Children's Hospital of Philadelphia®

2021
ANNUAL REPORT

THE ROBERTS INDIVIDUALIZED MEDICAL GENETICS CENTER

Ethan, 5, patient of the Roberts IMGC

LETTER FROM THE DIRECTORS

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.

As we reflect on this year, it doesn't seem possible that we would still be facing the challenges of the COVID-19 pandemic almost two years out. While the pandemic has reshaped our world and the way we practice medicine, it has also tested the mettle of not only our staff and faculty in the Roberts Individualized Medical Genetics Center (RIMGC), but of our society as a whole — locally, nationally and internationally. While we continue to innovate ways to accommodate our patients and families, assuring that they have timely access to the cutting-edge clinical genetic and molecular diagnostics they are entitled to, we are equally committed to not allowing the pandemic to derail our dedication to growing the program and advancing the field of clinical genomics. We have many accomplishments to celebrate from this past year, and we are even more in awe of our amazing and talented physicians, genetic counselors, investigators, administrative and research staff, trainees and students who have continued to push the envelope of clinical care and discovery while shouldering the increased responsibilities, stresses and uncertainties posed by the pandemic.

From a clinical perspective, the RIMGC has been at the forefront of developing programs to integrate telemedicine into the routine care of our families, and we successfully navigated through transitioning to almost fully remote clinical visits early in the pandemic and then seamlessly transitioning back to in-person visits once it was safe to do so. The lessons learned during these transitions have allowed us to make telemedicine a permanent part of our clinical services — to be used when necessary for patient safety, but also for the convenience of our families that live far away or when it is an unnecessary burden to come into the hospital in person.

The RIMGC continues to leverage its research network and pipeline to participate and contribute to global studies documenting the impact and clinical implications of COVID-19 as part of the Consortium for Clinical Characterization of COVID-19 by EHR (4CE) — pronounced "foresee." (*See references on next page.*)

Some of the milestones and accomplishments achieved in the RIMGC — clinical, research and educational — this past year that we are extremely proud of include:

- With more than 5,000 patient visits since we opened our doors in 2015, the RIMGC has become an established resource for clinicians across all of CHOP's divisions and programs and a destination for patients and families from the region, the nation and around the world.
- We expanded clinical service and research support in Ophthalmology, Immunology, Rheumatology, Endocrinology and the Division of Genomic Diagnostics (DGD).
- Research enrollment into the RIMGC Research Repository and Portal surpassed 3,000 subjects. This is an invaluable resource of clinical information, genomic data and aligned samples stored in our biorepository, available to all CHOP investigators and fueling tomorrow's breakthroughs.
- We continued to expand our Rare Diagnoses Program with the establishment of the Kabuki syndrome multidisciplinary clinic.
- We recorded multiple successful federal and foundation grant awards and seminal publications in the field of pediatric genomics.
- We completed research projects in collaboration with Endocrinology, ENT, Gastroenterology, Pathology, Surgery, Neonatology and Immunology.
- Our collaboration with the DGD to initiate and establish a genetic test stewardship program (Genetic Test Utilization Committee) strives to ensure equitable and appropriate genetic test ordering for inpatients at CHOP.

Many of these accomplishments, and others, are highlighted in this *Annual Report*, but it does not adequately underscore the incredible work and dedication of everyone in the RIMGC who has persevered through trying times to not only provide incredible services to our patients and families, but also to push the envelope to advance pediatric care, research, education and the field of clinical genomics to new heights. We are exceptionally proud to be a part of this remarkable group of professionals and consistently humbled by their professionalism and dedication to the mission of the RIMGC, as well as to the broader CHOP community within which we have been given the support and encouragement to thrive.

Ian Krantz, MD
Co-director

Livija Medne, MS, CGC
Co-director

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Note: Photos were taken prior to the pandemic or submitted by families.

WELCOME LETTER REFERENCES

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OUR TEAM

Ian Krantz, MD
Co-director
Attending physician, scientist

Līvija Medne, MS, LCGC
Co-director
Genetic counselor

Priyanka Adusumalli, MHA
Business administrator

Emma Bedoukian, MS, LCGC
Genetic counselor

Donna Berrodin, BS
Research database developer and manager

Justin Blair, MS
Bioinformatics scientist

Brandon Calderon, MBA
Administrative director

Paul Deppen, MS
Clinical and research coordinator

Batsal Devkota, PhD
Bioinformatics scientist

Sierra Fortunato, BS
Clinical and research coordinator

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

Audrey Lawrence
Clinical research assistant

Jacqueline Leonard, MSc, MS, LCGC
Genetic counselor

Deborah McEldrew, BS
Research technologist

Jasmine Montgomery
Practice manager

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.*

ANNIVERSARIES AND ACCOMPLISHMENTS IN 2021

The Rare Diagnoses Program of the Roberts IMGC has several milestone accomplishments to celebrate from this past year. First, the Center for Cornelia de Lange Syndrome (CdLS) and Related Diagnoses recently celebrated its 10-year anniversary. Since the Center for CdLS and Related Diagnoses was founded, we have provided care to more than 430 patients (inpatient, outpatient, telemedicine), held more than 100 monthly multidisciplinary clinics, enrolled more than 2,900 people in CdLS research, secured more than $15 million in grant funding and published more than 70 peer-reviewed manuscripts.

The CdLS team is incredibly grateful for the clinicians and researchers at CHOP, the CdLS Foundation, and collaborators from around the world who have given their time and insight to make the mission of this center a reality. Most importantly, we are continually inspired by the families that have given so much emotionally, intellectually and fiscally to create our center.

BEYOND CdLS

The Rare Diagnoses Program provides a medical home for individuals with many developmental genetic diagnoses in addition to CdLS and their families. Clinics cater to families from all over the world that may come for a diagnosis, to seek answers to questions their local physicians are at a loss to answer, or for targeted medical and surgical care. All families return home with a plan of care for their children and a medical resource that is a phone call away.

Equal to the clinical activities of the center are its research investigations. The identification of underlying causative genes for these diagnoses and the pathways in which they work is just the beginning of our mission to translate this knowledge into novel diagnostic and management tools and, eventually, into therapeutic tools.

FULL STEAM AHEAD FOR KABUKI SYNDROME CLINIC

The close of this academic year marked the first year of operations of the newly established Kabuki syndrome multidisciplinary clinic, another accomplishment. Quarterly clinics provided care to a total of 16 patients from eight different states, including as far away as Texas. The Kabuki team currently consists of specialists from Genetics, Gastroenterology, Endocrinology and Nutrition with plans to add an immunologist in the third quarter clinic this year.

Additionally, in 2022, the number of patients scheduled per clinic will increase from four to five families as a result of increased demand.

Both the CdLS and Related Diagnoses Center and Kabuki Syndrome Clinic are a culmination of years of dedicated work by a core team of clinicians and investigators at CHOP, coupled with the passion and vision of parents and families of children born with these respective diagnoses. We are proud to offer a medical home to these families at CHOP.

Amelia, 5, and her family appreciate the multidisciplinary Kabuki Syndrome Clinic.

NATIONAL 'EXCELLENCE' RECOGNITION

In November, Children's Hospital, along with the University of Pennsylvania School of Medicine (Penn Medicine), were jointly named a Rare Disease Center of Excellence by the National Organization for Rare Diseases (NORD).

CHOP and Penn Medicine represent one of 31 NORD Rare Disease Centers of Excellence across the United States. NORD established this Centers of Excellence program to promote outstanding treatment for rare disease patients regardless of disease or geography, elevate collaboration, improve standards of care, advance research and increase awareness about rare diseases in the broader medical and patient communities.

We're proud to have been selected for this "rare" accomplishment.

NORD®

OUTSIDE HELP FUELS CARE, RESEARCH

The Rare Diagnoses Center also continues its dedication to philanthropic fundraising efforts. We are thankful for and appreciative of all donations, both large and small, from the families and organizations that support our program. A portion of the clinical operations of the CdLS and Related Diagnoses Center continues to be supported by revenue generated from an endowment that was created from the generous donations of five families.

The PKS Kids Foundation also donated $20,000 this past year to support the ongoing research efforts of Kosuke Izumi, MD, PhD, on Pallister-Killian syndrome (PKS).

In addition, the Cool Cars for Kids (CCfK) nonprofit continues to be a major supporter of the RIMGC's Rare Diagnoses Center. Following CCfK's 4th Annual Philadelphia Concours d'Elegance event in July 2021, this organization made its largest annual donation to date of $75,000 and has donated a total of $250,000 since the nonprofit was established in 2017.

These funds donated to the Rare Diagnoses Center have been used to support the first international CHOPS syndrome family meeting and to establish the Kabuki Syndrome Clinic. Donations from CCfK will continue to support the establishment of new multidisciplinary clinics and provide small research grants for rare disease research.

Cool Cars for Kids is holding its 5th Annual Philadelphia Concours d'Elegance on June 25 (preview gala) and June 26, 2022, (car show and exhibition) at the Simeone Museum in Philadelphia, Pa.

This year's featured marques are the Ford Shelby Cobra and Dodge Viper, "A Celebration of the Snakes." Join us — and our Honorary Chairman, legendary Eagles Coach Dick Vermeil — next June for another fun-filled weekend of cars, food, games and music in support of the RIMGC's Rare Diagnoses Center. Visit coolcarsforkids.org and philadelphiaconcours.org for more information.

CASE CONFERENCES: RAMPING UP LEARNING, SHARING

Cara Skraban, MD, an attending physician in the Division of Human Genetics, is the Medical Director of the RIMGC. Dr. Skraban is the Associate Program Director for the combined Pediatrics-Genetics residency program and the Medical Genetics and Genomics residency program.

Dr. Skraban obtained her medical degree at the University of Virginia School of Medicine in Charlottesville. She completed her pediatric residency training at the University of Virginia in the Department of Pediatrics and her medical genetics residency at Children's Hospital of Philadelphia. After completing her clinical training, she remained at CHOP to undertake a postdoctoral research fellowship in the laboratory of Matthew Deardorff, MD, PhD, supported by an NIH T32 Training Grant. As a trainee, Dr. Skraban was instrumental in characterizing a novel genetic condition called WDR26-related intellectual disability syndrome, a diagnosis now known as Skraban-Deardorff syndrome. She has ongoing research efforts focused on the characterization of the clinical phenotype of these patients.

Early in the COVID19 pandemic, Dr. Skraban demonstrated her commitment to training when she spearheaded a weekly case conference. The main incentive was to continue education for residents, fellows, students and practicing clinicians. When outpatient clinics slowed in the initial months of the pandemic, physicians, trainees and genetic counselors were still able to learn from each other in this virtual platform. Though clinics are back in full force, the case conference continues weekly to allow for maximum learning opportunities and camaraderie among colleagues.

Beyond this educational activity, Dr. Skraban also serves as the Medical Director of the newly established Genetics Trainee Continuity Clinic and is one of the course directors for the Foundations of Clinical Genetics and Genomics in the Masters of Science in Genetic Counseling program at the Perelman School of Medicine. She is also involved in teaching residents and fellows in CHOP's Department of Pediatrics and medical students at the Perelman School of Medicine.

The RIMGC recognizes Dr. Skraban for her incomparable patient care, her dedication to teamwork and her focus on training the next generation of genetics professionals.

RIMGC AND DGD PARTNERSHIP ENHANCES PATIENT SERVICES

The RIMGC works with the Division of Genomic Diagnostics (DGD) in the Department of Pathology to provide clinical expertise for complex test interpretation and to optimize the use of diagnostic genetic testing at CHOP. These collaborative efforts greatly impact new test development in specialized areas of medicine and ensure the benefits of these tests are fully realized by our patients.

This past year, the RIMGC and DGD collaborated on a pilot stewardship program to ensure that genetic tests ordered for children admitted to the hospital are appropriate and relevant to their inpatient care. Through a daily review process, members of the RIMGC and DGD identified duplicative genetic test orders and other test orders that were not optimal for the suspected diagnosis of the patient. They then worked with the clinical care team to make adjustments when necessary.

CONVENIENT SAMPLE COLLECTION

To better serve our patients, the DGD also now offers DNA extraction from samples submitted in advance of receiving insurance authorization for genetic testing. This allows samples to be collected while a patient is in the hospital or at an outpatient visit and for the desired test to be ordered at a future date. Through these efforts, the DGD and RIMGC are working to ensure patients are receiving the right genetic tests at the right time.

The DGD also launched several new tests and improved upon existing tests this past year. The CHOP Medical Exome test was enhanced by incorporating copy number variant (CNV) calling. This combination of sequence and copy number variant analysis results in an increased diagnostic rate without adding to the test's cost or turnaround time. To support this test, the DGD also launched a targeted CNV test option, allowing for other family members to be tested specifically for a copy number variant that is identified in a patient.

NEW TESTS DELIVER FASTER RESULTS

New tests include a rapid next generation sequencing panel for hemophagocytic lymphohistiocytosis (HLH), a severe, potentially life-threatening systemic inflammatory syndrome. The HLH panel was designed in collaboration with the Immune Dysregulation Program and allows for expedited diagnosis of patients with HLH. This expedited diagnosis can guide treatments, such as bone marrow transplants, a potentially life-saving intervention. With a two-week turnaround time, this represents a significant improvement over existing commercial testing.

In October, the DGD launched a paired tumor/normal hematologic cancer panel, which was developed in collaboration with partners in Oncology. This test includes sequence and copy number analysis of both a bone marrow sample from a patient with a known or suspected hematologic malignancy, as well as analysis of another unaffected tissue from that patient. By comparing the results obtained from these two sample types, the significance of variants identified in a tumor can be more readily determined and acted on.

Thanks to ongoing work with our clinical partners, more new tests are on the horizon, including the launch of a mitochondrial content analysis test, development of a liquid biopsy test with Oncology, and development of a genome sequencing based suite of tests that will allow for faster and more flexible testing options.

OPHTHOGENETICS SPECIALIST GUIDES FAMILIES FROM DIAGNOSIS TO TREATMENT

RIMGC genetic counselors are embedded within Ophthalmology (Emma Bedoukian, MS, LCGC), Endocrinology (Jacqueline Leonard, MSc, MS, LCGC), the Neuromuscular Undiagnosed Program (Livija Medne, MS, LCGC) and the Immune Dysregulation Program (Ellen Xu, MS, LGC). A benefit for our genetic counselors being part of the RIMGC is that they maintain the support of Genetics colleagues. Other counselors from the team can cover these clinics when the counselor is unavailable, and they can rely on the expertise of their colleagues when working through difficult genetic or psychosocial cases. Our counselors do not work in isolation.

This year we highlight Emma Bedoukian's work within Ophthalmology. Bedoukian joined the Ophthalmology team in 2015 to work with Bart Leroy, MD, PhD. Since then, Tomas Aleman, MD, and Erin O'Neil, MD, have joined the team. In 2015, Bedoukian attended the Eye Genetics course from European Society of Human Genetics in Bertinoro, Italy, where she received the Robert Holden Award for a presentation about Brown-Vialetto-Van Laere syndrome.

In 2017, the Food and Drug Administration approved voretigene neparvovec-rzyl (Luxturna). This is an adeno-associated virus vector-based gene therapy indicated for the treatment of patients with confirmed biallelic *RPE65* mutation-associated retinal dystrophy. After this approval, Bedoukian took on the role of coordinating this gene therapy treatment for patients at CHOP. In 2018, she received the CHOP ICARE award for her efforts to increase accessibility at CHOP for patients with vision impairment.

Bedoukian has been leading the RIMGC Education Core since 2017. In this role, she has created and maintained onboarding documents for new genetic counselors, facilitated training for genetic counseling, medical and laboratory trainees, and spearheaded the creation of educational materials for patients and families. Bedoukian is dedicated to continuing and furthering educational opportunities for all. She has taken on the role of Co-chair of the Professional Development Committee in the Section of Genetic Counselors at CHOP for 2022.

At the national level, Bedoukian in 2019 took the initiative and successfully started a Special Interest Group in the National Society of Genetic Counselors (NSGC) focusing on Ophthalmology and Hearing Loss. As co-chair, she has been able to increase collaboration between genetic counselors by streamlining communication and by planning webinars, a journal club and study groups.

Bedoukian continues to contribute to presentations and publications about the genetic causes of ocular disorders. She is grateful for the amazing teachers she has in Drs. Leroy, Aleman and O'Neil and for the opportunities they provide her. She is continually impressed by the resiliency of her patients and their families.

Emma Bedoukian and James, 3

REDEFINING CONNECTION WITH FAMILIES

The goal of the Administrative Core of the Roberts IMGC has always been to connect with families and provide support during every step of their journey. In the past year, this ability to connect was redefined by the ever-adapting reality of commitment to care during a global health crisis.

Our administrative team has continuously reflected on one important question: How do we minimize burden to families while optimizing their holistic experience with our team? The delicate balance of logistical boundaries, emotional expenditure and time sensitivity remains in the forefront of our minds as we evolve the RIMGC experience to be increasingly efficient and holistically care-centered.

Through the occasionally intimidating process of authorization and pre-appointment logistics, our administrative core continues to put families first with consistent electronic communication at each step of the process. Families receive one MyCHOP message detailing receipt of a referral to our department and alerting them that we have submitted necessary documentation to their insurance companies. Once approval is obtained, they receive a text message alerting them they can schedule an appointment. This transparent communication allows families to be included in their own pre-appointment timeline and to call us at a time that works best for them.

If they require a follow-up visit, we offer Pennsylvania patients this ease of control again through ticket scheduling, when we send a MyCHOP message that gives them access to schedule a follow-up video visit with their specific provider themselves. This commitment to giving busy families tools

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

to determine what works most conveniently for them prevents administrative obstacles from hindering care. The RIMGC has marched fearlessly into the new age of technology spurred by an ever-changing world and continues to seek out new ways to include and connect with families.

The RIMGC advancing seamlessly during this past year is a tribute to the heart and tireless dedication of Jasmine Montgomery, who was both promoted to Practice Manager and celebrated 15 years at CHOP. Her calm composure is a balm to the nerves of anxious families, and her commitment to the center has elevated its reach to the community.

Tyrah Williams, the office coordinator for the RIMGC, has a palpable devotion to providing the best possible experience for families. Her coordination with our insurance authorization team helps maintain an efficient workflow and quick scheduling turnaround for our families.

Audrey Lawrence, our team's newest member, brings enthusiasm and consistent effort to the team's expansion of responsibilities. She integrates the clinical and research goals of the center with deep passions for both. The administrative trio profits from each member's strengths as we aim to ensure the best possible care experience for families.

The RIMGC consistently commits itself to forming deep connections with its families, rooted in respect, transparency and the common goal to find answers to inform the care of our patients.

PATIENT NUMBERS 2021

The addition of more than 700 patients last year boosted the RIMGC's total patient visits to more than 5,000 since it was created in 2015. We remain available to our patient families for in-person and telehealth visits.

703 NEW PATIENTS
38 FOLLOW-UP
30 GENETIC COUNSELOR FOLLOW-UP
120 GENETIC COUNSELOR VIDEO•NEW PATIENT
31 VIDEO•FOLLOW-UP
282 VIDEO•FOLLOW-UP•GENETIC COUNSELOR ONLY
25 CdLS AND RELATED DIAGNOSES CLINIC
6 KABUKI CLINIC

PATIENT SPOTLIGHT:

MEET JULIET

CHOP'S PERSISTENCE IN GENE RESEARCH PROVIDED ANSWERS — AND AWARENESS

When Juliet Papenberg failed the newborn hearing test a few hours after she was born, it wasn't unexpected. Her father, Matthew, has severe hearing loss, as do some other members of his family.

To be sure, mom Carly made an appointment at Children's Hospital of Philadelphia's Specialty Care Center in Princeton, N.J., where Juliet was evaluated when she was less than 2 weeks old. The auditory brainstem response (ABR) evaluation showed bilateral (both ears) moderate to moderately severe sensorineural hearing loss. Sensorineural hearing loss stems from a problem in the inner ear and is usually permanent.

"Once it was confirmed, I didn't waste any time," Carly says. "I started making appointments. I wanted to get as much in as possible before my maternity leave was over."

Through CHOP's Center for Childhood Communication, Juliet was fitted for and received hearing aids through CATIPIHLER (CHOP's Assessment and Treatment Implementation Program for Infants and Toddlers with Hearing Loss–Enhancing Rehabilitation). CATIPIHLER provides babies loaner hearing aids since they outgrow molds faster than insurers will approve the devices.

Juliet saw an ophthalmologist and an otolaryngologist (ears, nose and throat doctor) and began physical therapy and early intervention services — all before she was 3 months old.

Search for the Genetic Cause

Another visit was with the Roberts Individualized Medical Genetics Center (RIMGC) and its Genetics of Hearing Loss Clinic, where she was evaluated by Ian Krantz, MD, and genetic counselor Tiffiney Hartman, PhD, CGC. The family decided to try to find the cause of Juliet's hearing loss through genetic testing.

"We knew there was a genetic component since, on Matthew's mom's side of the family, he has an aunt and two cousins with hearing loss," Carly says. The family was also keen to know if Juliet's hearing loss was part of a more encompassing syndrome so they could make sure she was receiving all the care she needed. "Knowledge is power," Carly says.

At the time of that first RIMGC appointment in early 2020, AUDIOME, the CHOP-developed two-step comprehensive genetic test for the diagnosis of nonsyndromic hearing loss in children, looked for changes in 121 genes that can cause hearing loss. Juliet's genetic results test didn't match any of those 121 genes, so they didn't receive a diagnosis.

But the family did enroll Juliet in the RIMGC research protocol (pediatric genetic sequencing in health and disease), so her de-identified data was included in a study looking for genetic causes of hearing loss for patients with no answer from a clinical genetic test.

In January 2021, the AUDIOME test was expanded to look for variants in 133 genes. As part of the research, Juliet was identified to have a variant in a gene called *GATA3*, one the those additional 12 genes. This result was confirmed by a clinical test at no charge to the family.

Mutations in the *GATA3* gene cause HDR syndrome, also called Barakat syndrome, which is characterized by three components: hypoparathyroidism, sensorineural deafness and renal (kidney) disease.

HDR Syndrome Makes Sense

"With the HDR syndrome diagnosis, things started to make sense," Carly says.

For example, Juliet had repeated urinary tract infections (UTIs), which could have been from vesicoureteric reflux (VUR), when urine flows through the ureters (tubes) from the bladder to the kidneys; it should flow the other way to be expelled. Urologist Thomas Kolon, MD, was added to Juliet's list of doctors. In May 2021, she had an ultrasound showing both kidneys and ureters were normal, very welcome news. She takes an antibiotic to prevent future UTIs and will continue to be monitored by Urology.

Ongoing monitoring is important because people with HDR syndrome have varying degrees of severity and different times of onset for each of the three components of the condition. It's expected that as people get older, they are likely to present with at least some symptoms for all three. Symptoms can be very mild at first, but proactively looking for and identifying issues early allows for improved management.

Juliet has regular blood work to check for potential hypoparathyroidism — which is when the parathyroid glands, located in the neck near the thyroid gland, produce too little parathyroid hormone. Parathyroid hormone regulates calcium levels in the blood, and when it is out of balance, the patient can have muscle cramps, pain and twitching. Hypoparathyroidism is treatable by taking supplements, usually for life, to restore calcium and phosphorus levels.

Tiny Dancer

These days, Juliet, now 2 years old, can be found hugging her favorite baby doll or dancing with her 5-year-old sister, Ellie. "They're always having dance parties," Carly says. "Juliet adores her big sister — and her daddy. She's obsessed with Matthew."

Juliet understands she needs her hearing aids, but still pulls them out sometimes. Her speech is a little delayed. "She has a lot of language, but it's a matter of getting her to say it," her mom says. "She can be very chatty when she's playing, for instance, but other times she's quiet and more observant."

CHOP at the Ready

"We know we'll figure it out," Carly says. "My husband's hearing loss wasn't diagnosed until he was almost 4, and he always says, 'I turned out fine and so will Juliet.'

"Juliet has the advantage of such an early diagnosis and by the fact we have CHOP nearby to help us monitor everything. It's great that CHOP kept trying to find out the cause of her hearing loss. The HDR diagnosis is wonderful knowledge to have in the bank for her future."

Juliet, 2, will undergo additional screenings to monitor her health now that her family knows the specific cause of her hearing loss.

EVIDENCE IS IN: SOONER IS BETTER

The earlier a rare or complex genetic disease is diagnosed in a patient, the earlier critical treatment can begin. This is especially important in critically ill infants who may need their diseases managed in very specific ways.

The Roberts IMGC team joined four other clinical sites across the United States — Le Bonheur Children's Hospital in Memphis, Tenn.; Rady Children's Hospital in San Diego, Calif.; University of Nevada Medical Center Children's Hospital in Las Vegas; and Washington University St. Louis Children's Hospital — with the goal to determine if clinical whole-genome sequencing leads to change of management for these very sick infants based on having established the underlying primary genetic diagnosis. The findings were recently published in the journal *JAMA Pediatrics*.

The study included 354 racially and ethnically diverse patients from across the country with our RIMGC team enrolling a quarter (85) of the study participants. Infants had clinical genome-wide sequencing performed in a duo or trio format with a turnaround time of 15 days or 60 days based on randomized assignment that was blinded to the clinicians. The study participants' clinical course was followed for a total of 90 days post-enrollment.

Based on the data from all sites, genome sequencing doubled the proportion of patients who received a precise diagnosis of their condition from both arms of the study. The clinical presentation was very similar across all sites with infants: 57% with multiple congenital anomalies, 17.5% with single major structural difference, 15% with primary neurologic phenotype and 10.5% with another single clinical feature. Results showed a two-fold increase in change of management in both arms of the study. The majority of the observed management changes were condition-supportive care (subspecialty referrals and evaluations, change in medications). However, in 8% of patients with an established molecular diagnosis, change of management addressed the underlying molecular alteration.

"The clear and important link between establishing a diagnosis and improved care management lends much weight to the adoption of clinical whole-genome sequencing as a first-tier diagnostic test in critically ill newborns," say study co-author Ian Krantz, MD, Co-director of RIMGC.

Krantz and RIMGC Co-director Livija Medne, MS, CGC, were invited to join Ryan Tafft, PhD, the principal investigator from Illumina, for a Nature Genetics webcast on Dec. 15, 2021, discussing study results and providing case examples of early diagnosis impacting care and medical management.

The study was a true collaborative effort of our entire RIMGC team, with every genetic counselor, attending physician and study coordinator contributing to this study.

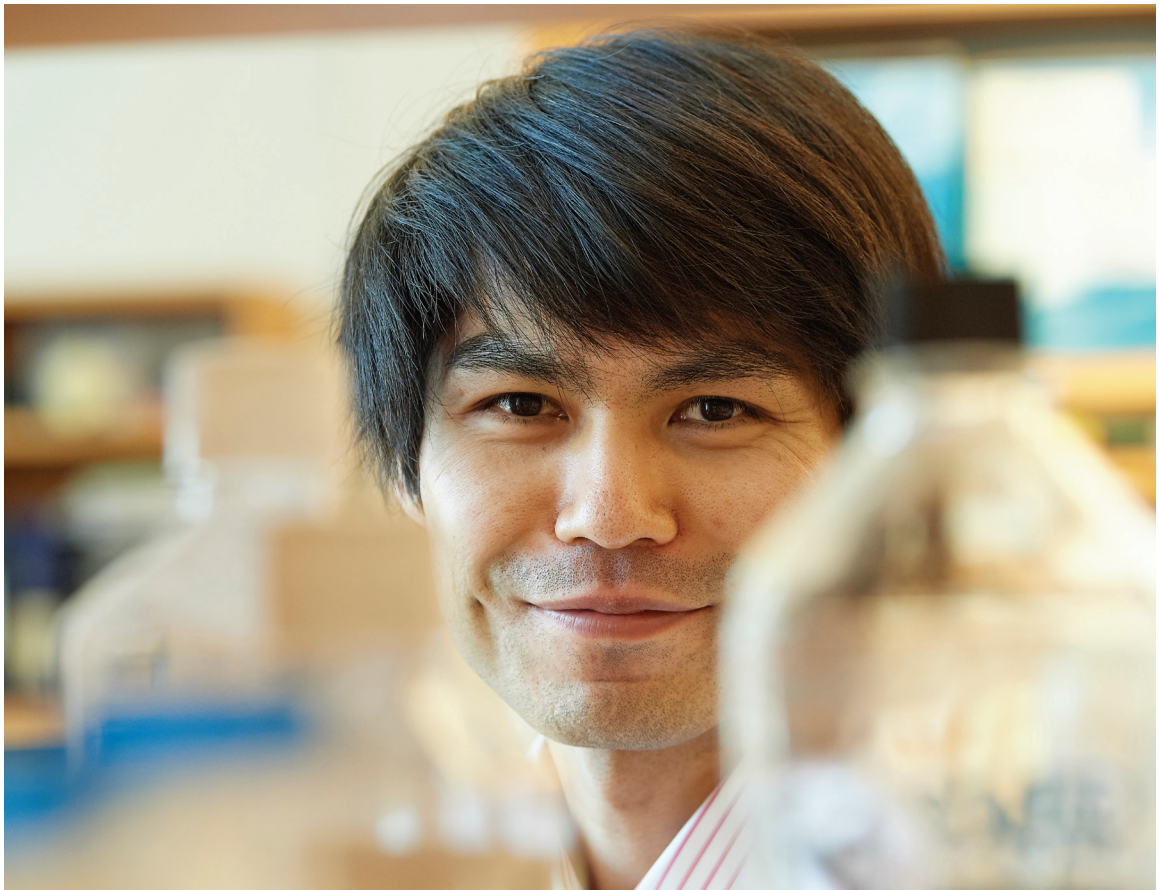
CHOP JOINS INTELLECTUAL AND DEVELOPMENTAL DISABILITIES RESEARCH CENTER BRAIN GENE REGISTRY COLLABORATION

With advanced genomic sequencing testing methodologies, an increasing number of genes have been associated with neurodevelopmental symptoms such as developmental delay/intellectual disability and autism. Over the last several years, Roberts IMGC team members contributed to the discovery of many such genetic diagnoses, including Skraban-Deardorff syndrome and NKAP-related syndrome. While these discoveries facilitated molecular diagnosis in children with neurodevelopmental symptoms, their clinical spectrum remains unknown, partly due to the lack of consistent clinical evaluation methodologies across many academic medical centers. To overcome this major obstacle, the RIMGC team became a part of the large multi-institutional collaboration study supported by the National Center for Advancing Translational Sciences of the National Institute of Health. Kosuke Izumi, MD, PhD, is leading the RIMGC's participation.

In this research study, the team will perform a standardized neurobehavioral testing battery and clinical evaluation of the subjects with 65 rare neurodevelopmental disorders with the aim to understand the clinical spectrum of these diagnoses. The 65 rare neurodevelopmental disorders include NKAP-related syndrome Dr. Izumi's group discovered in 2019.

CHOP is one of 13 research study sites and plans to enroll approximately 600 subjects during the study period. Since each individual genetic diagnosis is very rare, a multi-institutional collaboration is the only way to fully understand the entire clinical spectrum of these diagnoses. We hope that the insights uncovered by the study will lead to better clinical management of children with rare neurodevelopmental disorders.

Kosuke Izumi, MD, PhD, in his lab



SUMMER INTERNS: A STEP TOWARD DIVERSIFYING GENETIC COUNSELING

Historically, the majority of licensed genetic counselors in the growing field of genetic counseling have been white females. Increasing the diversity of genetic counselors is a major goal of everyone in the field.

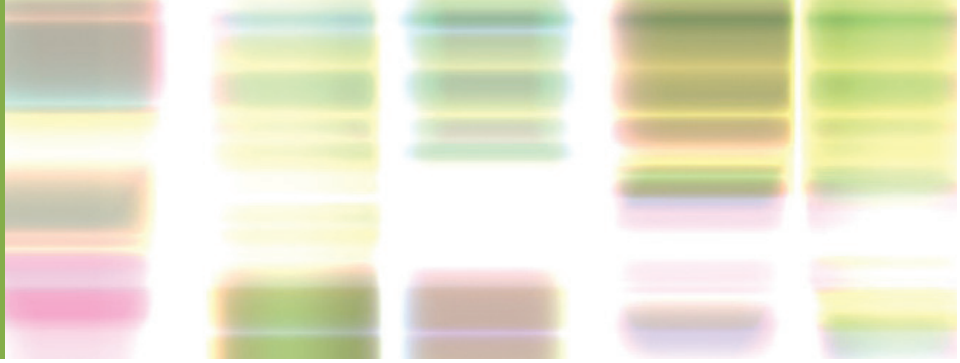
This past summer, the University of Pennsylvania Genetic Counseling program offered scholarships to three undergraduate students from underrepresented minority populations so they could gain further insight into the profession by shadowing and working with genetic counselors across various Hospital of the University of Pennsylvania and CHOP programs. The RIMGC financially supported one of these scholarships. RIMGC genetic counselors and physicians were eager to participate in the summer program and found multiple ways to interact with the interns.

Being able to shadow genetic counselors in clinic is an excellent way for students to get a feel for the career, to better understand the role of a genetic counselor on a day-to-day basis and to learn how genetic counselors impact patient care. Each intern was able to spend multiple days in clinic, shadowing a genetic counselor preparing for cases, interacting with patients and families, and discussing the case after each appointment. The interns were included in discussions about medical and family history, review of the electronic medical record, physical exam of the patient, medical management and genetic test ordering. They were also able to debrief with the genetic counselor to ask questions about their experiences in clinic.

While direct patient care is a primary role of genetic counselors, each counselor also spends significant time participating in other aspects of the job. Interns were able to spend time with several RIMGC genetic counselors during nonclinic time. For example, genetic counselors Tiffiney Hartman, PhD, Jacqueline Leonard, MSc, MS, LCGC, and Christopher Gray, MS, LCGC, attended Tuesday morning Genetics Rounds with the interns and led a one-hour "rounds debriefing" discussion with them afterward, which involved a question-and-answer session and GC-directed conversation about scientific and psychosocial topics relevant to that day's rounds.

Hartman participated in a "career path" discussion with the interns and answered questions about her decisions and life experience that led to genetic counseling as a career. All in all, it was a great experience not just for the interns, but for the genetic counselors as well.

Summer interns, from left, Maurice Wade, Maya Powell and Briana Brown spent time at CHOP.



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The RIMGC had the expertise to find an answer for Sadie, 13. Her diagnosis is so rare that she was the first person in the United States, and third person anywhere, to be diagnosed with it. This is why families from all over the world come to us for answers.

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Children's Hospital of Philadelphia®
Roberts Individualized Medical Genetics Center

www.chop.edu/imgc
IMGCclinic@chop.edu
267-426-7418