis. Devkota is also a bioinformatics lead representing CHOP in the Genomics Research Information Commons, a multi-institutional initiative created to share de-identified genotype, phenotype and biobank data for research.

Sierra Fortunato, BS,

a Bloomsburg University biology major, has held dual roles at the RIMGC for almost three years. One key role is a clinical research coordinator (CRC), providing interested patients and families opportunities to enroll in studies of the genetic causes of diseases and conditions. Whether in the inpatient or outpatient setting, she is readily available to assist physicians or genetic counselors with their research needs. She coordinates samples, retrieves samples, and updates and manages the database with patient information, ensuring it adheres to CHOP Institutional Review Board guidelines.

Fortunato also serves as a clinic coordinator for the RIMGC's Cornelia de Lange Syndrome and Related Diagnoses Center. Working closely with Genetics, GI, Physical Therapy and Child Development, she feels it has been eye opening to see how the center provides a medical home to families and helps improve so many lives. "It's been an incredible experience, and I have been extremely touched by countless moments during my time here," she says.

Fortunato also works closely with Ian Krantz, MD, and Sarah Raible, MS, LCGC, in the nonprofit Cool Cars for Kids, which strives to increase awareness of issues faced by families of children born with rare genetic diagnoses and raise funds for patient care and research. "As progress in genetics advances more and more than one could have ever imagined, I'm excited to be learning and growing as part of a great team of individuals here at the RIMGC," she says.

SHARING OUR EXPERTISE

Selected Publications from More Than 50 Published Articles

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PATIENT SPOTLIGHT

MEET MICHAEL

BY PARTICIPATING IN RESEARCH, FAMILY IS ADVANCING CARE

When Christina and Michael Nilson found out in the 20th week of pregnancy that their baby had congenital diaphragmatic hernia (CDH), extensive research and evaluations at three hospitals led them to put their baby's future in the capable hands of CHOP's Center for Fetal Diagnosis and Treatment (CFDT).

At CHOP, they found not only exceptional care, but opportunities to help advance treatment of CDH by participating in research.

With CDH, a hole in the baby's diaphragm muscle fails to close during development. That allows the stomach, liver, spleen and intestines to move up through the hole and into the baby's chest, displacing and interfering with the growth of the developing heart and lungs.

When the Nilsons came to CHOP for their first visit, they learned all about that — and more.

Confident in CHOP's care

"We came away from our first visit feeling that our son would be well taken care of at CHOP," Christina says. "We had a full day of testing and then met with the OB, surgeon, social worker and nurse. They laid it all out. We felt very confident in their multidisciplinary program."

Michael Jr. was born in the Garbose Family Special Delivery Unit, the world's first maternity ward in a pediatric hospital especially for healthy mothers delivering babies with known birth anomalies. He had surgery to repair the CDH at 3½ weeks old, and spent a total of 70 days in the Harriet and Ronald Lassin Newborn/Infant Intensive Care Unit and nine days in a pediatric medical/surgical unit before being discharged.

"He was doing so well, he didn't need to be on oxygen when we came home," Christina says. "He's our warrior."

During their time at CHOP, the family leapt at opportunities to help researchers learn more about what might cause CDH and how to best manage the condition. "We liked how research is intertwined with what they're doing on the floor at CHOP," Christina says. "We liked being a part of that."

The family enrolled Michael Jr. in a procedural study that was evaluating if outcomes improve when a baby's umbilical cord is cut after the newborn is intubated versus the current practice of cutting the cord first.

Search for genetic causes of CDH

"When they approached us to see if we would like to participate in genetic research on CDH, of course we said yes. We're very interested in finding out the genetics behind CDH — to help other families in the future and to further research in general," Michael Sr. says. "We want to help out as much as possible."

For the CDH gene study, a joint project of the RIMGC and the CFDT, both parents and Michael Jr. had blood samples taken. Initial analysis did not match the Nilsons' genomic sequence data with any genetic mutations known to be causative of CDH, but it did identify a novel variant in the *STAG2* gene.

STAG2 has been associated with other more involved, rare syndromic genetic diagnoses, such as cohesinopathies and Cornelia de Lange syndrome, which Michael Jr. does not have. As *STAG2* is on the X chromosome, he inherited the variant from Christina, who is also unaffected by any of the genetic diagnoses associated with *STAG2*. The RIMGC also tested the Nilsons' older daughter, Mia, and Christina's parents for *STAG2*, but they do not have the variant.

RIMGC genetic counselors explained all of this to Christina and Michael Sr., what it means now and what it could mean for the future.

By participating in CDH genetic research, the family has added to the growing body of information on causes of CDH. Right now, it is unclear if there is an association between *STAG2* variants and isolated diaphragmatic hernia, but answers could inform family decisions in the future. If a definitive link is found, each future pregnancy would have a 50% chance of inheriting the same *STAG2* variant from Christina, and it would be more likely to affect boys as they have only one X chromosome (boys are "XY") whereas girls (who are "XX") have another *STAG2* gene that may be able to balance out the effects of this variant. When Michael Jr. is ready to have children, he will have a 50% chance to pass along the *STAG2* variant to any of his daughters.

"We know we can receive genetic counseling at CHOP for future pregnancies to explore the potential risk of having another child with CDH," Christina says. In the meantime, Michael Jr. will be followed by the RIMGC in an annual visit.

Followed by Pulmonary Hypoplasia Program

Since his discharge right before the 2018 holidays, Michael Jr. has successfully weaned off a nasogastric (NG) tube for feeding and transitioned to table food, managed acid reflux, and undergone a double inguinal hernia repair. He is still being monitored for a broncho-pulmonary sequestration, which is a piece of lung tissue that grows outside of the lungs.

Blood samples from all of the Nilsons — Michael Jr, Christina, Michael Sr. and Mia — are advancing research.

"Another thing I like about CHOP is that it's not, 'We fixed him and we're done.' There's the PHP (Pulmonary Hypoplasia Program) that follows Michael and will continue to follow him," Christina says.

A child with pulmonary hypoplasia has small, underdeveloped lungs that can affect not only breathing but also heart function, ability to feed, hearing and overall development. The PHP tracks and treats all those possible side effects.

Running, playing, singing

For now, the challenge is keeping up with an active 21-month-old. Michael Jr.'s walking has turned to running. He babbles all the time and screams "Let It Go" at the top of his lungs when Mia watches *Frozen*. He loves spending time with Dad, especially watching and "helping" with yard work and riding on the back of Michael Sr.'s bike.

"If you saw him now, you would never know what he's been through," Christina says. "We are so grateful that we chose CHOP and look forward to continuing our support of genetic research." ■

RARE DIAGNOSES PROGRAM DRAWS MORE PATIENTS

Kennedi, pictured with her mother Jasmine, was diagnosed with CdLS at age 3.

The Rare Diagnoses Program, led by Sarah Raible, MS, LCGC, was established within the Roberts IMGC in 2018 to meet the hospital's growing need to provide a medical and research home for children and adults with rare genetic and developmental diagnoses. With an increase in broad scale testing, more and more children are being diagnosed with new and rare diagnoses that require lifelong centralized care by an expert team of clinicians and researchers.

The Center for Cornelia de Lange Syndrome (CdLS) and Related Diagnoses, established at CHOP in 2009, was fully integrated into this program to provide core wraparound services for children with CdLS and expand the capabilities of the center's integrated clinical and research mission. This integration has allowed the center to expand its services to more families impacted by CdLS and other related diagnoses.

Building on the successful model established for individuals with CdLS, the Rare Diagnoses Program continues to grow to meet the increasing demand for clinical services broadening the scope of its clinical and basic science research mission. In response to such demand, this past year our program announced the establishment of a new multidisciplinary clinic for Kabuki syndrome *(see Page 16),* another rare complex developmental diagnosis.

As the Rare Diagnoses Program grows, we continue to provide clinical services to an ever-expanding group of children and their families through established multispecialty clinics, inpatient and outpatient consults, virtual consults, and attendance at regional and national family meetings and to support research into these diagnoses.

The Rare Diagnoses Program embraces the mission of the RIMGC to provide individualized care and to make genetic and genomic services accessible to all individuals and to the physicians who care for them. ■

CENTER FOR CdLS & RELATED DIAGNOSES: 'NOBODY DOES IT BETTER'

The Center for Cornelia de Lange Syndrome and Related Diagnoses exists to provide clinical care and to improve the lives of children and adults with Cornelia de Lange syndrome (CdLS) and related diagnoses. CdLS is a rare multisystem developmental diagnosis with variable features including small stature, global delays, distinct craniofacial features, behavioral abnormalities and major malformations in the cardiac, gastrointestinal, and musculoskeletal systems. There is a broad spectrum in CdLS, ranging from mild to severe.

Mutations in five different genes, *NIPBL*, *SMC1A*, *SMC3*, *HDAC8* and *RAD21*, have been associated with CdLS with additional genes, such as *AFF4*, *BRD4*, *ANKRD11* and others having been more recently associated with clinical manifestations that overlap CdLS. The center provides care to individuals and families with other related diagnoses including Pallister-Killian syndrome, CHOPS syndrome and Kleefstra syndrome (9q deletion syndrome). Though these are all distinct diagnoses, each requires similar multidisciplinary care as all manifest common clinical issues, such as growth and cognitive delays, as well as multisystem involvement.

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 are 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.

Following the Mossman family's visit with the clinic in late 2019, the father of Lindsay, an 8-year-old with Pallister-Killian syndrome, says, "Nobody does it better than this group. I'm blessed to have them in our lives as we embark on this journey and all of the associated changes in our lives."

Our team has striven to address not only the clinical needs of families, but also — in collaboration with family support groups — to support their psychosocial needs. Our research efforts continue to yield new insights into the clinical and basic science issues relevant to the children we care for and to support young investigators interested in building careers focused on rare genetic diagnoses.

Our research efforts are funded by the CdLS Center Endowed Funds at CHOP, the National Institutes of Health, the PKS Kids Foundation and Cool Cars for Kids Inc. ■

CdLS CONSULTING TEAM

In addition to the RIMGC team listed on Page 2, these physicians also treat Rare Diagnoses Program patients.

Richard S. Davidson, MD
Division of Orthopaedic Surgery

Jaime Eilbacher, PT, DPT, PCS
Department of Physical Therapy

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

Michelle Lambert, MD, MSTR
Division of Hematology

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

COMING SOON: DEDICATED KABUKI SYNDROME MULTIDISCIPLINARY CLINIC

Kabuki syndrome is a rare genetic condition characterized by specific facial features, developmental delay and slow growth. Other features include congenital heart disease, feeding difficulties, cleft lip or palate, low blood sugar (hypoglycemia), kidney differences, hearing loss and seizures.

Kabuki syndrome is often not diagnosed at birth due to the wide spectrum of associated symptoms and facial features that change over time. As such, many children with Kabuki syndrome remain undiagnosed until evaluated by a clinical geneticist or they undergo comprehensive genetic testing.

Early diagnosis, medical intervention and regular monitoring are key for patients with Kabuki syndrome for several reasons. Some children have weakened immune systems and require Immunology care to help fight off infections. Some children produce too much insulin, called hyperinsulinism, and require Endocrinology care to stabilize blood sugars. Many children have complex medical histories and three or more providers involved in their care.

KABUKI SYNDROME CLINIC CONSULTING TEAM

Kosuke Izumi, MD, PhD
Genetics

Alyssa Ritter, MS, LCGC
Genetics

Nina Sainath, MD
Gastroenterology

Amanda Ackermann, MD, PhD
Endocrinology

To be named
Nutrition

Neil Romberg, MD
Immunology

In fall 2019, geneticist Kosuke Izumi, MD, PhD, genetic counselor Alyssa Ritter, MS, LCGC, multiple subspecialists and the RIMGC recognized the need for coordinated, multidisciplinary care for patients with Kabuki syndrome. The Kabuki Syndrome Clinic, part of the Rare Diagnoses Program within the RIMGC, brings together CHOP specialists from Gastroenterology, Nutrition, Immunology, Endocrinology and Genetics through the RIMGC to provide coordinated care for patients with known or suspected Kabuki syndrome.

> “Taking advantage of our medical staff’s expertise, we aim to provide world-class care to children with Kabuki syndrome.

“Kabuki syndrome is a genetic diagnosis requiring comprehensive medical care from multiple medical specialists,” Izumi says. “We established a team of medical professionals dedicated to the care of individuals with Kabuki syndrome. Taking advantage of our medical staff’s expertise, we aim to provide world-class care to children with Kabuki syndrome.”

This soon-to-launch clinic aims to decrease the number of visits each family requires to Philadelphia, coordinate care between multiple specialties for more efficient treatment and support families in their rare diagnosis journey. We also want to further the medical community’s understanding of Kabuki syndrome and contribute to research efforts by collaborating with families and other children’s hospitals across the country. ■

ACCELERATING AWARENESS, DRIVING RESEARCH, RACING TOWARD TREATMENT

The Philadelphia Concours d'Elegance, initiated in 2017, is an annual local fundraising and awareness event to support the RIMGC Rare Diagnoses Program. The event is presented by Cool Cars for Kids Inc. (CCfK), a nonprofit organization that aims to increase awareness of the issues faced by families of children with rare genetic diagnoses. Funds raised by CCfK are focused toward delivering care, providing support and driving research for children with rare genetic diagnoses with the ultimate goal of contributing a brighter future through development of novel treatments and cures.

Attendees enjoy the chance to sit in a few of the cars.

The annual Concours d'Elegance event is a two-day classic car show and competition held at the Simeone Automotive Museum. The event consists of a Friday preview gala dinner followed by the main Concours event — complete with judging, awards, music, local food vendors and family-friendly activities. The Concours features invited classic American and European automobiles, as well as a public car display.

The 4th Philadelphia Concours d'Elegance planned for late April 2020 was cancelled due the rapid spread of COVID-19. Though we were disappointed to cancel this year's event, the health and safety of our team, supporters and attendees is our utmost priority. Even during these challenging times, hope triumphs as we were amazed by the unwavering support and generosity of our supporters. Almost all of our sponsors for the 2020 event declined reimbursement in light of the cancellation, electing to have their 2020 event sponsorship donated for this fiscal year's fundraising or carried over to support next year's event.

Since the inaugural event in 2017, more than $175,000 has been donated to CHOP and the RIMGC Rare Diagnoses Program to support clinical and research operations.

The 4th Annual Philadelphia Concours d'Elegance has been rescheduled for Friday, April 30, and Saturday, May 1, 2021, at the Simeone Automotive Museum in Philadelphia. Grand Marshall for the event is Dick Vermeil, former head coach of the Philadelphia Eagles, who will be in attendance. For more information about Cool Cars for Kids and the Philadelphia Concours d'Elegance, please visit **coolcarsforkids.org**. ■

PATIENT SPOTLIGHT

MEET ROSALIE

CHOP IS THE PERFECT FIT FOR CHILDREN WITH KABUKI SYNDROME

The signs were so subtle that many doctors over several months had missed them: a slight thickening of the fingertips and toe pads, one ear that was sticking out a little more than the other, almond-shaped eyes, arched eyebrows, a high palate.

Elaine Zackai, MD, a clinical geneticist at CHOP, needed to spend only a few minutes examining then 4-month-old Rosalie August, pulling out her trusty jewelers' loupe for close inspection, before pronouncing, "We should test for Kabuki syndrome. I'm 100% sure she has it."

Kabuki syndrome, so named because children with it tend to have facial characteristics similar to a Japanese Kabuki mask, is a rare genetic condition affecting multiple body systems. Its presentation varies greatly across the population, both in symptoms and severity. And some issues don't present until the child gets older.

Genetic tests through the Roberts Individualized Medical Genetics Center confirmed Zackai's opinion, built on decades of experience, and everything fell into place. The elusive diagnosis helped explain not only the visible signs, but the many medical difficulties Rosalie was experiencing.

"As Dr. Zackai was leaving she told me, 'Don't Google it,' but I did," says Rosalie's mother, Dara. "At first I thought, 'No way.'"

Because Rosalie's father is half Japanese, Dara had another explanation for Rosalie's eyes. But the more Dara read about the full range of symptoms, the more she believed.

Birth hospital unaware

Rosie was born at a local hospital and spent a month in the newborn intensive care until she came home on a nasogastric tube because she had trouble getting enough nutrition by mouth. When Dara pointed out other troublesome features to the doctors there, like her fingertip pads and misshaped ear, "they made me think I was crazy," she says "But Rosie is my second child. I knew something was off."

Rosalie was in and out of the hospital a few times over the next three months before she was admitted to CHOP with low blood sugar. Dara had to keep startling Rosalie to keep her awake when she tried to give her a bottle. "She'd take a couple sucks then dose off," Dara says. "I knew that wasn't normal."

Once at CHOP, the diagnoses kept coming, and most — in retrospect — were related to Kabuki syndrome.

Hyperinsulinism and heart defects

Rosalie's low blood sugar was the result of congenital hyperinsulinism (HI), which is common in children with Kabuki syndrome. Since she didn't respond to the two front-line medications, she was started on continuous dextrose (sugar water) to boost her sugar to the safe range. As she has grown, she's needed less dextrose and now, at 3½ years old, may be able to get off dextrose all together, according to her team in CHOP's Congenital Hyperinsulinism Center.

Cardiologists found three small holes in her heart chambers, two ventricular septal defects and one atrial septal defect, that allowed oxygenated and deoxygenated blood to mix in the heart, which can sap energy and delay growth. Two of the holes have closed on their own, and the third is smaller.

Rosalie has had surgery to correct misaligned eyes (strabismus). She sees specialists in Orthopaedics for hip dysplasia (loose hip joints) and Gastroenterology for chronic constipation. Some conditions are connected to the tendency for children with Kabuki syndrome to have diminished muscle tone (hypotonia).

Across CHOP, Families Come First

"It seems like every time we come to CHOP, they find something new," Dara says.

Also on Rosalie's list of specialists: Neurology, Urology, Otolaryngology, Immunology, the Sleep Center, the Autism Integrated Care Program, Nutrition and the Feeding Clinic. She has been an inpatient numerous times, often for infections; frequent infections are another characteristic of Kabuki syndrome.

One consistent trait Dara sees no matter where within CHOP she and Rosalie visit: a family-first approach.

"Doctors need to be willing to listen to parents," Dara says. "Together, we need to brainstorm different solutions. CHOP is wonderful. Doctors don't dismiss what I say. They listen and think outside the box. If it wasn't for CHOP, my daughter would not be alive."

Coming Soon: Special Kabuki Syndrome Clinic

The Rare Disease Program within the Roberts IMGC recognizes that children with Kabuki syndrome need a team of specialists that understands the multifaceted and evolving nature of the syndrome to guide families.

To better serve these families, the RIMGC is launching a special multidisciplinary clinic just for them. In one appointment, they will meet with a clinical geneticist, genetic counselor, endocrinologist, gastroenterologist, immunologist and nutritionist. Additional pediatric specialists join the team as needed by a particular patient. Together, they'll map out a care plan tailored for each child.

"I'm thrilled," Dara says. "It will be a significant help for those of us in the Kabuki community. When we get this diagnosis, we're blindsided. It's overwhelming.

"The Kabuki Syndrome Clinic will help families answer the question we all have: What do I do now?"

Dollies and dancing

While CHOP is helping the family figure out the medical side, Rosalie is a busy 3-year-old who loves music, dancing and her baby dolls. "She loves to rock her dolls and give them kisses," Dara says.

She receives occupational and physical therapy at home, which is helping build up her endurance. While she isn't speaking much yet, she understands what she hears. "Rosie is high functioning," her mother says. "She'll follow easy instructions."

Some of Rosalie's other favorite activities are slipping some of her food to the family dog, sitting in a shopping cart and going on short walks.

"We don't know what the future will bring," says Dara. "Kabuki syndrome is so odd in that it is different in every child. That's why I'm so excited CHOP is having a special clinic for our kids. It's a phenomenal hospital." ■

RIMGC TEAMS WITH CHOP DIGITAL HEALTH INITIATIVE TO EXPAND CARE, RESEARCH

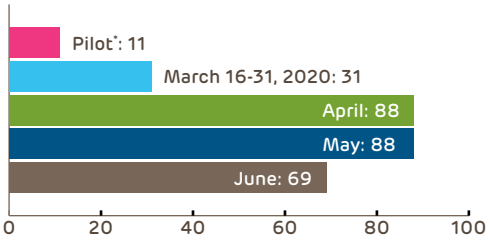
Clinical care remains a cornerstone of the RIMGC's mission. It is integral to facilitate access to genetic testing to children and families that are cared for by any of the many pediatric specialties at CHOP.

One way we increased access this year was to join forces with CHOP's Emerging Technology and Transformation (formerly Digital health) team. In 2019, the RIMGC embraced a telemedicine pilot project, led by Kate Fuller, MBA, and Bonnie Offit, MD, that facilitated offering genetic counseling follow-up by video visit. This allowed families to receive care via the MyCHOP patient portal from their phone, tablet or computer without coming to a physical CHOP office. Reasons for follow-up primarily included test education, test facilitation and return of results. During the pilot, we saw 124 patients.

Our involvement in the pilot project turned out to play a critical role in the RIMGC's transition to delivering genomic medicine during the COVID-19 pandemic. During the height of the pandemic, when working from home was advised for RIMGC staff, we were able to maintain near our typical number of outpatient visits, just via telemedicine instead of in person. This was beneficial to patients and families, that didn't need to travel during the pandemic, and to RIMGC clinicians, who were grateful caring for patients did not need to be postponed. There were some limitations to which patients could be seen via telemedicine, including location and family access to technology and their comfort with it. In the first 3 ½ months of the pandemic, we saw a total of 276 telehealth patients (171 new patient visits and 105 follow-up visits). ■

RIMGC Telehealth Visits

By month



**124 total visits during pilot, March 16, 2019 – March 14, 2020*

PheNomenal New Tool for Clinicians

The Roberts IMGC worked hand-in-hand with Emerging Technology and Transformation to create a consistent way for providers to document clinical findings in children with potential genetic diagnoses in CHOP's electronic health record, Epic. A new Epic tool, PheNomenal, was created to facilitate accurate capture of these clinical features, following the Human Phenotype Ontology (HPO) system developed by the Monarch Initiative and supported by the National Institutes of Health. HPO system is the international standard used to characterize clinical findings for all individuals undergoing broad-scale genomic testing, such as the exome sequencing test offered at CHOP.

Using PheNomenal allows integration and automation for clinics, genetic testing workflows and research. In its first year of operation, clinicians entered 6,632 HPO terms into the Epic records of 1,035 unique patients. It was important for patient record continuity to migrate the terms clinicians used before PheNomenal went live. To that end, the Digital Health team facilitated migration of 10,046 previously entered terms from 1,175 unique patient records. This project received full support from Bimal Desai, MD, MBI, CHOP's Chief Health Informatics Officer, as this approach will have future important benefits. PheNomenal is expected to have broad applications in the future, particularly for the CHOP Research Institute.

The RIMGC wants to thank the Emerging Technology team involved in the project: Malar Singaravelu, Nadya Aboras, Len Minkovsky, Nghi Vo, Manoj Ramachandran, Teresa Keates, Dennis Driscoll and Bimal Desai.

FOCUSED ON OUR FUTURE: A THANK YOU TO OUR DONORS!

The RIMGC is supported through the generous philanthropic efforts of the Roberts family, the Children's Hospital of Philadelphia, and many other families, foundations and donors. While we continuously seek additional federal funding (such as from the National Institutes of Health), philanthropy has been fundamental to providing exceptional and unparalleled clinical care and research to all families who seek care within the RIMGC. We are grateful for each gift, large and small, that helps support our work.

As always, we are humbled and amazed by the efforts of our donor families and our participating physicians, scientists, students and staff, who make the RIMGC a reality. It's the children and families we care for that provide the inspiration to keep us striving for constant improvement. Let's continue to build a brighter future for us all!

For more information about supporting the RIMGC, please contact Matthew Sware at **swarem@email.chop.edu**.

Philanthropy helps further research into rare diagnoses like Floating-Harbor syndrome , which was the diagnosis for 3-year-old James, shown with his dad, James Sr. The family also donates to CHOP.

Teddy, 8, and his family came to the RIMGC-sponsored CHOPS syndrome family day.

Children's Hospital of Philadelphia®

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