WHO WE ARE

The Roberts Individualized Medical Genetics Center (Roberts IMGC) at Children's Hospital of Philadelphia (CHOP) was established in 2014 to provide state-of-the-art, individualized clinical support to children and families undertaking genetic and genomic testing. It provides interpretative and educational support to clinicians pursuing this testing for their patients. The program also makes this rich phenotypic and genomic information available to researchers, advancing CHOP's mission and commitment to the future of genetic and individualized medicine.

The Center was endowed through a generous gift by the Roberts family in 2016. That gift and matching funds from CHOP also established a broader Roberts Collaborative for Genetics and Individualized Medicine that will promote synergized pediatric genetics care and breakthrough research in diagnostics, clinical management, patient support and counseling, resident and medical student training, informatics, and therapeutics.

Since not every clinician is comfortable assisting families with or answering questions about the complex genetic testing process, the Roberts IMGC's genetics professionals (genetic counselors and physicians) are available to recommend and explain a range of different genetic testing types and their implications for families.
The Roberts Individualized Medical Genetics Center has had another remarkable year of providing cutting-edge clinical services and management for children with genomic diagnoses and their families. This past year has been one of tremendous growth and expansion of services and research, with many of our new initiatives highlighted in this report.

The mission of the Roberts IMGC, the first pediatric individualized genomic program in the country, remains the same: to facilitate access to state-of-the-art individualized genomic testing and management for children, families and clinicians, and to promote integration of clinical and genomic information into the diagnostic and research efforts at Children’s Hospital of Philadelphia (CHOP).

In response to our rapid growth, we restructured to allow us to provide more efficient services, expand the populations we serve, to include adults who do not have access to these types of services, and facilitate a broad range of research initiatives. We have established four main pillars of focus within the RIMGC, all held together by an administrative core, led by Jasmine Montgomery:

• Clinical Services, headed by Cara Skraban, MD
• Rare Disease Program, headed by Sarah Raible, MS, CGC
• Educational Program, headed by Emma Bedoukian, MS, CGC
• Research Program, headed by Sawona Biswas, MS, CGC

With more than 2,100 patient encounters since we opened in July 2014, the RIMGC has become a destination for patients and families from the region, the nation and around the world.

Our team continues to expand. In the last year we welcomed a new genetic counselor (Jacqueline Leonard, MS, CGC), incorporated clinical and research expertise of two experienced CHOP genetic counselors (Sawona Biswas, MS, CGC, and Sarah Raible, MS, CGC) and welcomed a pediatric clinical geneticist (Louisa Pyle, MD, PhD). Our program has benefited from the recruitment of a clinical coordinator (Tyrah Williams), two clinical research coordinators (Jamilla Weatherly, MS, and Sierra Fortunato, BS) and research technicians (Maninder Kaur, MS, and Priya Vaidiswaran, MS).

This Annual Report features some activities from the various programs of the Roberts IMGC, highlights select statistics and research accomplishments, and illustrates the diagnostic journeys of a few families. While the activities and numbers are truly remarkable for such a young and innovative center, it is our patients and their families that serve as the inspiration to keep us pushing for answers and new therapeutic approaches buried in our genomic information.

The success of the RIMGC is built upon the many talented people working tirelessly to bring these breakthroughs to children. This important work would not be possible without the generous support of our benefactors. We are ever so grateful and humbled by each and everyone’s dedication.

Ian Krantz, MD          Līvija Medne, MS, CGC
Co-director            Co-director
OUR TEAM

Ian Krantz, MD
Co-director
Attending physician, scientist

Livija Medne, MS, LCGC
Co-director
Genetic counselor

Priyanka Adusumalli, MBA
Business administrator

Brandon Calderon, MBA
Administrative director

Matthew Deardorff, MD, PhD
Attending physician, scientist

Sierra Fortunato, BS
Clinical and research coordinator

Kosuke Izumi, MD, PhD
Attending physician, scientist

Maninder Kaur, MS
Research laboratory manager

Jacqueline Leonard, MSc, MS, LCGC
Genetic counselor

Jasmine Montgomery
Office administrator

Louise Pyle, MD, PhD
Attending physician, scientist

Sarah Raible, MS, LCGC
Genetic counselor

Cara Skraban, MD
Attending physician

Jennifer Tarpinian, MS, CGC
Genetic counselor

Priya Vaidiswaran, MS
Research technician

Jamila Weatherly, MS
Clinical research assistant

Tyrah Williams
Office coordinator

The Roberts Individualized Medical Genetic Center team, clockwise from far left: Sarah Raible, Jacqueline Leonard, Maninder Kaur, Jamila Weatherly, Kosuke Izumi, Matthew Deardorff, Cara Skraban, Tyrah Williams, Sawona Biswas, Jennifer Tarpinian, Emma Bedoukian, Co-director Livija Medne, Co-director Ian Krantz and Jasmine Montgomery
CLINICIANS INTERESTED IN PURSUING COMPREHENSIVE AND COMPLEX GENETIC AND GENOMIC TESTING FOR PATIENTS WHO LIKELY HAVE A GENETIC CAUSE FOR THEIR PRESENTING FEATURES CAN TURN TO THE ROBERTS IMGC FOR HELP.

OUR SERVICES

Genetic testing is complex. The Roberts IMCG’s genetic counselors, physicians and financial counselors are available to help referring clinicians and families navigate the pre- and post-testing issues that may arise, such as:

• Identification of the most appropriate genetic test, when necessary
• Review of medical history
• Phenotype capture by physical exam and/or 3-D face imaging
• Informed patient education and consent
• Insurance approval process
• Results review/genetic counseling when requested by the referring clinician
• Follow-up testing for additional family members, when necessary

Although the primary goal is to assist with exome and genome sequencing, the Roberts IMGC can also assist with most other types of genetic testing.

• In-house testing: For genetic testing done at CHOP, Roberts IMGC clinicians will work collaboratively with the Division of Genomic Diagnostics (DGD) to gather essential information that can be used in the analysis and interpretation of patients’ test results.

• Send-out testing: RIMGC clinicians will also assist with complex send-out testing, which may require a more detailed explanation and/or patient consent and/or insurance authorizations.

We also offer the opportunity for all patients to enroll in an ongoing research protocol approved by CHOP’s Institutional Review Board (see related story on Page 14). Research enrollment with the RIMGC allows for gene discovery, translation of genetic discoveries into novel therapeutics and, ultimately, improvements in patient care.

Once a referring provider has identified a patient for whom specific genetic testing is recommended, they can notify the Roberts IMGC. External referring clinicians can initiate contact with the Center by calling 267-426-7418. CHOP clinicians can place a RIMGC consult order in Epic or page the on-call genetic counselor at 14642.
In fall 2017, CHOP’s Center for Cornelia de Lange Syndrome (CdLS) and Related Diagnoses joined the Roberts Individualized Medical Genetics Center. The CdLS Center’s move serves as the seed to grow a rare disease focus within the RIMGC. The mission of the CdLS Center is to provide individualized medical care and to improve the lives of children and adults with CdLS and related diagnoses.

The CdLS Center is composed of an internationally recognized team committed to children with conditions affecting growth, cognition and multiple body systems. To provide the best care, we work together across many specialties and with primary care providers so every patient has a personalized care plan that optimizes development and quality of life. The CdLS Center is also an international leader in research. Not only is it committed to further understanding the mechanisms involved with these diagnoses; it is also focused on therapeutics.

The CdLS 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. The center’s clinical operations are supported by an endowment established in 2010 by five families. The overall goal of the CdLS Center is to provide a unique and vibrant medical and research home for these children and families.

As a result of the Roberts IMGC’s successful efforts, we recognize more and more children are being diagnosed with rare and complex genetic conditions, like CdLS, that require similar lifelong comprehensive care. Therefore, we are committed to explore new ways to expand and enhance a rare disease focus within the RIMGC to meet the increased demand and accommodate more patients and families. Integrating the Center for CdLS and Related Diagnoses into the RIMGC is the first step.

The long-term goal is to make this newly incorporated rare disease focus comprehensive, to include additional multisystemic genetic diagnoses.

We are continually humbled by every encounter with a new or returning family. They inspire every member on our entire team to be the best they can be and to expand the Roberts IMGC in new directions to create a brighter future for all.

Kennedi, 6, is cared for by multiple specialists in the Center for Cornelia de Lange Syndrome and Related Diagnoses.
NEW TESTS, FASTER RESULTS
BENEFIT PATIENTS

The Division of Genomic Diagnostics (DGD) and the Roberts IMGC continue to work closely together on various initiatives. This year, the DGD made noteworthy strides in two areas: improving existing tests and developing new ones.

TEST IMPROVEMENTS

Audiome Version 2: The Audiome is the hearing loss gene panel that initially went live in September 2016. A new version of the test, currently under development, will update the test methodology. These improvements will allow for streamlined analysis of the results and will shorten turnaround times, both of which will contribute to better patient care. Members of the DGD and the Roberts IMGC have worked together to determine the appropriate updates to this test. The new version of the Audiome is expected to launch later in 2018.

Exome: Exome analysis is a complex test that involves broad-scale sequencing of the approximately 20,000 human genes known to contribute to disease. Since exome analysis launched in 2014, the gene sequencing has been performed through a core laboratory outside the DGD at CHOP, with the analysis performed in the DGD. Exome sequencing has been brought in-house effective March 2018, which will shorten turnaround times.

NEW TEST DEVELOPMENT

Exome Reanalysis: Due to the amount of data generated through this sequencing process, analysis is limited to genes known to contribute to the clinical features seen in an individual. When a genetic diagnosis cannot be made on a patient’s initial exome analysis, it is important to re-evaluate the patient in clinic to look for additional symptoms that may implicate other genes that should be reviewed. Exome reanalysis is a diagnostic test that will allow clinicians to request a review of the genetic data previously generated through exome analysis, but filtering that data using an updated list of genes associated with the individual’s clinical features. This test will allow for the diagnosis of patients with an evolving clinical presentation without repeating the time-consuming and costly sequencing steps.

Very Early Onset Inflammatory Bowel Disease (VEO-IBD) Panel: The DGD launched the VEO-IBD panel in February 2018. This panel is based on performing exome sequencing, with review of data only for genes that are known to cause VEO-IBD symptoms. Having a predetermined list of genes allows for automation of the filtering process. It also allows for sequencing of a larger number of genes simultaneously than could be accomplished through other methods. This panel is the first of its kind available on a clinical basis for VEO-IBD, and results will help guide clinicians in managing their patients.

Mitochondrial Genetic Testing: To date, all testing for CHOP patients to identify mitochondrial DNA (mtDNA) mutations has been sent to outside clinical laboratories. Bringing mtDNA testing in-house will allow for more comprehensive diagnostic services to be performed on-site. CHOP expects to launch this testing later in 2018.
My husband, Matt, and I were ecstatic to hear “You’re having a girl.” We were already blessed with Matthew, who was 3. I was thoroughly engrossed in my visions of a little ballerina, playing dress-up and all those girly-girl treasures we were about to experience.

After a normal pregnancy, we chose to be induced when I was full-term. After 12 hours of labor, Julia Grace was born on Aug. 26, 2013. Since she swallowed fluid during delivery, she spent five days in the hospital on antibiotics. On day two of her life, doctors suspected something was “off” genetically based on certain physical features. She had a genetic test called chromosomal microarray analysis, which came back as “normal,” meaning she has the correct number of chromosomes. But it didn’t rule out any specific single gene syndromes or disorders.

At Julia’s 1-week newborn well visit, her primary care pediatrician at CHOP Care Network Indian Valley, Arrene Santos, MD, heard a heart murmur and sent us to cardiologist Paul Stephens, MD, at Children’s Hospital of Philadelphia. She had an atrial septal defect, which is a hole in the wall separating the top two chambers of her heart, and was later diagnosed with a mild valve defect.

We went on with life. At about 4 months, we noticed Julia always felt “soft” or “weak” when we held her. She didn’t cry like our son had and wasn’t too interested in reaching for toys. Dr. Santos kept us on track and suggested we reach out to the Bucks County Intermediate Unit (IU) for help. By 8 months old, Julia had a physical therapist who came to her daycare for therapy. Over time, we added occupational and speech therapy.

At Julia’s 18-month well visit, Dr. Santos agreed it was time for medical testing to try to determine a diagnosis to explain her global developmental delays. Despite her therapies, she hadn’t “caught up to her peers” as we had hoped.

MULTIPLE TESTS
She had physical examinations, an MRI of the brain, an EEG and rounds of blood work. The MRI showed some abnormalities. None of these tests, however, provided a diagnosis. Neurology referred us to CHOP Genetics.

In June 2015, we first met with geneticist Elaine Zackai, MD, who recommended exome sequencing done at the Roberts IMGC. Despite
many months of phone calls, voice mails, emails and letters, neither of her insurances would approve the exome sequencing test. As parents, we were determined to get a diagnosis to ensure we were doing everything within our power to help Julia grow and succeed. To our great advantage, the testing would finally be done with the help of CHOP’s Financial Assistance Program.

Before the test, we met with genetic counselor Livija Medne, MS, CGC, and geneticist Ian Krantz, MD, to review and update Julia’s history and begin the consent process, which included the potential to find out about risks for other diseases that any of us may have. Livija patiently explained the options and consequences of our choices.

On Dec. 7, 2016, when we were about to sing *Happy Birthday* to Matthew, who was turning 7, Livija called. I will never forget that moment and the words, “We found something.”

Julia was diagnosed with ARID1B gene mutation related Coffin-Siris syndrome (CSS). I remember my hands shaking as I tried to write that down, with Matt just as intent and scared as I was.

**ONLY 200 CASES WORLDWIDE**

Livija explained everything and answered our questions in a calm, professional, caring and knowledgeable manner. She explained there were only about 200 known cases of CSS in the world. She also said it was a de novo mutation (not inherited from Matt or myself) and that we could have more children with a very low risk of recurrence. Some CSS characteristics we recognized in Julia include global developmental delays, intellectual disability, a shortened pinky finger and/or toe nail, and hypotonia (low tone). We talked about resources, support and other things that I’m sure I was half listening to at that point.

I do remember Livija saying that Julia is the same little girl she always was, and that this diagnosis doesn’t change her. It only makes us more powerful now that we have the knowledge to help her.

After more than three years of uncertainty and worry, we had our diagnosis. Now what? It’s very difficult to explain the emotions of relief and fear when they hit you all at once.

Soon after, we met with geneticist Matt Deardorff, MD, PhD, Dr. Zackai and Livija at the Roberts IMGC. They extended complete support to our family as we learned more about the diagnosis, discussed next steps and voiced concerns for Julia’s future.

As devastating as it was to be in that room, I remember clearly the big smile on Dr. Deardorff’s face watching Julia dance around the room. He said, “I like her; she’s cool!”

**FINDING THE JOY**

There are no known progressive medical conditions associated with CSS, but we do know that Julia will most likely not be able to drive a car or live on her own. We hold the highest hopes for her future. Whatever brings her joy, brings us joy.

Julia’s development is improving each day. She has a fantastic team of professionals at CHOP and the Bucks County Intermediate Unit, and a large family whose love could overcome the largest of obstacles.

Julia is the most precious daughter we could ask for. She has taught us more about patience, acceptance and faith than we could have ever imagined. Everyone who comes in contact with her is genuinely touched by her innocence, joy and love of life — and her hugs are fantastic, too. You will never meet a happier child.

Because of Julia, we reflect into our own lives to realize what is truly important. Matthew is an amazing older brother who, without even realizing it, will grow up with an extra acceptance and sensitivity for all kinds of people. Raising a child with special needs has its major ups and major downs, but we wouldn’t change a thing.
As the reputation of the Roberts IMGC’s capabilities has grown, more patients have sought our help. We project to nearly triple our patient encounters in four years. We also see adult patients, providing diagnoses to families that have often waited decades for answers. We have seen approximately 100 adult to date. In concert with the Division of Genomic Diagnostics, we are able to offer additional tests for specific conditions, leading to personalized treatments.
GENOMIC TESTING

- FY2015
  - Projected Tests: 124
  - Familial Variant Testing: 14
  - Karyotype: 1016
  - mtDNA: 96

- FY2016
  - Projected Tests: 116
  - Familial Variant Testing: 31
  - Karyotype: 84
  - mtDNA: 96

- FY2017
  - Projected Tests: 71
  - Familial Variant Testing: 71
  - Karyotype: 59
  - mtDNA: 84

- FY2018 Q1–Q3
  - Projected Tests: 26
  - Familial Variant Testing: 26
  - Karyotype: 317
  - mtDNA: 52
Parents want nothing more than their children to be born healthy and to start off life without constraints. So when our firstborn son, Caleb, was diagnosed with hearing loss, we were understandably crestfallen. So many thoughts run through a young parent’s mind. Was it our fault? What could have been done differently? Will he have trouble socially and academically? The uncertain future is what makes the beginning of this journey so difficult. But thanks to the support of Children’s Hospital of Philadelphia and the resources there, we are happy to report that Caleb is a thriving young man.

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When we were in the information gathering phase, our pediatrician instructed us to take Caleb to CHOP for a full evaluation. That turned out to be a life-changing moment. The incredibly knowledgeable staff gave us straightforward information and helped us understand how we needed to support Caleb, both at home and in his classrooms. They assisted us with our application for hearing aids and loaned us a pair until his were ready. The staff introduced us to families that had kids with similar circumstances and pointed us to educational resources like literature and seminars.

Adapted from submission by Caleb’s parents, Laurie Judd and Jared Young

UNCOVERING THE ‘WHY’
Through the early part of the process, we did not learn what caused Caleb’s hearing loss, as genetic testing and other medical tests turned up negative. Through the years, as Caleb became more aware of his challenge, our emotional journey became his.

**FINDING ANSWERS — FOR CALEB**

“If we don’t know what caused it,” he reasoned, “we can’t know if it’s likely to get worse or better, or even if it’s something that can be fixed.” Fortunately, genetic analysis was improving rapidly as Caleb got older. CHOP eventually pointed us to its Roberts IMGC, explaining there were now new genetic diagnostic tests for hearing loss.

When Caleb was 10, he underwent genetic testing again. We were impressed by how thorough the discussions were with the genetics team, and we were very excited when they came back to us with insight that genetics were indeed the culprit. It may not be something that can be “fixed,” but we certainly understand more about Caleb’s hearing loss.

One of the wonderful characteristics of everyone at CHOP is how well they relate to their patients. Following our experience with the Roberts IMGC, Caleb was taking a life sciences course and needed to write a final term paper. One of the choices of topics was genetic disease, and they listed several to choose from. However, Caleb had taken a great interest in his own genetic mutations and got permission from the instructor to use his own case. Jennifer Tarpinian, MS, CGC, one of the genetic counselors at CHOP, eagerly accepted his inquiry for an interview and explained how recessive genes work, what a gene mutation means and answered many other questions. Needless to say, the CHOP team’s passion is infectious and inspired Caleb to pursue learning about his own genetics.

Parenting a child with special needs is an emotional journey for the whole family, and we are eternally grateful to CHOP for helping us navigate the unknowns and develop Caleb into the strong young man he’s become.

*Above: Caleb, 12, with his parents Laurie Judd and Jared Young. Below: He elected to write a term paper on his own genetic disease, receiving an assist from Roberts IMGC genetic counselor Jennifer Tarpinian, MS, CGC.*
The Roberts Individualized Medical Genetics Center continues to grow as an integrated clinical service and has established itself as the facilitator for genetic testing across the Hospital. During fiscal year 2017, we consulted with 767 patients, performed testing on 515 and made a diagnosis in 174 of those tested (22.7 percent). The remainder of tested patients — 341 (77.3 percent) — were either negative or had uncertain genomic findings. We strongly believe there is an underlying genetic explanation for the undiagnosed patients, but we are limited by current clinical technologies and capabilities.

The need for answers for unsolved cases initiated a plan to integrate our clinical service into CHOP’s research infrastructure.

TWO MULTIHOSPITAL STUDIES
In January 2017, we received Internal Review Board (IRB) approval for the Pediatric Genomic Sequencing in Health and Disease study, which allowed our team and any researcher at CHOP to share de-identified data and samples internally or externally with other academic collaborators/industry partners. We hope to enroll participants with any suspected genetic disorder and create an unmatched resource for investigators in any specialty.

Our clinical and research team comprises scientists dedicated to identifying new genetic diseases and developing new ways to treat children with genetic disorders. At the RIMGC, we aim to facilitate these gene discoveries, translate genetic discoveries into novel therapeutics and ultimately improve patient care.

RIMGC clinicians are also involved in a groundbreaking collaboration — Genomics Research and Innovation Network (GRIN) — that pools the resources of three premier pediatric academic medical institutions (CHOP, Boston Children’s Hospital and Cincinnati Children’s Hospital) to accelerate genomic discovery and foster a culture of data sharing.

A wealth of data is available through electronic health records, clinical trials and data registries, but it is not feasible for individual researchers to comb through this information and extract what they need to identify large patient cohorts with deep phenotyping. GRIN aims to make this process more consistent, precise and seamless for its investigators by establishing a common infrastructure that makes it easy for investigators to collaborate and share data. More information at grinnetwork.org.

IN DOGGED PURSUIT OF ANSWERS
In addition to these two large-scale research efforts, our clinicians also pursue research in specific conditions or pathways. Some examples:

• Kosuke Izumi, MD, PhD, is studying genetic disorders associated with global transcriptional alteration such as CHOPS syndrome and Kabuki syndrome.
• Ian Krantz, MD, is working to find the genetic basis of Cornelia de Lange syndrome (CdLS), nonsyndromic hearing loss and Pallister-Killian syndrome.
• Matthew Deardorff, MD, PhD, is investigating the genetic causes of skeletal syndromes, limb formation and CdLS.
• In 2017 a syndrome named Skraban-Deardorff syndrome was identified based on the WDR26 gene discovery by two RIMGC clinicians, Cara Skraban, MD, and Deardorff.
• Louise Pyle, MD, PhD, is interested in the differences of sexual development.

Genetic findings have important implications for our patients and families — they lead to improved diagnostic capabilities, counseling, care and support.

RESEARCH COORDINATOR HONORED
Sawona Biswas, the clinical research coordinator for the RIMGC, was selected from among 27 nominees as one of two winners of the 2018 Clinical Research Coordinator RE@CH Award in May. Ian Krantz, MD, RIMGC co-director, congratulated Biswas. “She has taken on running the Genomics Research and Innovation Network (GRIN), which … has so many moving parts and people involved. Sawona has really been the anchor of that study. We’re really excited about everything she’s done, and in addition to her incredible talents for coordinating these studies, she is an incredibly nice, pleasant person who the families love.”
As the Roberts IMGC grows, we identify particular areas where our patients would benefit from specific, focused expertise. The Differences of Sexual Development (DSD) and Endogenetics Clinic within the RIMGC was started in 2016 to provide gold-standard clinical genetic diagnostics and counseling for patients with endocrine, hormonal, pubertal and sex development differences. The clinic was founded by Louise Pyle, MD, PhD, and Emma Bedoukian, MS, LCGC, who developed close liaisons with specialists from the divisions of Urology and Endocrinology to provide integrated multidisciplinary care.

Differences of sexual development (DSD) include variations in the usual path of prenatal development of the reproductive system that cause traits we don’t usually expect in typical boys and girls. There may be unexpected patterns of development of gonads (the term for testes, ovaries or ovotestes), internal reproductive and urinary organs (uterus, fallopian tubes, bladder and urethra), or external genitalia.

DIFFICULT QUESTIONS
Causes include changes in a number of sex chromosomes or single gene differences, which cause variations in gonads, exposure to unusual levels of sex hormones or levels of response to hormones. Most commonly, DSD conditions are not life threatening, but present a patient and family with difficult questions about identity and fertility. Some individuals with DSDs may have a higher risk of cancer of their gonads, and research into this issue is a specialty of Dr. Pyle’s, along with identifying new genetic causes of DSD. These questions require support and counseling, and are informed by the genetic cause of a person’s differences. The DSD and Endogenetics Clinic offers testing to identify the genetic cause, and, together with social work support, provides genetic and general counseling.

The Roberts IMGC, in general, supports clinicians of all specialties interested in pursuing complex genetic testing for their patients who likely have a genetic cause for their presenting features. Currently, the DSD and Endogenetics Clinic is growing under Dr. Pyle and Jacqueline Leonard, MS, LCGC, a genetic counselor who joined the RIMGC team in July 2017. Leonard is particularly interested in providing genetic counseling for complex testing and addressing the counseling and support needs of the patients we serve.

EXPERTISE FOR DSD NEEDS
Overall, the DSD and Endogenetics Clinic has seen and evaluated more than 70 patients, consulting with and counseling families for a variety of endocrine and DSD-related genetic conditions, and determining and coordinating genetic testing as appropriate. Visits are available for patients for whom a clinician has a specific test in mind and also for patients who need full evaluations.

For patients who would benefit from an evaluation with the DSD and Endogenetics Clinic, external referring clinicians can call the Roberts IMGC at 267-426-7418. CHOP clinicians can place a RIMGC consult order in Epic or page the on-call genetic counselor at 14642.
When I was 4, I figured out I didn't have a sense of smell. It was odd, but not a big deal, and my doctor wasn’t worried about it.

If you're going to be missing one of your senses, I nominate smell. Not being able to smell didn’t stop me from anything I wanted to do. I played soccer starting at age 6 and started lacrosse in elementary school. I've been a cheerleader since 10th grade, and I also play the drums, guitar and piano in addition to acting and singing in school musicals.

But as all my girlfriends were going through puberty, I was not. They were developing in ways I wasn’t. At 15, I was 5 feet, 3 inches, which was still in the normal range, but I hadn’t had a growth spurt.

I'm a happy-go-lucky type, so it didn’t bother me much. Still, my pediatrician said I should see an endocrinologist to determine if something was going on that we needed to address. In August 2016, we had an appointment at Children's Hospital of Philadelphia with endocrinologist Maria Vogiatzi, MD, who is Director of the Adrenal and Puberty Center.

I had several tests including an MRI of my brain to see if my pituitary or hypothalamus looked abnormal, but unfortunately nothing was conclusive. I had an ultrasound of my pelvic area, and I had all the necessary organs. Dr. Vogiatzi advised me to come back in six months to see if things had started on their own. When they hadn’t, Dr. Vogiatzi referred me to Louise Pyle, MD, PhD, and Emma Bedoukian, MS, of the Differences of Sexual Development (DSD) and Endogenetics Clinic, within the Roberts RIMGC (see related story on Page 15). They ordered genetic testing.

A DIAGNOSIS: KALLMANN SYNDROME

The genetic testing results confirmed their and Dr. Vogiatzi's suspicions, based on my missing sense of smell; I had Kallmann syndrome. I had a mutation in the \textit{FGFR1} gene. \textit{FGFR1} mutations are the cause of about 10 percent of Kallman syndrome cases.

Together, the RIMGC and Endocrinology teams explained that Kallmann syndrome is a genetic condition in which my hypothalamus, a gland in my brain, does not produce certain hormones that tell my pituitary gland to release more hormones to tell my ovaries to begin puberty. Some people with Kallmann syndrome also have complications such a cleft lip or palate, absence of a kidney, shortened digits, deafness, and abnormal eye movement, but I didn’t have those symptoms.

People with \textit{FGFR1} mutations may have any range of puberty from normal to start-and-stall puberty (which is what I had) to no hint of sexual development, which is called complete gonadotropin-releasing hormone deficiency. While, other than no sense of smell, I don’t have any of the other symptoms associated with a \textit{FGFR1} mutation, it's important I understand the full
spectrum since any children I may have could have a different set of symptoms (there’s a 50 percent risk each of them could inherit the syndrome).

The good news is that some aspects of Kallmann syndrome are treatable with medications that take the place of the missing hormones. Genetic testing allowed Dr. Vogiatzi to tailor my treatment, since it identified the exact genetic cause of my Kallmann syndrome.

**CATCHING UP**

Now I’m on hormone-replacement therapy, and it’s working. I’ve already grown 2 inches taller, and I’m catching up to my peers. Dr. Vogiatzi tells me there is a strong chance I’ll be able to have children in the future, with the help of medication.

But that’s WAY in the future. As a high school junior, I’m super busy. In addition to sports, I also volunteer at Princeton Special Sports, serve as a peer leader at my school, work in an ice cream shop and organize an annual Alex’s Lemonade Stand to raise money for pediatric cancer research.

Having Kallmann syndrome is just part of who I am, but not the most important part.

*Jill, 16, learned from genetic testing she had Kallmann syndrome. Since her diagnosis, treatment has put her growth back on track.*
Kym Boycott, MD, PhD, joined us Feb. 21, 2018, as the presenter for the first annual Clinical Genomics Lectureship as part of CHOP Pediatrics weekly Grand Rounds. Dr. Boycott is a clinical geneticist at the Children’s Hospital of Eastern Ontario (CHEO), a senior scientist at the CHEO Research Institute and a professor in the Department of Pediatrics at the University of Ottawa.

Her research is focused on bringing together basic science and clinical medicine. In line with this, she presented at the Department of Pediatric Grand Rounds on “Canada’s Path Forward for Rare Genetic Diseases: Discovery to Translation.” She reviewed the highlights derived from genome-wide sequencing of individuals with rare disease and eloquently detailed scientific processes and psychosocial implications — reviewing tools and mechanisms as well as diagnostic and therapeutic opportunities.

It was interesting to compare and contrast the genomics workflows in different countries. Following her Grand Rounds lecture Dr., Boycott spent the day meeting with clinicians and scientists. She had a mentorship lunch with residents and fellows from the clinical and laboratory training programs. At the end of the day she presented on “Solving the Unsolved: Strategies to Identify the Remaining Genes and Diseases.”

Both of Dr. Boycott’s talks were received very well, and we were so pleased to be able to have her as the inaugural lecturer.

Thank you, Dr. Boycott!
SHARING OUR EXPERTISE

SELECTED PUBLIC TALKS


SELECTED ACADEMIC COMMUNITY TALKS


Livija Medne, MS, LCGC. Large Scale Genomic Testing in Clinical Practice. Presented at: Pediatric Grand Rounds, Center Hospitalier de l’Universite Laval. Quebec, Canada.


Matthew Deardorff, MD, PhD. SMC1A mutations cause atypical Cornelia de Lange Syndrome and a Rett-like Epileptic Encephalopathy. Presented at: SMC Proteins Meeting. Nanyo City, Japan.


Ian Krantz, MD. Precision Pediatric Genomics Initiatives. Presented at: World Precision Medicine Conference. Washington, D.C.

Ian Krantz, MD. Developmental Insights from Rare Disease Research. Presented at: Grand Rounds at Baylor University. Waco, Texas.


Ian Krantz, MD. Genetic Testing and Research for CdLS. Presented at: Cornelia de Lange Congress. Pesaro, Italy.
UNDERSTANDING WHEN ‘TRANSCRIPTION’ GOES AWRY

A research group, led by Kosuke Izumi, MD, PhD, has been studying an expanding group of pediatric genetic diagnoses termed disorders of transcriptional regulation (DTRs). Transcription is one of the cellular processes regulating how cells use our genetic information to execute complex biological functions of our body. Recent studies, including Izumi’s, indicate that many pediatric genetic diagnoses are associated with abnormalities in transcriptional regulation, or DTRs. DTRs include many rare genetic diagnoses such as CHOPS syndrome and Kabuki syndrome. Utilizing the cutting-edge genomic technologies and biochemical analyses, Izumi’s group is trying to understand the molecular mechanism of various DTRs with the hope of identifying potential treatment strategies for children with these diagnoses.


SELECTED 2017 – 2018 PUBLICATIONS


The importance of genetic testing as demonstrated by two cases of CACNA1F-associated retinal generation misdiagnosed as LCA. Men CJ, Bujakowska KM, Comander J, Place E, Bedoukian EC, Zhu X, Leroy BP, Fulton AB, Pierce EA. Mol Vis. 2017;23:695-706.
Here and on the cover:
When genetic testing did not explain Olivia’s eye lid differences, her father, Brian Gottshall, enrolled her in research. As more genes are linked to additional conditions over time, Olivia’s genetic material will be tested again and could reveal a diagnosis. In the meantime, after two surgeries the 18-month-old is a happy girl on the go, as genetic counselor Emma Bedoukian, MS, LCGC, observes.