Making History,

Transforming the Future

RADY CHILDREN'S INSTITUTE FOR GENOMIC MEDICINE

Fiscal Year 2023 Performance Report

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Stephen Kingsmore, MD, DSc

Our Vision

Dear Friends,

As the Rady Children's Institute for Genomic Medicine embarks on its 10th year, I feel incredibly rewarded by the accomplishments we've made in our short history. In this, our 9th annual Performance Report, we review the major milestones we've reached since the Institute's inception as well as the goals we've achieved in fiscal year 2023.

Recently, our work at the Institute has become even more personally significant. Over the past two years, my family joyfully welcomed two baby girls – my granddaughter who is healthy and developing typically, and my great-niece who we diagnosed with a genetic disease that currently has no effective treatment. We love each of these girls so deeply, and it is our greatest wish that both would have the opportunity to thrive and grow into happy, healthy adults. This is yet another reminder for me, so close to home, about why we continue to do what we do.

The Institute's vision is bold – we want to change the world – but with our finite resources, we can't achieve it alone. This is why, in addition to doing groundbreaking genomic research, we are forming partnerships with like-minded organizations across the globe. It's the reason we collaborate with other research institutions and business partners. It's why we spend a great deal of time on thought leadership – working to share our vision and activate to advance the field.

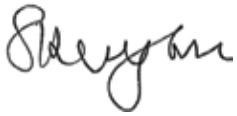
As you read this report, you'll see the Institute has continued to make history in FY23.

Additional milestones we achieved last year include:

- **Lynn Perez joined the Institute as Executive Director and the Hospital as Senior Vice President**. Lynn has deep experience in leading a research institute. As Executive Director, she manages Institute operations. This has dramatically increased the time I have to think creatively.
- **Initiated BeginNGS® – newborn screening for hundreds of disorders by genome sequencing – the most significant initiative in the Institute's history.** In the first year, 23 organizations joined as founding members, we expanded testing to over 400 disorders, and started an exploratory clinical trial at Rady Children's Hospital.
- **The massive operational disruption associated with the COVID pandemic ended.** Thanks to tremendous effort by Lynn, Tracey Lyman and our RCIGM leadership team members, we reduced our voluntary turnover rate from 30% to 8%.

I am so thankful to each member of the talented RCIGM team, as well as our dedicated board members and generous donors, for their contributions to our success. I could not be prouder of what we have accomplished thus far, and I am eager to continue our work together to transform the future of pediatric health care.

Gratefully,



Stephen Kingsmore, MD, DSc
President and CEO

Making History,

Transforming the Future

In the summer of 2014, after more than 18 months of planning, Rady Children's Hospital-San Diego launched its Institute for Genomic Medicine with a lead gift of $120 million from the Rady Family Foundation. A research organization embedded within the health system, the Institute was founded on the belief that every child who is critically ill with a condition of unknown origin deserves a rapid diagnosis.

Most of the time, a child's critical health problem has clear symptoms, and a diagnosis can be confirmed with common tests. And once clinicians have a diagnosis, they can focus on a plan for treating or managing the disease. But often a baby is born with an illness, or a family brings a sick child to the hospital, and, despite numerous tests and consults with specialists, clinicians are confounded about what is causing the problem. No one can pinpoint the reason for the illness – maybe it's a rare disease that only a handful of others in the world have experienced. Or, maybe it's so rare, it doesn't even have a name.

At least one in 20 children have a rare genetic disease. The financial burden of rare disease on the U.S. healthcare system is greater than $1 trillion. The incalculable human burden, however, is much more profound. On average, families of children with rare diseases spend nearly five years and visit more than seven specialists to get a diagnosis, if they ever get one at all. These families scour the internet to find others whose children have similar symptoms; they travel the world seeking out medical experts; their children undergo countless blood draws, evaluations, scans and trips to the hospital – all in the exhausting, agonizing pursuit of the answer to one question: "Why is my baby suffering?" **This is the diagnostic odyssey for a family whose child has a rare disease.**

It's an odyssey the Yiu family understands all too well (see pages 8-9 for their story).

The Rady Children's Institute for Genomic Medicine was established because its leaders and founders knew that answers to these kinds of medical mysteries could be hidden within a child's genetic code. And they knew advances in genomics and the emergence of personalized medicine held extraordinary promise to be the key.

Over the past nine years, through ambitious research and innovation, the Institute has made impressive strides in ending the diagnostic odyssey and we've made headway in ending the therapeutic odyssey as well. After pinpointing the root cause of previously unidentified conditions, our team then works to translate data into action (see pages 26-31 for news on this front).

The Rady Children's Institute for Genomic Medicine was established because its leaders and founders knew that answers to these kinds of medical mysteries could be hidden within a child's genetic code. And they knew advances in genomics and the emergence of personalized medicine held extraordinary promise to be the key.

Everything we've learned and achieved in our past has opened new doors to the remarkable places we're headed next — using next-generation technologies to identify genetic diseases, deploying artificial intelligence to more innovatively analyze data, implementing machine learning to help providers make care decisions, and contributing leadership and evidence to the growing movement to make screening by whole genome sequencing a standard of care for every newborn baby.

This Performance Report outlines the major achievements of Rady Children's Institute for Genomic Medicine in Fiscal Year 2023 (July 1, 2022 – June 30, 2023). The sections describe our milestones in

- Diagnostics
- Patient access and care
- Research
- Thought leadership and education
- Innovation
- Building support

These achievements demonstrate how the Institute is making history and manifesting the commitment to transform the future of pediatric healthcare through the power of RPM Rapid Precision Medicine™.

Meet Alex

The word *odyssey* is defined as “a long wandering or voyage usually marked by many changes of fortune.” And it’s no exaggeration to describe the Yiu family’s experience as the quintessential example of an odyssey. Alex Yiu was around 2 ½ years old in 2007 when his family first began noticing subtle changes in his motor skills and speech, and it wasn’t long before those changes caused enough concern to consult his pediatrician. From the beginning, Alex got his care at Rady Children’s Hospital; and despite numerous tests and consultations with specialists, a diagnosis remained elusive.

In 2012, doctors ordered genome sequencing, which Alex received at an outside facility because RCIGM had not yet been created. Still, the family got no answers. In the meantime, Alex continued to decline. He had seizures and severe muscle spasms. He lost the use of his hands, and eventually became unable to hold his head up, speak, eat, swallow or breathe on his own.

Over the years, Alex has been seen by 25 physicians across 16 specialties at Rady Children’s and is closely followed by pulmonary, otolaryngology, neurology, gastroenterology and rehabilitation medicine. Since 2014, his overall health management has been coordinated through Rady Children’s palliative care program. Alex’s mother, Caroline Cheung-Yiu, credits Dr. Marc-Aurele and Alex’s pediatrician, Dr. Sternfeld, as “the glue that keeps everyone on the same page.” Alex has been admitted to the hospital dozens of times, including 10 times in 2015 alone, when he was in hospice care for eight months. He returned to palliative care in 2016. In 2017, he spent six weeks in the intensive care unit and two more weeks in a pulmonary care unit for chronic respiratory failure. After more than three years of using a non-invasive breathing support device, his respiration declined to the point of requiring a tracheostomy, and he now relies on a ventilator 24/7. Alex’s ability to swallow also declined over a period of years, and after a series of grand mal seizures he could no longer eat safely by mouth, so he had a gastrostomy tube placed to deliver his nutrition.

In 2018, the Yiu family finally met with a change of fortune. A scientist at the organization where Alex’s genome had been sequenced put Alex’s DNA data through the analysis system again. This time, a variant on one of his genes was a match with an associated disease that had been discovered and added to the database after 2012.

The gene is called *IRF2BPL*, and the mutation of this gene causes a progressive neurodegenerative disorder called NEDAMSS (Neurodevelopmental Disorder with Regression, Abnormal Movements, Loss of Speech, and Seizures). After more than 10 years of relentless searching, at last there was an explanation for Alex’s condition. The disorder is so rare that Alex is one of just 19 recorded cases in the world.

The Yiu family's story underscores the rapid pace at which genomic discoveries are being made at RCIGM and around the world. There are children with gene variants whose significance is not understood today but may be discovered tomorrow or in the near future.

Now, armed with a definitive diagnosis, the Yiu family can focus on to their next journey: the treatment odyssey. Caroline says Alex remains unable to move or speak. His respiratory function continues to decline, but he is aware, remarkably cognizant and capable of communication. "Alex is incredibly strong and his 'Never Give Up' attitude continues to drive us all through the challenges," she says. Inspired by Alex's strength, the Yius are vocal advocates for funding research to find cures for rare diseases and have established a support group for other families in similar circumstances.

Support for Families on the Diagnostic and Therapeutic Odyssey

The Yiu family is building a community of people who wish to receive and offer support to each other as they navigate their rare-disease journeys. The group is called **CURE – a Community for the Complex, Undiagnosed, Rare and Extraordinary.**

Learn more at cureundx.com/.

> The commitment Ernest and Evelyn Rady and the Board have made is truly transformative. This Institute and gift will secure Rady Children's place at the leading edge of research, discovery and innovation into childhood disease and injury, and set national and international standards for pediatric care."

Donald Kearns, MD, MMM, then President and CEO of Rady Children's Hospital, speaking in 2015 about the gifts that launched RCIGM

Our Journey

TO TRANSFORM THE FUTURE

RCIGM History

The timeline on the following pages illustrates the key milestones in the history of Rady Children's Institute for Genomic Medicine. We are building upon this foundation of achievement to transform pediatric health care.

Dr. Gail Knight is Senior Vice President and Chief Medical Officer of Rady Children's Hospital San Diego. Since the idea for RCIGM was conceived, she has believed Rady Children's ability to provide its patients with rapid whole genome sequencing would be a differentiator in improving patient outcomes. "I knew that rapid whole genome sequencing was going to be impactful for patient care because of all the critically ill neonates that I had taken care of in my career without a definitive diagnosis," she says, "and I really felt that Rady Children's Hospital had the right people to do it. I knew that the neonatologists in our neonatal intensive care unit were committed to the idea that this was the right thing to do."

Gail Knight, MD, MMM

A History of Achievement

In less than a decade, Rady Children's Institute for Genomic Medicine has accomplished an impressive number of notable milestones in the work to transform pediatric genomic healthcare.

2013

- Business plan for RCIGM developed

2014

- $40M — RCHSD Board commits $40M to RCIGM
- RCIGM founded with Rady Family Foundation gift

2015

- $3.87M — Dr. Kingsmore brings $3.87M grant to RCIGM for NSIGHT rWGS® trial
- $2.5M — RCHSD Auxiliary funds $2.5M Endowed Chair in Neuroscience Genomics, Dr. Joseph Gleeson 1st chairholder
- $10M — $10M gift establishes Clayes Center for Neuro-oncology Genomics
- Dr. Stephen Kingsmore becomes CEO

2016

- Sanford Children's Genomic Medicine Consortium officially launches
- 1st national Frontiers conference
- 1st baby sequenced at Rady Children's Hospital

2017

- Partnership with Alexion begins, leading to GTRx®
- RCIGM Lab receives CAP accreditation and CLIA certification
- Scientific Advisory Board established
- 100 — 100th patient genome sequenced

2018

- 1st rWGS cost-effectiveness research published
- American Gastroenterological Association-RCIGM Research Scholar Award established
- State of California awards $2M to launch feasibility pilot, Project Baby Bear®
- 19.5 — 19.5-hour WGS record

Research · Education/Thought Leadership · Structure/Operations · Grants/Philanthropy · Sequencing · Partnerships/Alliances/Access

2018

- RCIGM named subawardee of Scripps Research $3.3M CTSA grant for GEMINI study
- Vermont Oxford Rady Children's Genomic Network launched
- 1,000th patient genome sequenced
- 11 clinical network hospitals nationwide

2019

- RCIGM receives $3.05M grant for Code Blue study
- Study published on 1st use of AI in clinical pediatrics for diagnostic use
- Blue Cross/ Blue Shield CA 1st commercial payor to cover rWGS

2020

- $1M gift from Marriott Foundation to fund sequencing
- Precision Medicine Clinic established
- Virtual Grand Rounds and Frontiers conference launched, expanding reach worldwide
- RCIGM receives $3.59M grant for SOMID study

2021

- RCHSD Board commits $60M to RCIGM
- Project Baby Deer initiates Medicaid coverage policy in MI
- Clinical network partner sites grow to 70
- 13.5-hour rWGS-to-diagnosis record
- Developed first prototype of GTRx care management system

2022

- Stephen Kingsmore named inaugural David F. Hale Chair in Pediatric Genomic Medicine
- Clinical network partner sites grow to 81
- $1.2M Conrad Prebys Foundation gift supports research to study technology to increase clinical utility of rWGS
- BeginNGS® launched, 388 disorders

2023

- 4,373rd patient genome sequenced
- Clinical network partner sites grow to 93
- 8 states with rWGS Medicaid policies
- BeginNGS 1st clinical trial, 411 disorders

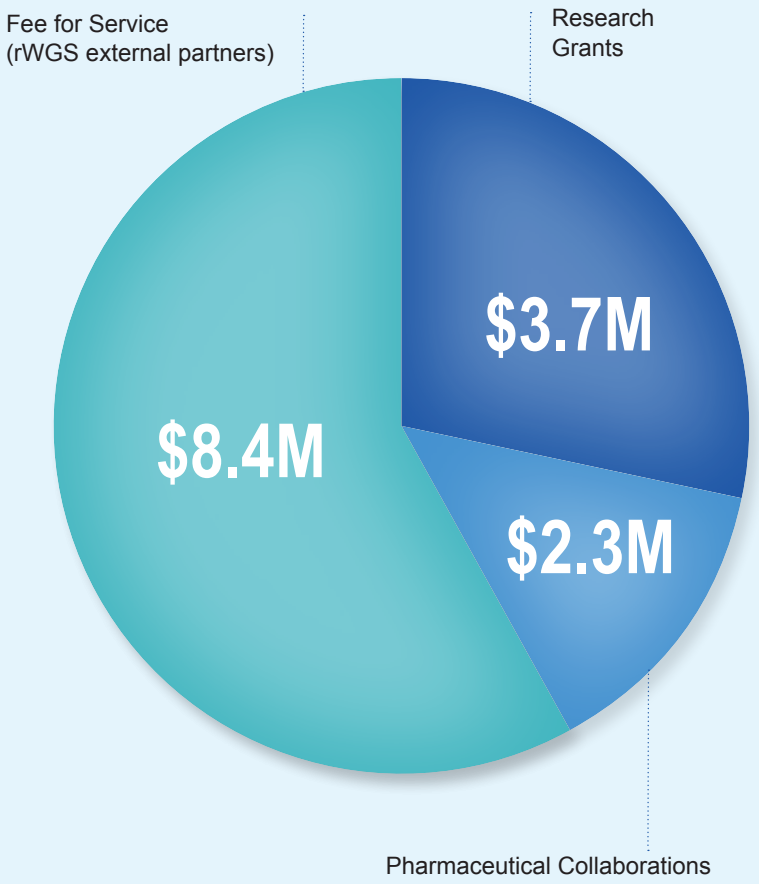
- Lynn Perez becomes SVP and Executive Director

RCIGM Impact
by the Numbers

As the Institute continues to evolve, our leaders periodically revisit our strategic plan to ensure we make a meaningful impact over time and move closer to achieving our vision. **During FY23, RCIGM's Board of Directors and executive leadership team began developing the framework of a new strategic plan that will define Institute priorities and guide our activities in the coming years.** Among these priorities will be continued focus on expanding children's access to rapid whole genome sequencing (rWGS); advancing research, science and innovation; and, through BeginNGS and other initiatives, working to establish whole genome sequencing as a standard of care for newborn screening.

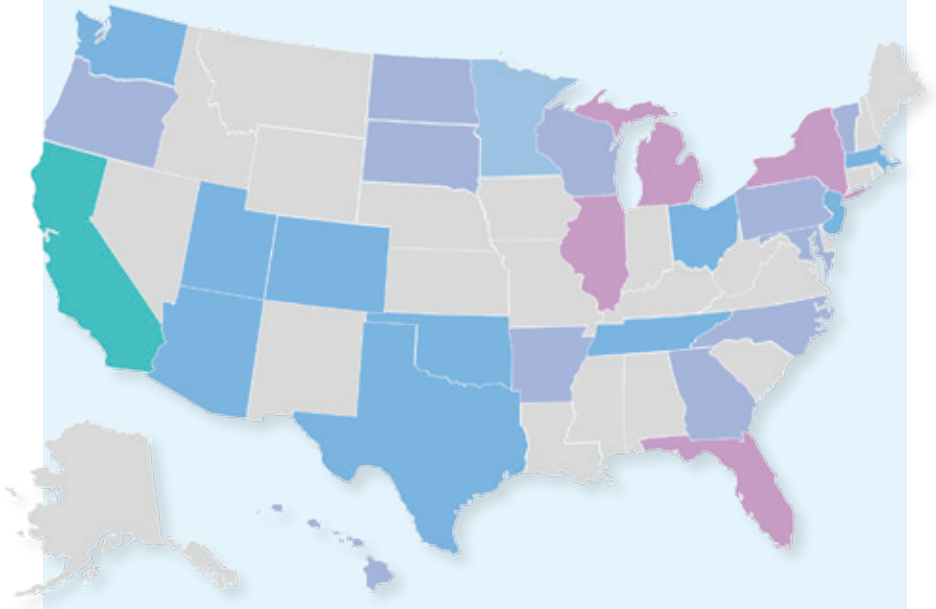
To ensure we stay on track with our strategic plan, we measure outcomes related to priority activities and report those metrics to the board each month. The following pages report the final outcomes related to our FY23 strategic activities.

Finance: FY23 Operating Revenue



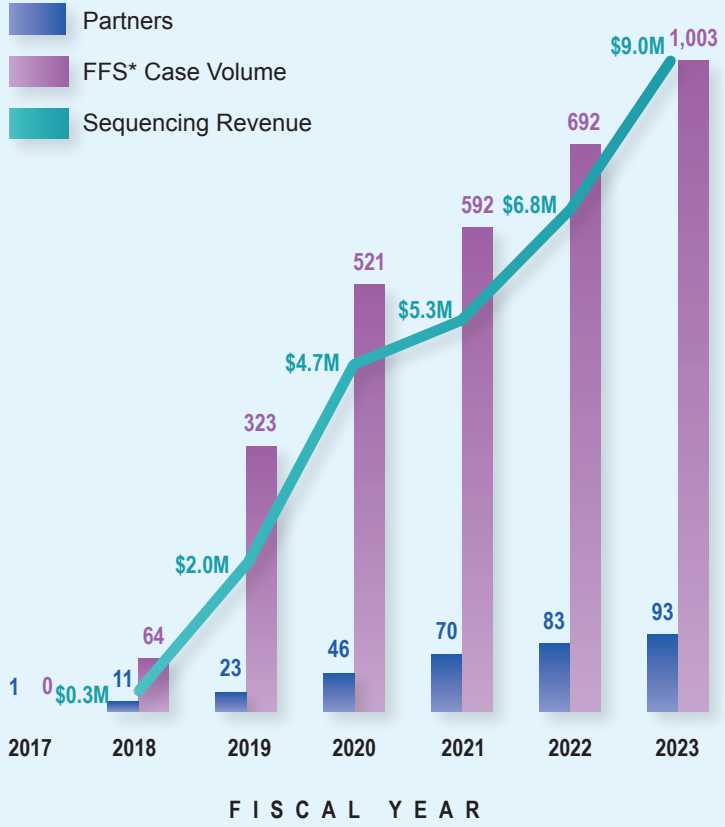
RCIGM Partner Network

93 partners in 28 states, 5 outside the United States



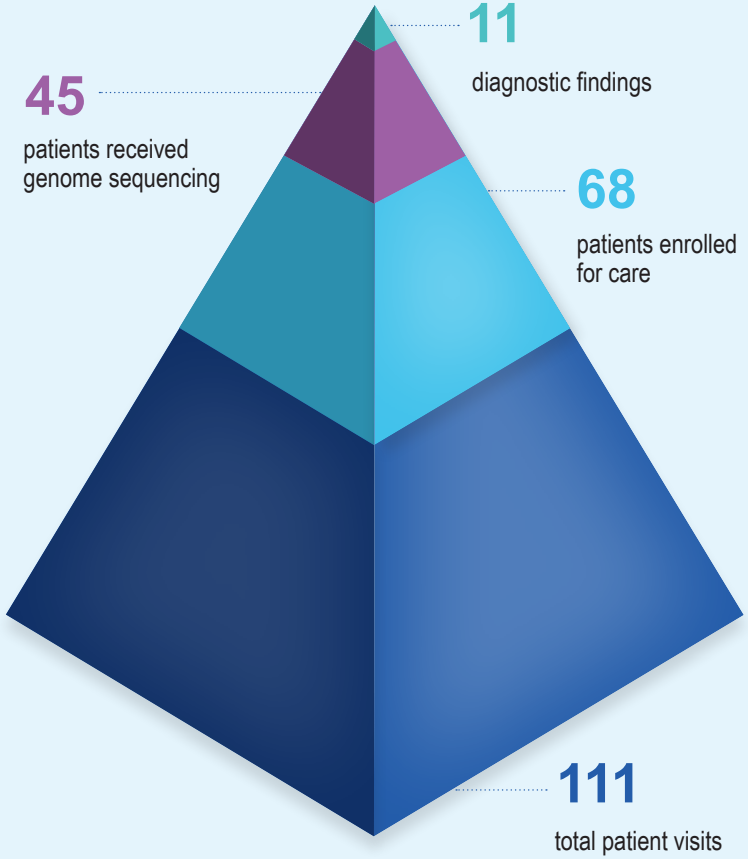
1 Site | 2-3 Sites | 4-10 Sites | 10+ Sites

Growth of rWGS Partner Network Over Time



*Fee For Service diagnostic rWGS

Volumes: FY23
Precision Medicine Clinic



People

Number of employees

86

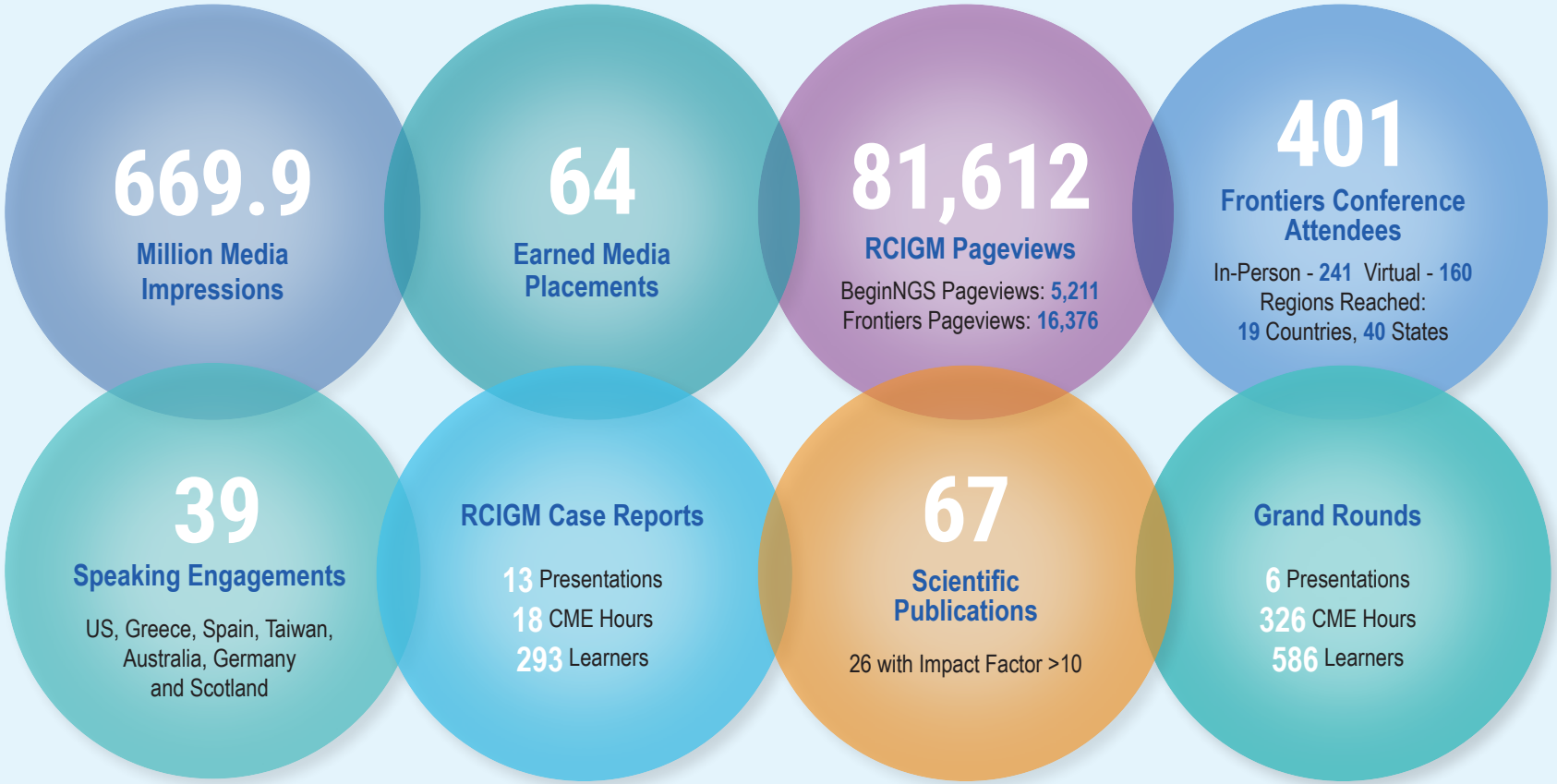
vs. 83 in FY22

Employee Retention

92%

8% turnover in FY23

FY23 Education, Engagement, Reach and Brand Awareness



The People of RCIGM

A critical part of the Institute's journey has been building a dedicated and talented team of people who execute the daily work required to achieve our shared vision. RCIGM started in 2014 with just three employees: by the end of FY23, the staff had grown to 86.

In addition to unifying the team around our inspiring mission, we strive to be a workplace where people feel included, empowered and appreciated. In FY23, we continued our focus on increasing employee engagement through various initiatives.

After a hiatus in FY22, the Institute resumed holding in-person quarterly all-hands meetings. In the revised meeting format, staff members enjoy flavored coffees while they get updates from RCIGM leaders and learn about one of the team's current projects. In addition, we began hosting monthly gatherings to celebrate birthdays, work anniversaries and other milestones. RCIGM Human Enterprise Manager Tracey Lyman says the gatherings have been a great way for employees to get to know each other better. "It's been a good opportunity to get our team together on a more social basis, especially within our hybrid work environment," she says. "Those face-to-face opportunities are just incredible."

In addition to creating opportunities for employees to hear what's going on and to get better acquainted with their colleagues, the Institute offered additional professional development opportunities in FY23. Fifteen staff members from various departments enrolled in a six-month project management course that allowed them to build and practice new skills that will benefit the Institute as well as their own long-term career goals. We also launched our first Leadership Training Series in February 2023 with 12 current and prospective leaders completing a 10-session leadership skill building course.

Thanks to these efforts, the Institute's overall employee engagement scores increased from 3.92 in FY22 to 3.94 in FY23. In addition, the Institute drastically improved employee retention with a reduction of more than 70% in employee turnover compared to FY22 (8.14% in FY23 vs. 30% in FY22).

Lyman sees potential to improve employee engagement even more in the future as leadership continues to solicit helpful feedback from employees. "There's always room to do better, but I'm proud to say we're on an upward trend," she says, "and I think our engagement scores and lower turnover rates are speaking to the success of our efforts."

RCIGM Staff Years of Service

0-2	2-5	5+	Total
44	25	17	86

“It’s been a good opportunity to get our team together on a more social basis, especially within our hybrid work environment. Those face-to-face opportunities are just incredible.”

Tracey Lyman, SPHR, SHRM-SCP, RCIGM Human Enterprise Manager

> The thing I most value is feeling like I can both get results quickly and be confident that the testing that was done was as sensitive as it could be."

Austin Larson, MD, Clinical Geneticist, Children's Hospital of Colorado

TRANSFORMING THE FUTURE WITH

Diagnostic Whole Genome Sequencing

300,000,000 Reasons

We Do What We Do

There are approximately 300 million people on the planet currently living with an undiagnosed rare disease. That's 300 million individual diagnostic odysseys potentially underway. We want to help end them all and then contribute to finding their treatment. The first step in this quest is making rapid whole genome sequencing accessible to more children, starting at home in San Diego County, then spreading across the US and beyond — to the farthest reaches of the globe.

To achieve these aims, it takes a cross-functional team of RCIGM's people from Information Technology/Information Management/Bioinformatics, Wet Lab, Interpretation/Reporting, as well as colleagues from Strategy and Business Development to address challenges in data interpretation, scalability and cost effectiveness with the implementation of diagnostic whole genome sequencing.

Thanks to the team's efforts, in FY23, **more than 300 children received a diagnosis across our 93 clinical network partner sites**, including our signature site at Rady Children's Hospital – San Diego. In addition, the Precision Medicine Clinic continued its outstanding coordinated care of kids with rare diseases (see pages 28-29) and we moved from the planning phase of BeginNGS® to the implementation stage (see pages 83-84).

The team also contributed to important research projects in FY23 including sequencing 557 genomes for Dr. Joseph Gleeson's research (see page 48) along with 529 dried blood spot genomes for the SOMI Infant Death study (see page 43). In addition, it started and/or completed several automation projects in FY23 with the goals of increasing diagnostic yield and reducing manual processing, which reduces turn-around time and/or improves quality.

Making strides in increasing diagnostic yield, our team added two new conditions we can now report out when found: Uniparental Disomy (UPD) and Trinucleotide Repeat Expansion (TRE).

UPD is an genome abnormality in which both parts of a chromosome pair are inherited from one parent, and the other parent's chromosome for that pair is missing. The condition causes Prader-Willi syndrome and Angelman syndrome, both characterized by intellectual disability, small stature and a host of other symptoms.

TRE is a type of genetic mutation implicated in at least seven disorders: X-linked spinal and bulbar muscular atrophy (SBMA), two fragile X syndromes of mental retardation (FRAXA and FRAXE), myotonic dystrophy, Huntington's disease, spinocerebellar ataxia type 1 (SCA1) and dentatorubral-pallidoluysian atrophy (DRPLA).

In FY23, the team also automated the identification of variants in the *DMPK* and *PHOX2B* genes, followed by clinical validation. This automation will expedite the process of identifying variants in these genes in the future and reduce the chances of human error and researcher bias.

Mutations in *DMPK* cause myotonic dystrophy type 1, characterized by progressive muscle wasting and weakness. More than 75 mutations in *PHOX2B* have been found to cause congenital central hypoventilation syndrome (CCHS). CCHS occurs in about one in 200,000 people and typically begins in infancy. It is characterized by shallow breathing, especially during sleep.

Another big achievement in FY23 was the successful annual inspection of RCIGM's laboratory — the Clinical Genome Center. The regulatory body that performs these inspections recognized our lab's quality systems and processes with zero deficiencies.

> "I'm incredibly proud of the way our team works together. It's amazing how much we have accomplished thanks to their diverse talents. Their work is foundational, but transformative. I know many children have benefited already and will continue to reap the results in the future."
>
> **Wendy Benson**, Chief Strategy and Innovation Officer, Rady Children's Institute for Genomic Medicine

We expanded access to rWGS for even more children by adding 12 more clinical network partners. Plus, our team advanced reimbursement efforts, adding Louisiana, Florida and Arizona to the list of states whose Medicaid programs pay for rWGS in inpatient settings. There are now eight states whose Medicaid programs offer this benefit (see item on Project Baby Deer's accomplishments in Michigan on pages 24-25). Making reimbursement a reality is a big step in transforming rWGS from an analysis of last resort to a routine, standard-of-care test for patients who need answers.

In FY23, RCIGM completed its first sponsored testing arrangement with Inozyme Pharma. The arrangement engages clinical sites to rapidly identify potential patients for Inozyme's pediatric clinical trial for a condition called generalized arterial calcification of infancy (GACI). GACI is a rare genetic disorder of the circulatory system that causes dysfunction and potential failure of major organs, such as the heart, lungs and kidneys.

"I'm incredibly proud of the way our team works together," says Wendy Benson, RCIGM's Chief Strategy and Innovation Officer. "It's amazing how much we have accomplished thanks to their diverse talents. Their work is foundational, but transformative. I know many children have benefited already and will continue to reap the results in the future."

Conversation with a Champion:

Q&A with Caleb Bupp, MD, FACMG, from DeVos Children's Hospital

Dr. Caleb Bupp is a medical geneticist and Division Chief of Medical Genetics and Genomics at Corewell Health West and Helen DeVos Children's Hospital in Grand Rapids, Michigan. He is a leading champion of Project Baby Deer (PBD), a statewide initiative designed to increase access to rapid whole genome sequencing (rWGS) for children. Bupp answered some questions about PBD, which was inspired by the success of RCIGM's Project Baby Bear®.

Q: So how did PBD actually get going in Michigan? How did it evolve?

A: The seed was planted when Dr. Kingsmore presented at DeVos Grand Rounds in 2017. He was talking about things that were coming, what we should be aware of and engaging in. Then, in 2018, RCIGM helped us test six cases with support from our hospital foundation to understand the impact of WGS on care and outcomes. The results of that experience were really compelling. Not much later, we heard a presentation on Project Baby Bear at the 2019 Frontiers Conference, which inspired a conversation about launching a similar project in Michigan.

We went back home and did a joint presentation with the Michigan Health and Hospital Association that June, and later that year a growing number of hospitals and administrators lent their support. We launched PBD in 2020 and continued to expand the program ever since. Within a year, Michigan became the first state to make rWGS a covered benefit for eligible infants enrolled in Medicaid, which means Michigan Medicaid will reimburse hospitals for rWGS testing separate from their standard daily-rate payments for hospital stays.

Q: What were some of the major accomplishments of PBD in FY23?

A. Coverage started in September 2021, and we're now starting to see actual reimbursement happening, which is a great step forward. That coverage policy made a big difference in other hospitals becoming more engaged in requesting rWGS testing. Also, RCIGM helped us develop a set of educational materials for hospitals that are just getting started ordering the testing. But the biggest thing is probably the paper we had published [Breaking Barriers to Rapid Whole Genome Sequencing in Pediatrics: Michigan's Project Baby Deer" – *Children*, January 2023]. I think anytime you can get into the literature just helps move the needle a little bit.

Q: How has it been working with RCIGM in launching and growing PBD?

A: I think the phrase that comes to mind is "doors wide open." There's been an incredible level of transparency – a kind of teaching-other-people-to-fish type of situation. And it is really

nice to go into something that feels new and novel, particularly in your institution or your state, and to go with a friend who's done it and who's willing to help you. That's just a massive advantage to start into something, and it was certainly a key part of the success and the ongoing work.

Q: PBD is a very collaborative effort – no single organization or individual "owns" it – but you're certainly one of the chief ambassadors of the project. What does that mean to you, and what gets you excited for the future?

A: I think any time that you get the opportunity to champion something so wildly beneficial, that's the kind of thing that gets you up in the morning. You don't get too many opportunities in your career to have something come along that will help your patients, help their families, help you, help your hospital, help your health system, help your state. Like, dang, that's just pretty rare. So, I think for me, that's been the greatest joy and reward.

As for the future, my hope is that this is a sort of a self-fulfilling cycle, that one improvement leads to another, leads to another. And I feel like we're ultimately going to see that one state collaboration will lead to another because there's a bit of a 'FOMO' [fear of missing out] to this. One state sees another one do it, and they're like, "Oh, wait, now we have to do it." So, it's fun to have played a part in helping get that started and figure out where we're gonna take it from here.

> She just said, 'When you guys told me what she had, I broke down crying. You just lifted this weight that I've carried for 11 years that I did this, even though I tried everything possible to have a healthy pregnancy. You don't know how much it means to know that this wasn't something that I did.'"

Genetic Counselor Jerica Lenberg, MS, LCGC, describing how a patient's mother reacted to her daughter's diagnosis

TRANSFORMING THE FUTURE WITH

Genome-Informed Care Delivery

At Rady Children's Institute for Genomic Medicine, we tirelessly collaborate on innovations and studies that document the clinical and economic value of rapid whole genome sequencing (rWGS) in critical neonatal and pediatric care. We then work to translate that research and innovation into delivering genome-informed care that's tailored to the individual patient to improve outcomes. We call this RPM Rapid Precision Medicine™.

RCIGM researchers recently collaborated on a study with colleagues at Cedars Sinai Medical Center and OSF Children's Hospital of Illinois to demonstrate the clinical value of rWGS for patients in the pediatric intensive care unit (PICU). **Findings of the study were published in the January 2023 issue of *Critical Care Medicine*. The study, "A Multicenter Cohort Analysis of Rapid Genome Sequencing in the PICU,"** determined that diagnoses of genetic disorders in the PICU population frequently resulted in changes in care during hospitalization.

In our ongoing effort to deliver genome-informed care, in FY23, we continued the operation of the Precision Medicine Clinic (PMC) at Rady Children's Hospital. In the PMC, professionals from several disciplines coordinate the multi-faceted care required by children diagnosed with or suspected of having a rare genetic disorder (see pages 28-29).

Of course, we hope treatments will become available someday for all rare diseases. But today, the vast majority of more than 7,000 genetic disorders don't yet have therapies. However, even when a disease has no known treatment, having a genetic diagnosis is valuable in the care of a child. "The moment you understand a disease is life-limiting, it restores decision-making capability for the family," says Dr. Stephen Kingsmore. "It becomes about 'what are your wishes?' They get to control these decisions. It becomes about precision palliative care."

Customized, Coordinated Care:

The Precision Medicine Clinic

FY23 marked three years since the Precision Medicine Clinic (PMC) opened its doors. A collaborative partnership between the RCIGM and Rady Children's Hospital's clinical division of genetics, the PMC combines rare-disease research with clinical care for children with confirmed or suspected genetic disorders.

Dr. Kristen Wigby, the founding Medical Director of the PMC, explains the benefits of the clinic's interdisciplinary model. "Families that have a child with a rare disorder often have the burden of so many appointments," she says. "There's so much that they're trying to coordinate that it was really important to us to make the process as easy as possible for them."

Rather than a family making separate visits to multiple specialists, it's all covered in one visit to the PMC. "In the same room, you have the doctors – genetics and neurology. You have a genetic counselor, and you have the research team there," says Wigby. "And, at the same time, we offer all families the opportunity to participate in rare disease research." If a family decides to participate in research, they can meet with the research team the same day if their schedule permits.

The PMC Team reviews each new patient's history and results from previous tests to determine the most appropriate next steps. Sometimes the next step is whole genome sequencing because the patient didn't have prior access to it. Other times, the patient has had sequencing, but results were inconclusive, so the team serves as a fresh set of eyes to re-examine the genome data and determine whether additional testing is warranted.

There is much about the human genome that is not yet understood. Scientists still have much to learn about complex genetic mechanisms and gene-environment interactions that likely play a role in health and disease. Wigby explains current reports don't always capture relevant information. "So that's where our team goes beyond just getting your genome report,"

> "Families that have a child with a rare disorder often have the burden of so many appointments. There's so much that they're trying to coordinate that it was really important to us to make the process as easy as possible for them."
>
> Kristen Wigby, MD

she says. “It’s taking those next steps to try to help families, continue to work for answers, to connect them with other research and collaborations, and then to launch families on their treatment journeys.”

Dr. Jennifer Friedman is the PMC’s Director of Therapeutics. The treatment odyssey can now begin for one of her patient families thanks to her recent discovery of a new disease gene called *DAGLA* (see pages 40-41). And one of Wigby’s patients from the PMC recently began a new treatment for symptoms of a disorder she and her colleagues linked to the *ARF1* gene (see page 51). Additional research on the underlying biology of *ARF1* enabled Wigby to recommend a promising targeted dermatologic therapy for a painful rash associated with the child’s disease.

“That’s always what we’re really excited to do is to bring it full circle – all the way to the treatment,” says Friedman. “So not only are we providing the diagnosis, but we can actually do something about it.”

Increasing Patient Access to New Technologies

Sometimes despite a strong suspicion of a genetic reason for a child’s disease, whole genome sequencing doesn’t provide a diagnosis. Dr. Kristin Wigby explains what feels to care providers like a bit of a dead end: “We’ve done their genome, we’ve taken an extra-close second look, we’ve done all we can, yet we don’t have an answer. We know these kids have some underlying medical problem causing their condition; we want to get answers for their families.”

In FY23, the Institute received research funding that may help our care providers find those answers. The Danaher Foundation awarded a $75,000 program grant to explore cutting-edge technologies, such as long-read sequencing and methylation profiling, to tackle some of the most difficult diagnostic odyssey cases.

“We’re very grateful to have this support,” says Wigby, “because it allows us to go above and beyond to try to find answers for our patients.”

Meet Mario:

rWGS® Reveals Genetic Explanation for Heart Failure

Mario Luna is a typical 14-year-old kid who loves basketball and hanging out with his friends. But what happened to him on January 12 is anything but typical. With almost no warning, the Culver City eighth grader's heart began to fail. It started with a stomachache, but soon after, Mario's heart was beating uncontrollably, and his breathing grew labored.

By the next day, Mario was on a heart-lung bypass machine at Children's Hospital of Orange County (CHOC). His heart that had been pumping at a normal rate was now beating up to 240 times per minute – as if he had been sprinting a quarter mile. His life that had been so normal was now in grave danger.

Dr. Jason Knight from CHOC referred Mario to Rady Children's Hospital-San Diego, where he could receive the specialized care he needed. By the time Mario was admitted on January 15, his heart function had deteriorated so much that doctors put him into a medically induced coma to allow his heart to rest.

"When Mario came to us, he was so sick that his body couldn't keep up with the heart function that he had," says Dr. Matthew Bock, director of the Rady Children's heart transplant program.

"We didn't know if there was an infection that had attacked his heart, or if he was having arrythmias that were causing it or some other form of hereditary kind of problem."

To figure out why Mario's heart was suddenly failing, his care team ordered several tests, including ultra-rapid whole genome sequencing from RCIGM. That test revealed the answer: Mario had a mutation in a gene called *TTN*. This gene produces proteins called titins that help heart muscle cells stick together and contract properly. Due to the gene mutation, Mario's body couldn't make normal functioning titins, which led to his heart problems.

Armed with this information, Mario's doctors knew what needed to be done. Because there is currently no medication or other therapy to treat this condition, the only option was a heart transplant. Mario and his family were shocked at the sudden turn of events. "My whole world just came crumbling down because I was like, how do we go from stomachache to heart transplant so quickly?" says Mario. But he felt confident the transplant would return him to health. "I didn't even hesitate. I just went for it and said, 'Let's not waste time.'"

> "I feel amazing. I feel pretty good about having a brand-new heart and just living my life."
>
> **Mario Luna**, Rady Children's patient

After only four days on the transplant list, Mario received a donor heart. The surgery was a success and Mario's road to recovery began. Fortunately, his donated heart is not affected by the *TTN* mutation, and he can expect to make a full recovery.

Jerica Lenberg, a genetic counselor with RCIGM and Rady Children's, describes the value of complete clarity that comes with having a specific explanation for a patient's problem. "Mario's condition was so poor, they would have done the transplant regardless, but without the results of the genome sequencing, they would never have known why the heck this teenager has an enlarged heart that's failing." says Lenberg.

In addition to providing important information to an individual and his care providers, the benefits of having genetic test results can extend beyond the patient. "Not only can we remove the question mark on why this happened," says Lenberg, "We can also ask who else might be at risk in the family." Now Mario's family is aware and can make decisions based on their own risks for the same genetic condition.

Today, Mario is a very grateful young man. He credits his amazing recovery to his donors, and his experience has inspired him to encourage others to be organ and blood donors. With a new heart, he feels empowered to return to playing basketball and spending time with friends like a typical teen. "I feel amazing. I feel pretty good about having a brand-new heart and just living my life."

To read more about Mario's story and to watch a video about his experience, go to radygenomics.org/mario.

> There's growing favor for the idea of doing rapid whole genome sequencing not as our final thing, but doing it from the start. We're in a great space to be part of that here."

Amber Hildreth, DO, FAAP

TRANSFORMING THE FUTURE WITH

Research and Science

Research and Science —

The Backbone of Our Work

The backbone of our work is unlocking the complexities of genetic disease through scientific research.

We are accelerating the pace of discovery and building the evidence base to advance delivery of Rapid Precision Medicine™ as the standard of care for children with genetic diseases.

The Institute is fortunate to have a diverse team of thought leaders in the areas of pediatric genomic medicine. They have a broad spectrum of interests and expertise that range from fetal anomalies to rapid whole genome sequencing for neonates, to pediatric brain tumors and teenagers with psychiatric disorders. RCIGM researchers focus on a variety of genetic conditions and take different approaches including prospective and retrospective studies, work in wet labs and developing algorithms to analyze data.

Each story in this section introduces you to one of RCIGM's brilliant investigators and highlights some of their most significant achievements in FY23. To transform the future, Institute investigators are pursuing projects with multi-faceted purposes, including the following:

Expanding understanding of the genome and improving diagnostic yield to end the diagnostic odyssey
Researching the utility of new sequencing technologies and unlocking insights from genomic and phenomic data (see pages 36-43).

Advancing technology
Creating and implementing new technological tools such as AI and machine learning to efficiently process immense amounts of data more accurately and efficiently (see pages 44-49).

Implementing clinical utility
Working to increase access to diagnostic rapid whole genome sequencing and advocate its use as a standard of care and practice (see pages 50-51).

Improving knowledge about specific diseases
Advancing knowledge about causes and treatments for specific disease types (see pages 52-59).

Ending the therapeutic odyssey
Discovering information to affect positive change in care management and outcomes, moving closer to a day when we can develop therapies for children with rare genetic disorders (see pages 60-61).

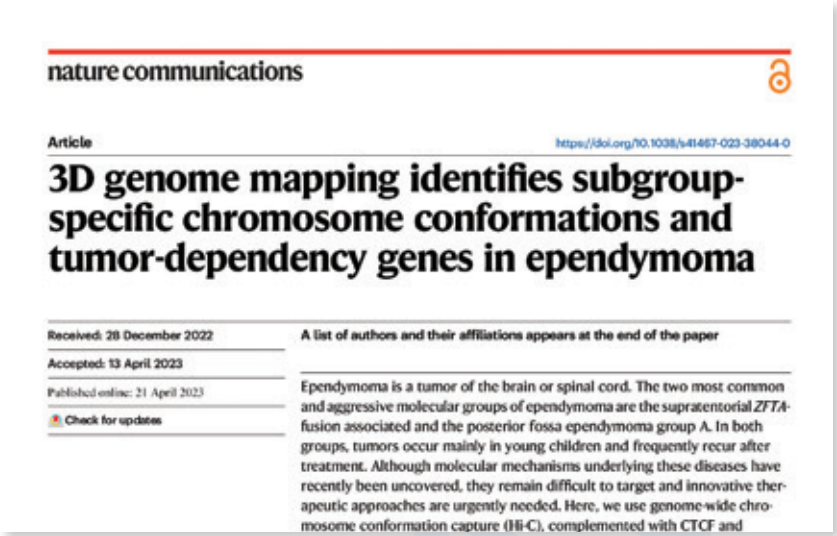
Building partnerships
Seeking out partnerships with other institutions and industry who share our vision; breaking down silos to form synergies by combining our unique strengths (see pages 62-67).

Seeking answers for all
Keeping in mind the importance of diversity, equity and inclusion, knowing rare diseases affect children of every race, religion and socio-economic background (see pages 68-69).

Scientific Publications

An important objective indicator of investigators' success is having manuscripts published in scientific journals describing the results of their work. "This was a banner year for publications by our research team," says RCIGM President and CEO Dr. Stephen Kingsmore. "I believe this metric measures us getting better at our jobs." In FY23, RCIGM researchers had 67 manuscripts accepted for publication in scientific journals. Twenty-six of the 67 publications were in journals with an impact factor greater than 10. The stories within this section mention several of these outstanding papers published in a variety of journals. Here we feature two other especially impactful manuscripts published in FY23:

> This was a banner year for publications by our research team. I believe this metric measures us getting better at our jobs."
>
> Stephen Kingsmore, MD, DSc



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3D genome mapping identifies subgroup-specific chromosome conformations and tumor-dependency genes in ependymoma

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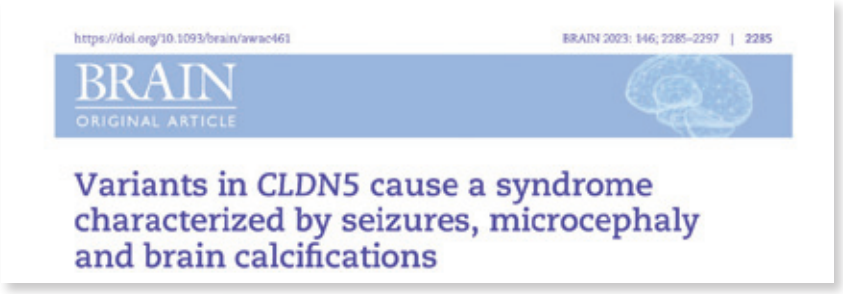
Ependymoma is a tumor of the brain or spinal cord. The two most common and aggressive molecular groups of ependymoma are the supratentorial *ZFTA*-fusion associated and the posterior fossa ependymoma group A. In both groups, tumors occur mainly in young children and frequently recur after treatment. Although molecular mechanisms underlying these diseases have recently been uncovered, they remain difficult to target and innovative therapeutic approaches are urgently needed. Here, we use genome-wide chromosome conformation capture (Hi-C), complemented with CTCF and

Nature Communications, April 21, 2023: "3D genome mapping identifies subgroup-specific chromosome conformations and tumor-dependency genes in ependymoma"

Konstantin Okonechnikov, Aylin Camgöz, Owen Chapman, Sameena Wani, Donglim Esther Park, Jens-Martin Hübner, Abhijit Chakraborty, Meghana Pagadala, Rosalind Bump, Sahaana Chandran, Katerina Kraft, Rocio Acuna-Hidalgo, Derek Reid, Kristin Sikkink, Monika Mauermann, **Edwin F. Juarez**, Anne Jenseit, James T. Robinson, Kristian W. Pajtler, Till Milde, Natalie Jäger, Petra Fiesel,Ling Morgan, Sunita Sridhar, Nicole G. Coufal, Michael Levy, Denise Malicki, **Charlotte Hobbs**, **Stephen Kingsmore**, Shareef Nahas, Matija Snuderl, John Crawford, Robert J. Wechsler-Reya, Tom Belle Davidson, Jennifer Cotter, George Michaiel, Gudrun Fleischhack, Stefan Mundlos, Anthony Schmitt, Hannah Carter, Kulandaimanuvel Antony Michealraj, Sachin A. Kumar, Michael D. Taylor, Jeremy Rich, Frank Buchholz, Jill P. Mesirov, Stefan M. Pfister, Ferhat Ay, Jesse R. Dixon, Marcel Kool, **Lukas Chavez**



Brain, June 2023: "Variants in *CLDN5* cause a syndrome characterized by seizures, microcephaly and brain calcifications"

Ashish R Deshwar, Cheryl Cytrynbaum, Harsha Murthy, Jessica Zon, David Chitayat, Jonathan Volpatti, Ruth Newbury-Ecob, Sian Ellard, Hana Lango Allen, Emily P Yu, Ramil Noche, Suzi Walker, Stephen W Scherer, Sonal Mahida, Christopher M Elitt, Gaël Nicolas, Alice Goldenberg, Pascale Saugier-Veber, Francois Lecoquierre, Ivana Dabaj, Hannah Meddaugh, Michael Marble, Kim M Keppler-Noreuil, Lucy Drayson, Kristin W Barañano, Anna Chassevent, Katie Agre, Pascaline Létard, Frederic Bilan, Gwenaël Le Guyader, Annie Laquerrière, Keri Ramsey, Lindsay Henderson, Lauren Brady, Mark Tarnopolsky, **Matthew Bainbridge**, **Jennifer Friedman**, Yline Capri, Larissa Athayde, Fernando Kok, Juliana Gurgel-Giannetti, Luiza L P Ramos, Susan Blaser, James J Dowling, Rosanna Weksberg

Research Grants

Our impressive strides in breakthrough genomic research are possible only through the generous support of research grants. In FY23, the Institute was fortunate to be awarded $303,000 in federal funding and $128,000 in other grants as follows:

Translator NIH grant of $78,000. December 2022, Dr. Charlotte Hobbs, primary investigator.

Clinical Translational Science Award (CTSA) grant (sub awardee) of $225,000 for each of the next seven years. March/April 2023, Dr. Stephen Kingsmore, primary investigator and Dr. Charlotte Hobbs, co-investigator (For more information on the CTSA grant, see page 64).

Danaher Community Impact grant of $75,000. December 2022, Precision Medicine Clinic.

SENSE Foundation Brussels two-year grant of $53,000. December 2022, BeginNGS®.

Solving Mysteries

Using Genome Sequencing

When you hear Dr. Erica Sanford Kobayashi speak about her work, you start to feel she might have missed her calling as a detective. But then you realize she is a detective of sorts – it's just that she's trying to solve mysteries about why children get sick and die when there's no clear reason.

Dr. Sanford often sees babies and young children who have been admitted to the hospital with life-threatening illnesses she strongly suspects have a genetic cause. Sometimes, whole genome sequencing confirms those suspicions. Other times, despite her confidence in a genetic reason for a baby's condition, conventional sequencing doesn't point to a mutation to explain the problem.

Sanford explains, "Sometimes I think to myself, there's 100% no way this kid doesn't have a genetic diagnosis." She recalls a patient she saw recently who had acute liver failure and whose sister had died of acute liver failure nine years prior, yet sequencing didn't result in a genetic explanation. "I thought, this is just not *not* genetic," says Sanford, "I wonder, are we just missing something that we couldn't find currently?"

Sanford and her colleagues recently conducted a study to help answer that question. The study used new technology called long-read sequencing with the hope of improving the diagnostic rate of genomic diseases, which has been mostly stagnant at around 35% for about 10 years. **Sanford was first author of a paper, published in October 2022 in *Scientific Reports*, entitled "Approaches to long-read sequencing in a clinical setting to improve diagnostic rate," detailing the team's findings.** Using long-read technology, they discovered a new gene mutation to explain a baby's severe immunodeficiency. Short-read sequencing, the current industry standard, missed identifying this mutation because of its limitations in interpreting certain areas of the human genome. This research suggests that long-read technology has several advantages over short-read sequencing and gives new hope for solving more mysteries about what causes rare and ultra-rare diseases.

> "The DNA you're born with is the DNA that you will die with. So, the data will still be just as good in 20 years. It would be great to just have it now, then we'll be able to do so much more with it over time."
>
> Erica Sanford Kobayashi, MD

This paper is just one of seven that Sanford published in FY23. She also helped author a paper published in March of 2023 describing a project in which she and her colleagues developed an automated way to determine which babies in the neonatal ICU may be candidates for whole genome sequencing. Sanford was a key player in writing the grant application for a $1.2 million award from the Conrad Prebys Foundation that funded this project. (For more details on the Conrad Prebys Study, see pages 44-45.)

Sanford also is part of a team working on a study to better understand how often genetic diseases are to blame for infant deaths. Using blood samples from routine newborn heel sticks, she has been helping sequence the genomes of approximately 1,000 babies from San Diego County who died before they turned a year old. She and her colleagues use AI software to identify samples suspected of having gene mutations. Then they individually analyze those samples, giving them a score that indicates the likelihood that a variant was the cause of the baby's death. This painstaking analysis is contributing to a growing body of evidence showing that performing routine newborn screening using whole genome sequencing could prevent many infant deaths by identifying genetic diseases in time to intervene with life-saving treatment. (For more information on the SOMI Infant Death study, see page 42.)

Sanford also sees value in newborn screening by whole genome sequencing far beyond infancy. She explains that while human genomes have millions of variants and it would be impossible to diagnose every potential health problem at birth, having a person's genomic data readily available could be very useful in solving some enigmatic health problems even if they show up later in a person's life. "For example, if a 9-year-old comes in with acute liver failure, now we can look for mutations related to liver failure," says Sanford. Having a patient's genomic data easily accessible also can be critical when time is of the essence or when clinicians are making decisions about certain therapies to apply or to avoid. "The point is, the genome doesn't change. The DNA you're born with is the DNA that you will die with. So, the data will still be just as good in 20 years. It would be great to just have it now, then we'll be able to do so much more with it over time."

Major RCIGM Investigator Roles in Gene Discovery

Gene discovery is the process of identifying novel genes implicated in causing rare disease.

Since 2017, RCIGM investigators have played a major role in the discovery of the following 17 genes, thereby enabling disease diagnoses and offering hope for future prevention or cures:

2017 ***YY1***
2019 ***VARS***
2020 ***SETD2***
2021 ***SNAP25, HNRNP, CHD5***
2022 ***CLDN5, DAGLA, NFS1, ZMYND8***
2023 ***HERC2, HDAC4, HUWE1, GIT1, DLG4, GABRB3, SENP7***

Moving the Field Forward Through

Gene Discovery

Matthew Bainbridge is RCIGM's Associate Director of Clinical Genomics Research. He has a bachelor's degree in microbiology, a master's in computer science and a PhD in genome science and genomics. So how does a guy with such an impressive title and complex-sounding educational background answer the common question "What do you do for a living?" Bainbridge, an affable man with a dry wit, says his answer to most people is pretty simple. "I tell them I take new technologies and find weird things in kids' genomes, and try to get a diagnosis for them," he says. "And in the end, hopefully, that means we can find a treatment for those kids."

Bainbridge had several achievements in his work in the past year, but when asked what the biggest highlight was, he mentions a paper he authored, entitled **"The genomic landscape of familial glioma," which was published in *Science Advances* in June 2023.** The paper details findings from a study in which he and his colleagues proved that mutations in a gene called *HERC2* are associated with glioma. Glioma is a type of cancerous brain tumor, and the highest-grade gliomas are among the most aggressive cancers with the lowest survival rates. Thankfully, these cancers are quite rare, but sometimes several members of a single family develop glioma. This study aimed to learn more about why some family groups get glioma and to advance efforts to better treat it and perhaps eventually prevent it altogether.

One of Bainbridge's collaborators on the study was Melissa Bondy, the chair of Cancer Epidemiology at Stanford University. Her role was to identify people with familial glioma and collect samples of their DNA for genome sequencing. DNA sequencing results in an immense amount of genetic data. An average person can have three million to five million genetic mutations – most of which won't cause any problems. So, with that many mutations, how can we possibly find which one or two are causing a person's disease?

This is where Bainbridge comes in. He writes algorithms to analyze the sequencing data and narrow it down to find the genetic variants that look most suspicious. In other words, this analysis helps him find the "weird things" in these peoples' genes that you wouldn't see in people who don't have glioma.

Bainbridge is especially excited to have found the association to glioma on *HERC2* because it's about 10 times larger than most genes, which means that it naturally has more mutations than a regular-sized gene. Adept in forming analogies, he explains, "It's like, if you type out one page, you might have one typo. But if you type out a book, you'll have 1,000 typos." Bainbridge's algorithms helped cut the data in a way that enabled them to pick out the faulty signal in *HERC2*. "I was super proud of that," says Bainbridge, "because it's really hard to work on these large genes."

> "I take new technologies and find weird things in kids' genomes, and try to get a diagnosis for them. And in the end, hopefully, that means we can find a treatment for those kids."
>
> Matthew Bainbridge, PhD

After the algorithm pinpointed mutations in *HERC2* as a likely cause of glioma, Bainbridge's colleague from Baylor University, Ben Deneen, performed what is called functional testing. Deneen replicated the same *HERC2* mutation in mouse models, and those mice developed gliomas. Thus, the team proved the mutation in *HERC2* was pathogenic, thereby confirming a genetic cause for glioma.

How will this discovery advance the field of knowledge about familial glioma? Bainbridge explains, "What will happen now is more people will start studying it, they'll start looking at penetrance, which is how likely a person with a certain mutation is to actually get the disease." He says some researchers who currently focus their studies on *HERC2* will start concentrating on glioma. And some researchers who focus on glioma will start looking more at *HERC2*.

This glioma study has grant funding for another year, and Bainbridge expects even more discoveries to come of the ongoing investigation. In addition to *HERC2*, the team has found several other genes they suspect play a role in causing glioma. Bainbridge says, "We have another cohort of people who we'll be sequencing, so this next group will likely help us confirm some of those."

Relentless Pursuit
of Diagnosis and Gene Discovery

One day in 2013, a family walked into the office of Rady Children's pediatric neurologist Dr. Jennifer Friedman hoping she could help their 2-year-old son. Shortly after his birth, his parents noticed that he had abnormal eye movements and held his head facing down while gazing upward. These symptoms were especially noticeable after he woke up in the morning or after a nap. He had missed many of his developmental milestones, and, although he learned to walk, he had an unsteady, wide-based gait and fell frequently. He also had low muscle tone and trouble speaking.

Dr. Friedman hadn't seen a patient with this particular combination of symptoms before, and she was determined to help the family understand what was causing their son's condition. An extensive evaluation ultimately didn't reveal a diagnosis. She needed to look further. At the time, genomic sequencing wasn't widely available, so with the family's consent, in 2015 she recommended her patient enroll in a research study in collaboration with colleague Dr. Ali Torkamani at Scripps Research. The patient's exome was sequenced and Torkamani noticed an interesting variant in a gene that had not previously been associated with any disease. The gene was called diacylglycerol lipase alpha (*DAGLA*).

DAGLA is a component of the endocannabinoid system – a system in the body that helps regulate and balance many important functions including learning and memory, sleep, eating, immune responses, muscle formation, nerve function and motor control.

To investigate whether the *DAGLA* mutation was to blame for her patient's condition, Friedman and her colleagues assessed *DAGLA* enzymatic activity in cells with the child's *DAGLA* gene mutation compared to normal cells. They found nothing abnormal from this functional test, so couldn't prove the mutation was responsible.

Several years into the diagnosic odyssey, Friedman and her patient's family still had no answers. So, Friedman entered information on the patient's phenotype and genotype (see sidebar for definitions) into GeneMatcher[1], a web-based program that enables connections between clinicians and researchers from around the world who share an interest in the same genes. For four years, Friedman's patient was the only entry for *DAGLA*. In 2019, three more cases were entered; in 2020, two more; and, then another three were added in 2021.

The researchers working to find a diagnosis for these nine children were located in several countries around the world: the United States, Germany, Canada, Italy and France. They compared the patients' genotypes and found they had seven distinct variants in the *DAGLA* gene, but all the variants were of the same type and were located in a similar place on the gene. A comparison of the children's phenotypes revealed a remarkable overlap. The patients had many symptoms in common such as developmental delays, abnormal eye movements, unsteady gait and the characteristic chin-down posture. Further laboratory studies were done in collaboration with Dr. Svasti Haricharan at Sanford Burnham Prebys Medical Discovery Institute. By analyzing the clinical and laboratory data, **Friedman and her colleagues were able to describe a new pediatric neurologic condition they named neuro-ocular *DAGLA*-related syndrome**. Its acronym, NODRS, reflects the condition's distinctive "nodding" head posture.

In October 2022, nine years after the family came seeking help for their son, the journal *Brain* published a paper on the study entitled "Endocannabinoid dysfunction in neurological disease: neuro-ocular *DAGLA*-related syndrome." It was a meaningful moment in Friedman's career as a care provider and researcher. "This was the culmination of years of work to diagnose one of my patients and collaborate, not only with RCIGM input but with groups around the world to try to describe this condition," she says. "We did this, obviously, with the idea that by providing diagnoses for these kids; we then have hope to develop effective therapies."

The American Academy of Neurology selected *DAGLA* as a "breaking science" movement disorder and invited Friedman to present on the topic at their annual conference in April 2023.

Scientists are still working to fully understand how *DAGLA* variants cause disease, and there is still much work to be done to develop effective therapies. However, there is hope on the horizon for treatments: In light of the *DAGLA* discovery, Friedman adjusted some aspects of her patient's care, and the family is seeing some promising results.

[1] Sobreira N, Schiettecatte F, Valle D, Hamosh A. GeneMatcher: A Matching Tool for Connecting Investigators with an Interest in the Same Gene. Hum Mutat. 2015 Jul 29. doi: 10.1002/humu.22844. PubMed: 26220891.

Phenotype: the **observable characteristics or traits** of an organism produced by the interaction of the genotype and the environment. It is the physical or molecular expression of one or more genes.

For example, the *phenotype* of people with cystic fibrosis could commonly include several of the following:

- chronic bronchitis
- chronic sinusitis
- gastroesophageal reflux disease
- constipation or diarrhea
- diabetes
- malnutrition
- delayed development
- infertility (males)
- osteoporosis
- asthma
- nasal polyps

Genotype: all or part of the genetic constitution of an individual or group.

The genetic makeup of a person with cystic fibrosis may include one or several mutations in the gene called *CFTR* (cystic fibrosis transmembrane conductance regulator).

Meaningful Steps

Toward Identifying and Treating Genetic Diseases for More Children

You could say Dr. Stephen Kingsmore wears a lot of hats. As President and CEO of Rady Children's Institute for Genomic Medicine, he leads the entire team toward achieving the organization's vision. In addition to his leadership role, he also could rightly claim the title of Chief Evangelist. Dr. Kingsmore is a speaker at roughly 20 events per year where he talks about the importance of advancing genomic medicine. On top of those responsibilities, he is a scientific investigator, searching for ways to save babies' lives and improve their outcomes through whole genome sequencing.

A key indicator of an investigator's productivity is having a paper published in a peer-reviewed scientific journal. By any measure, Kingsmore had a stellar year. He and his colleagues had more than 20 papers published in FY23.

Pressed to choose which of the papers he feels was the most significant in FY23, Kingsmore pointed to "A genome sequencing system for universal newborn screening, diagnosis, and precision medicine for severe genetic diseases," which was published in *American Journal of Human Genetics* in September 2022. The paper describes how a large team at the Institute worked with industry partners to demonstrate the feasibility of universal newborn screening (NBS) for about 400 severe genetic diseases by rapid whole genome sequencing (WGS). Their research showed how NBS-by-WGS could augment traditional NBS to start treatments for these diseases at or before the onset of symptoms.

The paper is a significant step in the quest to establish NBS-by-WGS as a new standard of care. Why? Kingsmore says, "It's very important that this evidence is part of the public scientific record. Specifically, it shows exactly how many babies are likely to benefit, compared with traditional NBS." The Institute is collaborating with a large consortium of stakeholders and organizations to advance NBS-by-WGS from research to clinical testing in an effort called BeginNGS®, pronounced *beginnings* (for an update on BeginNGS, see pages 83-85).

To explain the pressing need to establish a program like BeginNGS, **Kingsmore and several other distinguished scientists published a thought leadership piece in *American Journal of Medical Genetics* in January 2023. The paper, "Are we prepared to deliver gene-targeted therapies for rare diseases?",** draws attention to the anticipated exponential growth in the number of gene-targeted therapies that will be available soon. "We're looking forward to an era over the next five years when there's going to be an explosion of new therapies. Many, many childhood genetic diseases that don't have effective treatments today will have treatment available in the near future," says Kingsmore. He says the paper essentially asks "Are we as a medical establishment ready to go find those kids and improve their outcomes?" The paper's authors make recommendations for adjustments to ensure the healthcare system will be ready. "This

paper points to a fresh urgency to drive adoption of diagnostic genome sequencing, and also adoption of BeginNGS," says Kingsmore, "because the gap is widening between what we *could be doing* for these children and what we're doing for them today."

Another way Kingsmore is measuring the burden of treatable childhood genetic diseases is to investigate the proportion of infant deaths that are attributable to these diseases – again using WGS. He explains that the current way the public health system classifies infant mortality predates the ability to decode the human genome. This system has classified infant deaths in the same very broad categories for over 50 years, and it hasn't kept pace with our understanding of the underlying mechanisms of disease – such as genetic diseases. Therefore, it has been impossible to know the burden of genetic disease on infant mortality by looking at national vital statistics. In response, Kingsmore and his colleagues at the Institute and UCSD performed WGS on 112 San Diego infant deaths with medical records at Rady Children's Hospital to reconstruct what difference it would have made if a genetic disease had been identified before death. As it turns out, the difference was significant. "What we found was that, irrespective of race or ethnicity, genetic diseases were the number-one cause of death, not what the death certificates said," says Kingsmore. The team found genetic diseases were associated with 41% of infant deaths. They also noted that effective or somewhat effective treatments were available for 30% of those genetic diseases, suggesting that early WGS may have led to those deaths being avoided.

> "The gap is widening between what we *could be doing* for these children and what we're doing for them today."
>
> Stephen Kingsmore, MD, DSc

The team published their findings in February 2023 in *JAMA Network Open* in the paper "Reclassification of the Etiology of Infant Mortality with Whole-Genome Sequencing." Kingsmore says there are two key takeaways from the study. First is the need to modernize the way we classify infant death. Second, and more importantly, is the need to recognize that genetic diseases are a major public health issue. "Previously, shining a spotlight on premature birth and sudden infant death syndrome as causes of infant mortality led to improved outcomes. Now, it's time for us to shine the spotlight on genetic diseases and focus attention on improving outcomes in affected babies," says Kingsmore.

The results of the study add to the case for implementing NBS-by-WGS to save lives and improve outcomes. "BeginNGS has the potential to decrease infant mortality substantially," says Kingsmore. "Let's decode babies' genomes at birth so they don't die of undiagnosed, treatable genetic diseases."

Technology + Innovation + Partnership = a Winning Formula to Support

Doctors who Care for Babies

Imagine you're a doctor in one of the 214 California communities that are medically underserved. Last night, a baby boy was admitted to the neonatal intensive care unit; despite 10 years of training and five years of experience as a neonatologist, you're not sure it will be helpful to order whole genome sequencing (WGS) on this tiny baby. In most NICUs across North America, WGS is still not a first-tier test – meaning it is not among the initial diagnostic tests ordered by doctors. Most neonatologists have not been trained in genomic medicine. How will you decide whether to order rapid whole genome testing for the baby who was admitted last night?

Dr. Charlotte Hobbs, RCIGM's Chief of Research and Clinical Management, says it's a frequent dilemma neonatologists face. WGS is a test not covered by most payors. Often neonatologists are unable to order whole genome sequencing without the baby first having a clinical genetics consult. "The neonatologist wants to know if this baby is like other babies who have had whole genome sequencing. Would other neonatologists who see a baby like this order whole genome sequencing?" says Dr. Hobbs.

Hobbs and her colleagues Drs. Matthew Bainbridge and Erica Sanford had this dilemma in mind when they launched a study to determine if an electronic tool could help NICU caregivers prioritize ordering whole genome sequencing for their patients that need it most. The Conrad Prebys Foundation funded the study, which launched in October of 2022. In it, the research team introduced clinical natural language processing (CNLP) and machine learning into the space of whole genome sequencing. Their exciting new approach came about thanks to a combination of technology, innovation and collaboration, and the tool they developed is called the Mendelian Phenotype Search Engine (MPSE).

A key collaborator in the study is Professor Mark Yandell from the University of Utah. Yandell and Hobbs used data from both the University of Utah Primary Children's Hospital and Rady Children's Hospital to build the tool.

Clinithink, a company based in the United Kingdom, also partnered on the project. Their innovative technology enabled a natural-language processing (NLP) program to sift through medical records and translate doctors' disparate notes into a standardized terminology called Human Phenotype Ontology (HPO). By having standard terms across health records, the MPSE tool can easily compare records against each other. Thanks to this technology, a process that would take months for a human to complete takes the MPSE tool mere seconds.

After comparing records, MPSE will assign a baby a score based on how similar it is to other babies who have benefited from WGS in the past. The more similar the cases, the higher the score.

Hobbs emphasizes that the MPSE score can be a valued supplement to a physician's own clinical assessment. "The physician can use the information from MPSE in their decision-making," says Hobbs. "It's another piece of data to help them decide whether it seems appropriate to order whole genome sequencing for the baby who was just admitted into the unit." And it's not just a one-time score a baby gets after admission. The tool continues to scan the baby's record and issues a new score each day. If the baby's symptoms change during the time they're hospitalized, the doctor receives updated information to consider.

Additional critical research collaborators were Hobbs's colleagues at RCIGM, including Edwin Juárez, PhD, a data scientist who led the collaboration to develop the algorithm to classify patients and to extract unstructured notes from patient health records (see pages 46-47 for more on Juárez's role in advancing RCIGM's work). The information management team at Rady Children's also were important contributors. "We absolutely could not have done this without them," says Hobbs.

In March 2023, Hobbs, Yandell and their colleagues shared their initial findings in "Automated prioritization of sick newborns for whole genome sequencing using clinical natural language processing and machine learning," a paper published in *Genome Medicine*. The paper shares specific details about how the MPSE tool they developed accurately identified babies selected for WGS by clinical experts from Rady Children's Hospital in San Diego and the University of Utah. In addition, they found the MPSE scores strongly prioritized diagnostic cases over non-diagnostic cases. Through this initial phase of the study, the team demonstrated the feasibility of using automated means to prioritize acutely ill infants as candidates for WGS.

> "Our hope is that someday this tool could be distributed to physicians who take care of critically ill babies in medically underserved areas and resource-poor settings."
>
> Charlotte Hobbs, MD, PhD

The study is ongoing, and the research team continues to meet weekly to improve the MPSE, which thus far has only been studied in use at Rady Children's. While further study and enhancements are necessary, Hobbs and her colleagues envision a future in which the tool is widely available. She says, "Our hope is that someday this tool could be distributed to physicians who take care of critically ill babies in medically underserved areas and resource-poor settings. MPSE is using machine learning and artificial intelligence responsibly to help support physicians when they ask, "Is this a baby who could benefit from whole genome sequencing?"

Using Tech and *Ternura* to Improve

Children's Lives

In his LinkedIn profile, here's how Edwin Juárez describes himself: "Expert on the interfaces between Genomic Medicine, Data Science, and Computer Science. Passionate about making a positive impact in the lives of patients." After you meet him, you understand what a powerful combination of qualities that is.

In February 2022, Juárez joined RCIGM as a data scientist. Simply stated, data science is the study of data to glean useful insights. Studying data – especially vast amounts of data – often requires knowledge in mathematics, computer science, artificial intelligence and machine learning. With a background in math and a PhD in electrical engineering, Juarez has contributed his technical skills to advance several projects since joining the Institute.

One such project is a study in which Dr. Charlotte Hobbs and Professor Mark Yandell led a team to develop an automated tool to help neonatologists make decisions about ordering whole genome sequencing for critically ill infants (see pages 44-45 for details on the study). Juárez understands the high stakes involved in these decisions. "In the NICU, every decision that the attending physicians and the medical staff makes is super important, and days are crucial," he says. "Making a decision a day early, or even a few hours earlier, can significantly impact the life of these babies."

For this study, Juárez collaborated with RCHSD's Information Management team to extract electronic health records for babies in the hospital's ICU and use technology to turn unstructured text notes into more standardized terms. This process enables a sort of "apples-to-apples" comparison to see if a critically ill baby looks clinically similar to other babies who benefited from whole genome sequencing. "It's been quite a big feat to get this piece of technology integrated into this hospital system," says Juárez.

Juárez is confident about the positive impact technology can make in complex situations like these. "That's where I feel AI

> In the NICU, every decision that the attending physicians and the medical staff makes is super important, and days are crucial. Making a decision a day early, or even a few hours earlier, can significantly impact the life of these babies."
>
> Edwin Juárez, PhD

and machine learning and technology can come in, and obviously never replace, but enhance the physicians' decision-making process," he says. "So, if it can help them make a decision a just little bit faster, or a little bit more confidently, then I think we're making a big impact on these babies."

Juárez's enthusiasm for his work is palpable. "I'm so excited because this project is accomplishing one of our biggest goals, which is to improve care for patients," he says. "But this is also an expression of who I am, academically speaking. I've been steering my entire professional career to be doing precisely this."

Prior to joining the Institute, Juárez worked at the University of California San Diego where he helped develop an algorithm that enables scientists on the Molecular Tumor Board (MTB) to examine the gene expression in aggressive pediatric brain tumors. Now, as a member of the Institute's team, Juárez trains other professionals to run the analyses for the MTB, and he focuses on developing the next generation of analytical tools for the project. (For more information on the MTB, see page 60.)

When asked about what he views as one of the biggest challenges of his job, rather than explaining some complex technical difficulty, Juárez talks about the awesome responsibility of working to help sick children. Each day when he logs into the RCHSD electronic health records system, he sees a photo of one of their patients. "It's the first thing I see, and it hits me every time, stirs all kinds of emotions," he says. "I didn't know how deeply it was going to affect me."

He searches for the right word to describe the feeling, ultimately landing on a word in his native Spanish language: *ternura*, which translates to a feeling of tenderness or endearment. It's a feeling one often gets when looking at a baby, and it's amplified when that baby is critically ill. "It's a good reminder for me, this is why I'm doing what I'm doing. This is why I get out of bed," says Juárez. "But handling those emotions can be difficult. It's not something that as an engineer you're trained to do. But it's important. We're all human beings. And that human aspect is super important."

Motivated by the opportunity to make a meaningful impact in children's lives, Juárez is eager to apply his data science expertise to help RCIGM drive the next wave of development in precision medicine. He believes the Institute is poised to lead the way because the Institute can attract talented data science experts; it has a gold mine of data; and, it has begun developing critical infrastructure. "Just think about the legacy that RCIGM can have, five years from now, 10 years from now, 50 years from now," he says. "We have the potential to have a huge impact not only for our patients, but also for how other hospitals and health care organizations react and integrate data science into their systems."

Creating New Methods

to Find Mosaic Needles in Genetic Haystacks

With more than 20,000 genes in the human body containing more than three billion base pairs of nucleotides, it's always a challenge to pinpoint a gene mutation. But some mutations are easier to find than others. A mutation that shows up in every cell in a person's body is called a germline mutation, and it's easier to detect using whole genome sequencing. Somatic mosaic mutations only show up in a small percentage of a person's cells, and they're extremely difficult to find. Dr. Joseph Gleeson, an RCIGM researcher and the director of the neurogenomics program at Rady Children's Hospital explains, "These mosaic mutations might be present in only one out of 100 cells or five out of 100 cells. And the typical software that we use is blind to them, it just doesn't see them."

So, what do you do if you're trying to more easily and reliably identify mosaic mutations, for example, the kind known to play a role in causing epilepsy in children? Well, if you're Joe Gleeson, you partner up with a bunch of other smart people at RCIGM to build a new tool that makes it possible. And you call it DeepMosaic.

Dr. Gleeson describes DeepMosaic as a very special computer program that's like a laser beam, focusing in on the mosaic mutations. "These mutations are in a very small percentage of cells in the patients' brains, so we had to develop a whole new method using AI to train a neural network to spot them," he says. In testing, DeepMosaic outperformed all other existing mutation detection methods it was compared with.

In collaboration with his research colleagues, Gleeson wrote a paper about this technological breakthrough named **"Control-Independent Mosaic Single Nucleotide Variant Detection with DeepMosaic." It was published in January 2023 in *Nature Biotechnology*, one of the world's top scientific journals**. Gleeson is enthusiastic about the potential for DeepMosaic. "It gives us a whole new window into disease, especially pediatric disease where we think mosaic mutations play a really important role," he says. "Now we're going to be able to use this program on cases where we couldn't find answers before."

Gleeson wasted no time putting DeepMosaic to work to start finding answers. The tool recently played an indispensable role in revealing a gold mine of information about the causes of focal epilepsy – a type of epilepsy that doesn't respond to medications and is concentrated in just one part of the brain (the "focus"). While medications don't help children with focal epilepsy, surgical removal of the focus has proven to be an effective treatment. Many neurologists have long felt there could be genetic mutations in the focus area that cause the condition, so Gleeson and other leaders at Rady Children's started an international consortium to investigate. The consortium includes pediatric neurologists from several organizations across the United States, as well as others in Japan, Italy, Brazil, South Korea, Turkey, India, Germany and Ukraine.

> [DeepMosaic] gives us a whole new window into disease, especially pediatric disease where we think mosaic mutations play a really important role."
>
> Joseph Gleeson, MD

Dr. Joseph Gleeson is the Rady Children's Hospital Auxiliary Endowed Professor of Neuroscience and Director of Neuroscience Research at RCIGM.

In FY23, the consortium completed a project in which they used multiomics to study resected brain samples of 283 patients from across their institutions. "Multiomics means we don't just apply one method, we use multiple methods, because using only one method, we might miss the cause," says Gleeson. "We're doing genomics, we're doing transcriptomics. And then we're doing animal models, to really understand the causes and make sure we learn as much as we can from the patient material."

Thanks to the use of these multiple tools, including DeepMosaic, the consortium study found 69 genetic causes of focal epilepsy, 60 of which were previously undescribed. The researchers identified four distinct classifications of genetic pathways that cause these forms of epilepsy. **The findings were published in a paper titled "Comprehensive Multiomic Profiling of Somatic Mutations in Malformations of Cortical Development," which appeared on the cover of *Nature Genetics* in February 2023**. "This is the new classification system that we think is going to be adopted by epilepsy specialists thinking about focal epilepsy," says Gleeson, "and we think it's going to lead to new therapies."

Gleeson and his colleagues believe they've just begun to scratch the surface of understanding this condition. "We need a lot more patients. I think if we continue to recruit patients, we're going to keep finding new genes, and that's going to lead to new understandings," he says. The consortium recently recruited another 100 patients from around the world, and they've started to profile them with DeepMosaic. Undoubtedly, they'll soon add even more. Since the Nature Genetics publication came out, more neurology and neurogenetics programs have come forward to become part of the consortium.

While Gleeson is encouraged by what he and his colleagues have accomplished thus far, he is keenly aware that the diagnostic odyssey continues for the majority of rare disease patients. "There's about 60% of patient cases we can't solve using the current technology, and cures can't come without causes," he says. "So, we need to keep evolving, keep trying new things, keep collaborating with other researchers, because we're developing some of these tools ourselves within the Institute that will hopefully be the future best practices."

Pursuing Gene Discovery

and Using Genome Sequencing to Enable Genome-Informed Care Delivery

Every day, genetics researchers are uncovering more information. And with the sharing of each new discovery, clinical providers have more knowledge to help them make decisions about the best way to treat their patients. This is genome-informed care delivery. Dr. Kristen Wigby is one of several RCIGM researchers who made significant contributions in building the body of genomic knowledge in FY23.

The ability to improve genome-informed care delivery starts with understanding which tests work best to diagnose a sick child. **One of Dr. Wigby's accomplishments in FY23 was concluding a five-year study called Genomic Medicine for Ill Neonates and Infants, or GEMINI**. She was co-primary investigator of this prospective clinical trial on infants in the NICU that were suspected of having an underlying genetic disease. The $8 million study, funded by the National Institutes of Health, examined the results of two different types of sequencing tests on 400 infants in six separate children's hospitals across the United States. One type was a targeted gene-sequencing panel called NewbornDx and the other was a rapid whole genome sequencing test (rWGS®) run in the RCIGM lab.

Wigby, Dr. Stephen Kingsmore and their colleagues found that while the turnaround time of rWGS results was slightly longer than the targeted test, rWGS yielded a significantly higher number of diagnoses (49% vs. 27%). Results from the rWGS informed a change in clinical care in nearly 20% of the infants in the trial, and regardless of whether testing revealed a diagnosis, 76% of clinicians reported viewing rWGS as useful or very useful in clinical decision-making. **The team's article, "Rapid Whole-Genomic Sequencing and a Targeted Neonatal Gene Panel in Infants with a Suspected Genetic Disorder," was published in the July 2023 issue of *JAMA Network***.

A clinical provider herself, Wigby was co-director of Rady Children's Precision Medicine Clinic (PMC). Through the PMC, a multi-disciplinary team cares for children who are diagnosed with or suspected of having rare genetic disorders. Families whose children are seen at the PMC have the option to participate in genetics research, which may ultimately yield new information on their child's condition. (For more information on the PMC, see pages 28-29)

Wigby shared an example of how she and her colleagues recently discovered the genetic link to one of her patients' unusual symptoms. It started with a pediatric dermatologist who referred a 2-year-old male patient to the PMC. His parents took him to the dermatologist because of a painful rash on his hands and feet. "The dermatologist was really astute, and noticed this little guy was medically complex," says Wigby. "Besides the skin rash, he also had unique facial features, developmental delays and hearing loss." Before his visit to the PMC, genetic counselor Jerica Lenberg reviewed all the genetic variants that had been reported on prior testing and she noticed a candidate gene called *ARF1*.

The term *candidate gene* refers to a gene that is believed to be related to a particular trait, such as a disease or a physical attribute. The team ran whole genome sequencing on the patient to rule out any other readily identifiable diagnosis. When no obvious answer materialized, they put the gene into GeneMatcher, an online database that enables connections between clinicians and researchers from around the world who share an interest in the same genes.

Wigby describes what happened next. "We matched with an international group that was identifying more children with variations in *ARF1* and through a review of similar clinical presentations across different patients, we were able to identify many common signs and symptoms." She explains that many of the children had several features in common, including some with a similar rash, which helped the group understand how variants on the *ARF1* gene affect multiple pediatric patients. **In April 2023, the *Journal of Medical Genetics* published the team's paper describing the clinical and molecular aspects of the genetic condition they named *ARF1*-related disorder and recently submitted a second paper about the role of *ARF1* in the immune system to *Nature Communications***.

"To us, this case was just really interesting. We met this patient early in his journey. We started at the beginning, before his condition was recognized as a genetic disease - it wasn't even a thing," says Wigby. "And now, every time we see the family for follow up, we can update them about what we've learned and what we know. To be able to get to this point of understanding his disease is a big deal."

Advocating for Early Genome Sequencing to Diagnose and

Treat Neonatal Liver Failure

One day in 2016, just minutes before a Rady Children's Hospital surgical team was to begin a procedure called an intraoperative cholangiogram with possible Kasai procedure on an infant with severe liver disease, the operating room phone rang. The team stopped to answer. On the other end of the line were Dr. Amber Hildreth and her colleagues with news that they had just received the genome sequencing results for the baby. According to the test, the baby had a genomic deletion that included the *JAG1* gene. This meant the cause of his liver disease was not biliary atresia as previously considered, but a genetic disease called Alagille syndrome (ALGS), the symptoms of which often mirror biliary atresia. The Kasai operation, while helpful for babies with biliary atresia, does not benefit babies with AGS and can actually worsen their outcome. The surgeons immediately called off the procedure.

Back then, Dr. Hildreth was a new fellow at RCIGM. Today, she is a pediatric gastroenterologist, specializing in liver disease and liver transplant for kids. She also is an RCIGM clinician scientist, and she still loves to share this story as an example of how whole genome sequencing can inform care for children with early-onset liver disease, helping pinpoint diagnoses and thereby target appropriate treatment.

In FY23, one of Hildreth's proudest accomplishments was completing and submitting a proposal to the NIH for a K08 award – a five-year training grant for junior faculty. While not funded on the first submission, she received excellent feedback from the NIH and will be resubmitting her application this fall. "My aim is to improve outcomes of patients with pediatric liver disease," says Hildreth, "One piece of it is by utilizing rapid whole genome sequencing earlier in the evaluation. If we can obtain a genetic diagnosis, we can likely avoid doing more invasive diagnostic procedures."

Early sequencing also can inform treatment decisions such as whether a transplant should be done right away, could wait until a child is older, or wouldn't be effective at all. In the case of the infant from 2016, Hildreth believes the sequencing was life saving. "The patient ended up getting a transplant around 6 years of age, but he wouldn't have made it to 6 years of age if he had gotten the Kasai surgery."

Hildreth is currently vice chair of the advocacy committee of the Society for Pediatric Liver Transplant. **She is proud to have contributed to a manuscript along with colleagues from RCIGM and Mayo Clinic, which was published in *Liver Transplantation* in July of 2022. The manuscript, "Ultra rapid whole genome sequencing, a paradigm shift in the pre-transplant evaluation of neonatal acute liver failure,"** was a case series of three patients, each with a

genetic diagnosis of neonatal liver failure. Of the three patients, only one had a diagnosis for which a liver transplant was a suitable treatment. Hildreth and her colleagues assert that compared with typical genetic evaluation, urWGS has a superior diagnostic rate, clinical utility and cost efficiency as a first-line test for these critically ill infants. “That paper really speaks to where we are in the liver world right now – we’re shifting our thoughts about genetic testing,” says Hildreth, “There’s growing favor for the idea of doing it not as our final thing, but doing it from the start. We’re in a great space to be part of that here.”

Hildreth plans to continue her work to further prove the clinical utility of rapid whole genome sequencing and advocate for its use as a standard test in diagnosing and treating babies with acute liver disease everywhere. In the meantime, she’s pleased to say that, today, Rady Children’s Hospital surgeons will not perform a Kasai operation without first ruling out Alagille syndrome or other genetic causes of neonatal liver disease through whole genome sequencing. Says Hildreth, “They all want a genome to be done in advance to avoid potentially doing a surgery on a baby who doesn’t need it.”

> “My aim is to improve outcomes of patients with pediatric liver disease. One piece of it is by utilizing rapid whole genome sequencing earlier in the evaluation.”

Amber Hildreth, DO, FAAP

Pursuing Better Care for Babies

Before They're Born

Every year in the United States, about 40,000 babies are born with a congenital heart defect (CHD). It's the most common type of birth defect in the country and Dr. Rebecca Reimers has seen firsthand the often-devastating impact of the disease. It affects not just the health of babies but also the well-being of young families who struggle under the tremendous emotional and financial strain of caring for a child with CHD.

That's why it's Dr. Reimers' passion to diagnose CHD and other fetal anomalies early and, where possible, recommend interventions that can eliminate or reduce the impact on babies and their families.

Reimers is triple board-certified in obstetrics and gynecology, maternal fetal medicine, and clinical genetics and genomics. Through her training at Tulane and Harvard medical schools, she developed a keen interest in prenatal screening, diagnosing fetal abnormalities and transitioning patients to high-quality, family-centered perinatal care when a baby is diagnosed with an abnormality.

In August 2022, Reimers returned to her native San Diego to begin her first year of practice and join RCIGM as a researcher.

Her work is focused on genetic testing for fetuses with congenital heart differences noted in pregnancy to help prepare them for life after birth.

A KL2 Scholar at Scripps Research Institute and a board member of the International Society of Prenatal Diagnosis (ISPD), Reimers is an accomplished physician-scientist. **This year she helped author a position statement from the ISPD on the use of non-invasive prenatal testing to detect fetal chromosomal conditions, which was published in the journal *Prenatal Diagnosis***. Also, **at the annual ISPD international conference in Edinburgh in June 2023, she delivered a presentation on fetal phenotyping**. She played a key role on the team that helped implement the first two phases of the BeginNGS® pilot (see pages 83-85 for information on BeginNGS).

Reimers says her proudest achievement in the past year was having her research proposal approved in April 2023. She and her colleagues are now enrolling pregnant women carrying babies diagnosed with heart defects. Reimers will perform whole genome sequencing on fetal DNA acquired from participants' prenatal tests to look for underlying reasons for the heart defects. "The goal is to prove genomic sequencing is the best first step for women who want diagnostic testing done during pregnancy," she says. Reimers anticipates the testing will point to a genetic cause for a heart defect in 15–30% of the babies.

Some fetal disorders have options for treatment – for example, enzyme replacement therapy, gene therapy and fetal surgeries – which can optimize a situation before birth. "These treatments could mean a baby might need much less medication, much less monitoring and have a better long-term outcome," says Reimers.

And regardless of whether a fetal treatment exists, Reimers believes having an early diagnosis is invaluable to a family, giving them more time to prepare – learning about the health issues their baby might face and getting connected with expert physicians – and reducing stress as they enter the delivery and newborn period.

"The first step is diagnosis," Reimers says, "You can't ever treat someone for a genetic disorder unless you know that it's there." And by starting treatment earlier, she says, "Certainly, you have a better opportunity to transform someone's life."

> "The goal is to prove genomic sequencing is the best first step for women who want diagnostic testing done during pregnancy."
>
> Rebecca Reimers, MD, MPH, FACOG

Getting to the Heart of

Congenital Cardiac Disease

Dr. Nathaly Sweeney spends a significant number of her working hours taking care of tiny babies with severe heart defects, yet she'll tell you the most challenging part of her job has to do with accessing and analyzing data for her research. Sweeney is a pediatric cardiologist and has been a physician investigator with RCIGM since 2017. Her primary research goal is to end the diagnostic odyssey – to explain the *cause* of congenital heart disease – for more children and their families.

There are at least 18 structural types of congenital heart defects. Sweeney explains that sometimes doctors can find a *pathogenic* gene variant that points to a definitive diagnosis – a proven reason for a baby's heart disease. However, more frequently doctors see variants they believe *could have* caused the disease, but they don't know for sure. Those are called *variants of uncertain significance* (VUS). "When I look at patients with congenital heart disease, we can only diagnose about 30% of them," says Sweeney. "There's a large percentage not being diagnosed. For many of them, we suspect a genetic cause, but we're not able to pick it up."

Having a diagnosis is key to determining the best course of treatment for a child and it provides valuable information to a family, so Sweeney is determined to improve upon that diagnostic rate. But scientists need more information on a VUS before they can prove whether it is pathogenic. This is why she spends most of her time trying to develop algorithms to study genetic VUS. "We need new ways of looking at the DNA," says Sweeney.

The National Institute of Child Health (NICH) and University of California San Diego (UCSD) recently granted a three-year career development award for Sweeney to continue this investigation in a pilot study. Sweeney plans to publish findings from the study in the spring of 2024. She is hopeful the pilot data will help her procure additional grants that will enable her to access and analyze more genetic data for children with congenital heart disease, thereby improving her odds of finding the same variants in other children with the same heart defects. "That's why it's important for me to get a database, because now I can compare children who look like each other clinically," says Sweeney. "And then once I get a common variant, can I look at it at different levels? Will it cause the same heart defect in an animal model, for example, in zebrafish or in a

> "The work that we're doing with whole genome sequencing is helping me to be a better doctor. It's empowering me to take better care of my patients."
>
> Nathaly Sweeney, MD, MPH

mouse? If I can see that, that's more information we can use to vet these variants of uncertain significance."

Sweeney also is interested in investigating how whole genome sequencing can inform the treatment of children with critical congenital heart disease. She explains that these children often require a lot of clinical resources and frequently need surgery in infancy, which comes with large risks of complications, some of which can last a lifetime. She also wants to learn whether knowing the genetic causes of congenital heart disease early can result in better neurodevelopmental outcomes, for example reducing problems with speech and language, behavioral issues and learning delays. In addition, she sees an opportunity to further study the reasons for disparities in outcomes of children with congenital heart defects, which can vary greatly depending on factors such as race, geographic location and socio-economic status.

Sweeney feels these types of studies help more people in the field of pediatric cardiology begin to embrace the value of whole genome sequencing over more traditional heart disease gene panels. She says evidence is emerging to show whole genome sequencing really does improve outcomes for babies with congenital heart disease. She looks forward to seeing it more widely adopted as a standard screening. "I'm very proud that we're able to offer this to families at Rady Children's," says Sweeney. "The work that we're doing with whole genome sequencing is helping me to be a better doctor. It's empowering me to take better care of my patients."

Collaborating to Help Children

with Severe Behavioral Health Disorders

On February 23, 2023, Dr. Aaron Besterman hit 'send' on an email to more than 20 people, celebrating the official launch of a research study that had been more than two and a half years in the planning. The recipients were staff from across Rady Children's Hospital including members of the Genomics Institute, the emergency department, the psychiatry department and the Autism Discovery Institute team. All were collaborators and advisors who helped Besterman in designing and planning the study called Mental Health Crises in Youth with Intellectual and Developmental Disabilities (MHC-IDD).

A child psychiatrist and genetics researcher, Besterman's work is focused on the genetics of childhood mental health conditions and psychiatric disorders. When asked about the aims of the new study, he first explains the type of youth it is meant to help. "Some kids with intellectual and developmental disabilities have significant problems due to their underlying condition – they may have a lot of irritability that can manifest as aggressive behavior or self injury," says Besterman. He says the families of these children often come to the Rady Children's Hospital emergency department in crisis because their children are injuring themselves or others. "It's a major problem," he says. "These kids will often sit in there for days or even weeks, because there's really no place for them to go and safely be outside of an emergency room."

The MHC-IDD study was started with seed funding from RCIGM and is expected to take up to four years to complete. During that time, Besterman and his colleagues hope to uncover information that will help create a better system to care for this vulnerable population. "In order to develop a better system, we need to understand who these kids are and what their needs are in a more comprehensive way," he says. Part of that comprehensive understanding includes patients' genetic makeup. Besterman believes there is great potential for genomics to play a more central role in psychiatric care, informing treatments and improving outcomes for kids with mental health disorders. "The goal is for us to develop a model that will be able to predict which kids may be at highest risk for these sorts of crises, so that we might intervene earlier and avoid the need for emergency management."

This is the first time a study of this kind has been conducted in an emergency room setting. That's significant because Besterman says, historically, kids who have severe aggressive behaviors and require emergency room care have been excluded from these studies.

So far, the team has enrolled seven patients, with a goal of recruiting 150. In addition to studying the patients' genetics, the team will review patients' medical records for clinical clues

and collect information on psychosocial factors such as their home life, their strengths and weaknesses, and psychological profiles. Besterman is grateful to all his collaborators, especially to Dr. Tanya Vayngortin, a champion of the study within the Rady Children's emergency department, and to clinical research coordinator Corrine Blucher who runs the day-to-day aspects of the study.

Families of these children also have expressed gratitude to the research collaborators. "These are families who struggle through really traumatic experiences for long, long periods of time," Besterman says. "So just the mere fact that someone recognizes that, is paying attention to it, and is trying to make things better… I think it's really meaningful to them."

The MHC-IDD study is just one of several ways Besterman is working in cooperation with others to advance the field of psychiatric genetics (See additional collaborations described on pages 62-67). Insights can't come soon enough for the families of approximately 700,000 youth who are admitted to a hospital for mental health crises each year. From the closing line of Besterman's celebratory email to the project team, it's clear he's optimistic about the possibilities. "I truly believe our collaborative effort will provide valuable insights into the underlying risk factors for mental health crises in this vulnerable population, leading to improved care and outcomes," he wrote. "I am confident that together, we can make a meaningful difference in the lives of these kids."

"I truly believe our collaborative effort will provide valuable insights into the underlying risk factors for mental health crises in this vulnerable population, leading to improved care and outcomes. I am confident that together, we can make a meaningful difference in the lives of these kids."

Aaron Besterman, MD

Advancing Precision Medicine

for Children with Brain Tumors

The Molecular Tumor Board at Rady Children's Hospital-San Diego was created in 2017 and consists of physician-scientists, clinicians and researchers in the field of tumor genetics. The board recommends advanced testing, including rapid whole genome sequencing, for some children with tumors in the brain or spinal cord. The members of the tumor board study the results of these tests and try to detect novel mutations and pathways involved in tumor growth.

Patients must qualify to participate in the Molecular Tumor Board study. Dr. Megan Paul, a pediatric neuro-oncologist, is the new clinical director and PI of the board. Dr. Paul has been involved since she was a fellowship trainee in 2018. To explain who qualifies for the study, she says, "We nominate patients who have either exhausted all of their standard options or those who have tumors that have no standard of care and only have palliative care options available."

Because these children have so few avenues for treatment, Paul says their families are very supportive of the project and eager to participate so they can learn as much as possible about their disease and help scientists in the quest for new therapies.

In parallel with that urgency, Paul says in recent years there has been explosive growth in the understanding about the molecular differences between tumors. The Molecular Tumor Board is mining that wealth of information with the goal to directly benefit patients. "In 2023, we're learning as much as anyone could about patients' tumors," says Paul. "We investigate the DNA, RNA and epigenome of each patient's tumor to find its unique characteristics and to identify precision care. We have seen diagnoses change based on more precise, laser-focused characterizations."

After five years of being involved in the project, Lukas Chavez recently became its scientific director. A PhD-level cancer researcher, he works in the lab to study the causes that lead to the development and progression of pediatric brain tumors. A large part of his time is spent doing computational work because patients' tests result in a mountain of DNA data that must be analyzed. "We have about three billion base pairs and more than 20,000 genes in our DNA, and any one of those could be mutated, rearranged or affected," says Chavez. "We look at all of them, so we need the computer to do that."

The other work in Chavez's lab focuses on identifying new interventions that inhibit tumor growth. The team looks at biopsies of tumor tissue and derives models from these tumors – sometimes in a petri dish, but also in mouse models. In these models, researchers test various chemical compounds and genetic inhibition experiments, which have the promise to result in personalized treatments for these very rare tumors that currently have none. "I think we have a high potential for clinical

> This is an attempt at personalized medicine for children who have brain tumors because these diseases are rare. But now, due to incremental technological and scientific advances, we can characterize tumors more and more precisely. With greater and greater precision, the likelihood of discovering effective treatments increases."

Megan Paul, MD

impact," says Chavez. "A treating neurooncologist has the discretion to actually prescribe a drug that might be suggested due to our molecular and functional analysis, and that might change the course of the treatment."

In FY23, this effort translated into a small clinical trial for relapse medulloblastoma, and there are hopes of it evolving into a larger trial in the future. The trial involves sending tumor tissue for direct drug testing, which Paul says is unprecedented. "It's very novel and isn't part of most centers' practice to get genetic information sort of married with drug data," she says. "This is an attempt at personalized medicine for children who have brain tumors because these diseases are rare. But now, due to technological and scientific advances, we can characterize tumors more and more precisely. With greater and greater precision, the likelihood of discovering effective treatments increases."

To date, thanks to generous funding from the Joseph Clayes III Charitable Trust, Drs. Paul and Chavez and their colleagues have analyzed the molecular structure of tumors in nearly 60 patients. They are currently writing their first publication to describe their approach and findings. The Molecular Tumor Board demonstrates how a rich collaboration between Sanford Burnham Prebys, RCIGM, RCHSD and UCSD has a broad impact, offering fresh hope to these children and families.

Chavez and Paul are motivated by the idea that their work will change the conversations they have with families in the not-so-distant future. "I often have to say, 'There's very little we understand about this tumor,' so we have to make educated guesses about what to do," says Paul. "In the future, we can say, 'We *used* to not understand this tumor very well. But now we know a lot more, and here's what we're going to do to help you.'"

Lukas Chavez, PhD

Better Together:

Transforming the Future through Collaborative Synergies

A sure way for scientists and physicians to reach goals faster is to establish synergistic partnerships with others who share their aims and whose strengths complement their own. This is why the Institute values collaborations so highly. We make infinitely more progress when we leverage our combined talent, relationships, facilities and technology. Partnerships often allow us to achieve more rigorous results more quickly. By solving problems and identifying research approaches together, we accelerate advances made in clinical translational science.

All the researchers at RCIGM collaborate with others to complete studies and report their findings. The following are examples of synergies that Institute investigators have created or continued in FY23:

- **Dr. Aaron Besterman** is teaming up with **Benjamin Smarr, PhD, a professor of biomedical engineering from University of California San Diego**. The Department of Engineering at UCSD recognized Smarr and Besterman with the GEMSTONES Award, which supports collaborative projects between clinical disciplines and engineering. Smarr and Besterman are working with several others to study whether using wearable devices to monitor physiological data can help predict when a child with a behavioral health disorder might be escalating toward a crisis.
- Besterman also won an award from the Academy of Clinician Scholars at UCSD to help fund a study he is doing in partnership with **Dr. Christopher Bartley at the National Institutes of Health Clinical Center**. Bartley, who was a psychiatry resident with Besterman, is an expert in psychoimmunology, which is the study of the role of the immune system in psychiatric illness. They are combining whole genome sequencing along with a sophisticated immune assessment to help determine whether the onset of psychosis in children is a symptom of an autoimmune disorder. The award from UCSD funds the immune testing for the patients enrolled in the study, while RCIGM covers the genome sequencing.
- **Dr. Matthew Bainbridge** is coordinating with **InVivo Biosystems** to understand the effect of variants on a known disease gene called STXBP1. The team is introducing multiple variants into the STXBP1 gene in tiny worm models to see how the variants affect the worms. A special video camera captures data that helps determine whether the variants are pathogenic or benign.
- **Dr. Jennifer Friedman** began establishing a partnership with **Hudson Freeze, PhD, at Sanford Burnham Prebys**, who studies a large group of genetic disorders called congenital disorders of glycosylation (CDG). CDG is a chemical malfunction in the body that can cause a wide range of health

problems in children. Friedman and Freeze will be joining a consortium headed at Mayo Clinic and will collaborate in a natural history study through RCIGM's Precision Medicine Clinic that will advance knowledge about CDG.

- **Dr. Amber Hildreth** has been collaborating on a project with **Orchard Pharmaceuticals**. Orchard has developed a gene therapy for a specific type of pediatric neurological condition, which, if administered before the onset of symptoms, can prevent the symptoms altogether. This neurological condition shows up in children with gallbladder abnormalities, so Hildreth is helping identify patients who fit the profile of potentially developing this disorder.

- **Dr. Charlotte Hobbs** and **Dr. Edwin Juárez-Rosales** joined forces with **Mark Yandell, PhD, at University of Utah** and **Dr. Chris Tackaberry, MD, CEO CliniThink**, to develop an automated means to prioritize patients for whole genome sequencing (see pages 44-45 for details about this important study).

- Rady Children's Hospital was approved as a site for a study of an enzyme replacement therapy (ERT), and **Dr. Nathaly Sweeney** is the principal investigator of the research in collaboration with **Inozyme Pharma**. The study will use whole genome sequencing to help diagnose children with a genetic heart disorder called general arterial calcification, which is associated with untimely death in the neonatal period. Inozyme has developed an ERT specifically to help children with this disorder.

- For several years, RCIGM has maintained a strong partnership with **Scripps Research Translational Institute. RCIGM is a subawardee of a seven-year, $48.6M grant they received in June 2023 from the NIH's National Center for Advancing Translational Sciences**. As part of the nationwide Clinical and Translational Science Awards (CTSA) Program, the funds will support continued progress in transforming human health research through technology-focused innovations. RCIGM is the Translational Institute's clinical partner in that research.
- RCIGM also is part of a CTSA companion initiative called the **Genomic Information Commons (GIC)**, a group of eight children's hospitals collaborating to build and maintain a huge database of genomic and phenotypic information from their combined patient records. The database is being developed using technology that protects patient privacy and allows GIC members to query one another's data without the data ever moving outside of their individual environments. Once established, this new, federated system will enable researchers to look across a much wider set of data for their studies. For example, researchers at RCIGM have access to electronic health records for about 2.3 million patients at Rady Children's. The GIC system will allow a query of more than 20 million records. This much larger dataset will be especially valuable when searching for clues about rare diseases that might affect fewer than one in 2,000 children.
- Over the past eight years, RCIGM has cultivated a strong relationship with **Sanford Burnham Prebys**, whose scientists come together with pediatric oncologists to through Rady Children's Hospital's Molecular Tumor Board to learn more about the unique makeup of rare, aggressive pediatric brain tumors (see page 60).
- Other great examples of more recent collaborations are RCIGM's **BeginNGS® Consortium** (see pages 83-85) and participation in the ICoNS alliance (see page 82).

> It's really important to have these national and international collaborations where we in the combined cohort can profile tumors in large numbers, and then we can start to see patterns emerge. It is so important to put resources, databases and molecular profiles of these tumors together as a community."
>
> Lukas Chavez, PhD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Partnership Perspective

Q&A with Tom Defay from Alexion

Since 2016, Rady Children's Institute for Genomic Medicine (RCIGM) and biopharmaceutical company Alexion, AstraZeneca's Rare Disease group, have been growing a strategic partnership with the shared goal of accelerating the diagnosis and treatment of critically-ill newborns with rare genetic disorders. Alexion, along with other peer companies, is also a founding member in RCIGM's BeginNGS® Consortium that aims to accelerate newborn screening by rapid whole genome sequencing to help diagnose and treat genetic diseases. Tom Defay, Deputy Head of Diagnostic Strategy and Development at Alexion, sat down with us to answer questions about this important alliance.

Q: How did Alexion's partnership with RCIGM begin?

A: My former boss and Dr. Stephen Kingsmore had known each other for years, so when Stephen was visiting Boston, he said, "Hey, let's get together." For that first meeting, we came into the room not expecting a whole lot, but we knew Stephen is a world expert on diagnosis and we were sort of a special forces team that dealt with interesting intractable problems. So, we wanted to see what was possible and think about where we might make a big difference.

Q: What has been the "secret sauce" that has led to such a long-standing cooperation?

A: I think that first meeting showed what it would be like working together. Within the first 30 minutes, we were all standing around the whiteboard debating different ways we could do some really important things for data science, really challenging each other. Now we meet about four times a year, and every time we talk about new things, challenging our thinking and discussing how we can transform the lives of patients. We've been able to make really substantive differences on multiple occasions, not just because of our shared passion for shortening the diagnostic odyssey for patients with rare disease, but also that willingness to challenge the norms and do something substantive.

Q: What accomplishment of this partnership are you most proud of?

A: The one that makes me smile the most is working with natural language processing – using machine learning technologies to examine the free-form physician notes in the patient record and identify what phenotypes, or characteristics, were described. This is important because when time is of the essence, you need to rapidly be able to digest a patient's medical record, including phenotypes, and combine it with their genomic data. It makes me smile because most people didn't feel it was possible to do this with enough precision and sensitivity to have it be relevant to diagnosis. But we were committed to challenging the norms to see what was possible. Ultimately, that project helped lead to two Guinness World Records for fastest DNA sequencing technique, at the time, that we performed with Dr. Kingsmore.

Q: You're Deputy Chair of the BeginNGS Consortium. What has you most excited about this program?

A: The thing that gets me most excited was a retrospective study we completed last year. Most people in the field doubted that we could run the study in a way that would be possible to effectively scale for hundreds of thousands of patients. The results of our study helped reassure the field that this is really something that will work moving forward. Stephen and I have presented on that study multiple times, being able to show to the rest of the field that, hey, this is possible. This is something we can do. (See page 42 for more about this study.)

Q: Why do you think it's important for pharma and biotech companies to partner with programs like BeginNGS?

A: The vision is to transform the screening and diagnosis of patients. We want rare disease patients to get diagnosed as early as possible – early enough to potentially make a very big difference in their care. The reason we want to do it is because it has the potential to help a greater number of patients. I think you've seen a number of pharmaceutical companies have joined in these types of partnerships because we feel getting these kids diagnosed is critical to enabling good care.

Q: What would you say is the most impactful thing that Alexion's partnership with the Institute is doing to transform the future?

A: We're bringing our data science and technology expertise forward to advise on solutions and capabilities that RCIGM can use to advance their research and clinical work. We've also created a lot of momentum with the BeginNGS® Consortium. Rady is about to complete the first prospective trial of the BeginNGS platform, and we're taking important steps toward expanding the use of whole genome sequencing to help more children in the United States and potentially globally.

Alexion's team received the 2022 AstraZeneca CEO award acknowledging their partnership with Rady Children's Institute for Genomic Medicine to help transform the diagnostic odyssey for people living with rare diseases. The award is the highest internal recognition the company offers and signifies appreciation for the team's work in helping patients and moving the fields of science and technology forward.

ALEXION
AstraZeneca Rare Disease

Transforming the Future for All:

Ensuring Diversity, Equity and Inclusion in Research

At RCIGM, we are mindful of the importance of racial and ethnic diversity in the occurrence and progression of pediatric rare genetic disorders. Similarly, we understand that having a diverse workforce enhances our study designs and interpretations of study findings. Equitable access to genomic medicine is one of our key priorities.

In a perfect world, all cohorts of patients participating in medical research would reflect the racial and ethnic makeup of the general population. Yet for many reasons, it can be challenging to recruit a diverse group of research participants. The National Human Genome Research Institute is committed to promoting diversity, equity and inclusion to achieve the highest level of genomic innovation, reduce health disparities and foster health equity in areas related to genomics and genomic medicine.

More than half of live births in San Diego County are born to mothers who belong to underrepresented minority groups, and 35% of its people are of Hispanic descent. Asians and Pacific Islanders are also well represented.

For the BeginNGS® clinical trial, we are seeking partner sites that will ensure our cohort reflects the racial, ethnic, gender and socio-economic diversity of the general population.

In addition, the Institute's staff is quite diverse. Members of our team include people of different races and ethnicities, nationalities, ages, religious backgrounds, genders and sexual orientation who contribute their important perspectives as we go about our work. Our patients and research participants can see themselves represented in the makeup of our staff, and we mindfully adapt our enrollment strategies and communication

> Rare genetic disorders don't discriminate. They affect children in every racial and ethnic background, every gender and socio-economic level."
>
> Kristin Wigby, MD

approach to meet these families where they are. We also are increasing our understanding of the cultural sensitivities members of different racial and ethnic groups may have about participating in genetic research.

“It has been really helpful for some of our Spanish-speaking families to hear and see someone that looked like them in the Precision Medicine Clinic,” says Dr. Kristin Wigby. “It’s been important to us to help bridge the gap for families of diverse backgrounds and be mindful of who really could benefit that’s not otherwise going to have access.”

RCIGM data scientist Dr. Edwin Juárez speaks for many at the Institute who look forward to continuing to play a part in increasing equity in research and clinical care. “One question that it’s always on my mind is, how can we make this accessible to more people who have historically not been catered to in our medical system?” he says. “It is our role as humans in designing these studies to make sure our decisions are ethical and consistent with what we should be doing – embracing the diversity.”

The Scientific Advisory Board

Sincere thanks to these distinguished members of the RCIGM Scientific Advisory Board. They play an important role in calibrating our research goals and overseeing our progress. We appreciate their guidance on scientific direction, innovation and strategic partnership for the Institute.

SAB Chair
Eric Topol, MD
Bio: https://www.scripps.edu/faculty/topol/

Carlos Bustamante, PhD, MS
Bio: https://profiles.stanford.edu/carlos-bustamante

Isaac Kohane, MD, PhD
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Jill Mesirov, PhD
Bio: https://medschool.ucsd.edu/about/leadership/pages/jill-mesirov.aspx

Stephen W. Scherer, PhD, FRSC
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Sheldon Schuster, PhD
Bio: https://www.kgi.edu/people/sheldon-schuster/

Robin Steinhorn, MD
Bio: https://profiles.ucsd.edu/robin.steinhorn

> Science knows no country, because knowledge belongs to humanity, and is the torch which illuminates the world."
>
> Louis Pasteur

TRANSFORMING THE FUTURE WITH

Thought Leadership and Education

An important part of RCIGM's model is to act as a learning healthcare system because we ultimately want to make a significant impact on the health of millions of children. We want to change the world, but we know we can't do it alone. This is why we dedicate ourselves to serving as thought leaders and educating others about the vast potential of advancing genomic medicine in pediatric populations. Furthermore, we are committed to forming relationships with like-minded people in academia, biosciences, medicine and industry to collaborate on achieving our shared vision to advance the field of genomics to benefit mankind.

EDUCATION

In FY23, the Institute continued to lead the way in helping new and experienced clinicians expand their expertise through several learning opportunities including:

- **Rapid Precision Medicine™ Grand Rounds** – In these informative sessions, clinicians and researchers explore how clinical genomic research is being used to improve patient management. **In FY23, the Institute presented six sessions to a total of 586 participants.**
- **Genomics 101** – This free, online course is designed to provide any learner with foundational knowledge of genomics and the practice of genomic medicine at RCIGM. **In FY23, 264 people completed the learning modules.**
- **Frontiers in Pediatric Genomic Medicine Conference** – RCIGM hosts a multi-day conference to share knowledge and offer networking to the community of people interested in the latest developments in rapid whole genome sequencing and newborn genome sequencing (see pages 76-77 for details on the FY23 conference).

American Academy of Child and Adolescent Psychiatry Annual Meeting, October 2022, in New York, New York – **Dr. Aaron Besterman** and his mentor, Dr. John Constantino, were the selected speakers for the James C. Harris, MD Developmental Neuropsychiatry Forum. Their talk was entitled *Clinical and Translational Implications of a New Wave of Discovery in Neuropsychiaric Genetics.*

European Society of Human Genetics Conference, June 2023, in Glasgow, Scotland – RCIGM Senior Director of Clinical Operations **Kasia Ellsworth** gave a talk entitled *Ultra-Rapid Genome Sequencing for Genetic Disease Diagnosis and Therapeutic Intervention in Neonatal and Pediatric Intensive Care Units.*

7th Rare Disease Symposium of the Eva Luise and Horst Köhler Foundation, May 2023, in Berlin, Germany – **Dr. Stephen Kingsmore** presented a keynote lecture entitled *The Future of Newborn Screening is Starting Now.*

World Orphan Drug Congress Europe, November 2022, in Barcelona, Spain – **Wendy Benson** was part of a panel on the future of genomics in newborn screening.

National Society of Genetic Counselors Annual Conference, November 2022, in Nashville, Tennessee – **Lisa Salz** and **Jerica Lenberg** co-facilitated a pre-conference workshop entitled *Genetic Counseling for Critically Ill Patients: Roadmap for Professional Development and Patient-Centered Care,* and **Dr. Amber Hildreth** presented on the topic of whole genome sequencing and solid organ transplant.

5th Annual China International Import Expo, November 2022, in Beijing, China - **Russell Nofsinger** presented on the History and Progress of Diagnostic rWGS.

WORLDSymposium™, the annual research conference dedicated to sharing advances in the field of lysosomal diseases, April 2023, in Orlando, Florida – **Dr. Charlotte Hobbs** served on a panel that spoke on the topic of the utility of whole genome sequencing for both critically ill and healthy babies.

In addition to in-person presentations across the globe, **RCIGM thought leaders presented in eight virtual events in FY23**.

Presentations/Speaking Engagements

In addition to offering numerous educational opportunities, **Institute thought leaders shared their insights and discoveries at 39 professional conferences and other events in FY23**. These team members came from a variety of disciplines and spoke on a wide array of topics including business, research, patient care, bioinformatics and more. The map at left shows locations where RCIGM team members shared their knowledge with audiences all over the world. A sampling of these conferences are described in the callout boxes. For more information about FY23 speaking engagements, visit https://radygenomics.org/events/.

Developing Talent

The Institute also is committed to **developing talented people**. We take pride in seeing our **former researchers extend the impact** of our important work when they move into roles at other institutions.

This includes people like **Dr. Robert Wechsler-Reya** who helped start the Rady Children's Molecular Tumor Board. He is now Professor of Neurological Sciences in Neurology at Columbia University and at Herbert Irving Comprehensive Cancer Center (HICCC) at Columbia University Medical Center in New York, where he is also the Director of Brain Tumor Research.

It also includes **Dr. David Dimmock**, Chief Medical Officer at Creyon Bio, a company that is using technology to develop new medicines to treat rare diseases.

And at the end of FY23, **Dr. Kristen Wigby**, co-founder of the Precision Medicine Clinic, started an exciting new position as an endowed chair of genomics at University of California, Davis (see pages 74-75).

Fond Farewell

While it's difficult to say goodbye to talented people who leave RCIGM, it's also exciting to celebrate our colleagues' new professional opportunities and to see them carry forward their training and talent to make an impact in other places. This year we wished a fond farewell to Dr. Kristen Wigby who had been with the Institute since its inception. We congratulate her for earning the distinguished position of Children's Miracle Network Endowed Chair in Pediatric Genetics at University of California, Davis.

Wigby joined RCIGM as a fellow in Medical Genetics and Genomics in June 2015. At the conclusion of the fellowship in 2018, she joined Rady Children's Hospital as a medical geneticist, and in 2019 she became an assistant professor in the department of pediatrics at University of California, San Diego.

During her tenure, Wigby worked relentlessly to bridge genetics, genomics, research, clinical care and the laboratory. She split her time serving both Rady Children's Hospital and RCIGM as a clinical geneticist and consultant for the RCIGM lab. In 2020 she co-founded the Precision Medicine Clinic and became its clinical director. She also served in the hospital's Turner syndrome and metabolic clinics.

As a researcher, Wigby studied clinical features in females with Trisomy X and was a leader in developing guidelines for the multidisciplinary care of females with Trisomy X. She also defined the features of Kabuki syndrome in infants. She was an investigator in numerous studies related to autism, Angelman syndrome, Prader-Willi syndrome, genomic sequencing in ill infants and many more. She is an author on nearly 40 published research papers since 2018.

Beloved by her patients and their families, Wigby is known as an empathetic, dedicated and detail-oriented caregiver. She always goes above and beyond in working for her patients' best interests and uses her position and status to advocate for others.

In addition to her clinical and research accomplishments, Wigby has been an influential educator. She represented RCIGM at numerous national and international conferences and internal presentations, and she has been the primary supervisor and mentor for many interns, residents and fellows.

Beloved by her patients and their families, Wigby is known as an empathetic, dedicated and detail-oriented caregiver. She always goes above and beyond in working for her patients' best interests and uses her position and status to advocate for others.

Wigby is a respected colleague and a dear, supportive friend. While everyone at RCIGM will dearly miss working with her on a daily basis, we're thrilled that she'll continue to support the Institute in an advisory role. Further, we look forward to working with her and the team at UC Davis – one of our Project Baby Bear sites. We wish her and her family well in their new home in Sacramento and look forward to partnering with her to continue transforming the future of pediatric genomic medicine.

Frontiers Conference:

Sharing Knowledge, Cultivating Alliances

Rady Children's Institute for Genomic Medicine was proud to host the Frontiers in Pediatric Genomic Medicine Conference, April 19 and 20, 2023. After a two-year hiatus from in-person conferences, we were thrilled to host the event in person against the backdrop of the beautiful Pacific Ocean at Scripps Seaside Forum in La Jolla, California. For those who couldn't attend in person, we offered the conference in a virtual format as well. **More than 400 people from 40 US states and 20 countries participated in the seventh annual event.** The audience included a diverse array of stakeholders in pediatric care and outcomes including researchers, clinicians, administrators, biotech and pharmaceutical professionals, patient families and advocates in the rare genetic disease space.

Through **more than 20 presentations and panel discussions,** conference participants learned about a variety of research and programs that are leading toward rapid whole genome sequencing becoming a first-line standard of care.

The conference was composed of two focus areas: Rapid Whole Genome Sequencing (rWGS) and Newborn Genomic Screening (NBS). During the rWGS section, the audience learned about several topics including RCIGM's GEMINI study, long-read sequencing technology, the SOMI Infant Death study, the power of advocacy to drive progress, results from Project Baby Bear in Michigan and the economic utility of rWGS, just to name a few.

In the NBS section, participants heard about newborn screening projects underway with other organizations around the world including Screen4Care, First Steps and programs at Harvard, RTI International and Genomics England. And, of course, leaders from RCIGM shared the latest news about the BeginNGS® initiative, inviting stakeholders to join the BeginNGS Consortium as thought partners (for more information on BeginNGS, see pages 83-85).

Frontiers Conference Sponsors

The conference included compelling discussions about the public health challenges and opportunities related to screening all newborn babies for genetic diseases. A panel discussion with two families whose children benefited from whole genome sequencing was a powerful reminder to all about the potential to use this technology to improve outcomes for even more children and families in the future.

Inspiring the Next Generation of

Genomic Professionals

Not long after she enrolled at University of California, Santa Barbara, Amy Peckham declared biology as her major with the intention to attend medical school. Eventually, she determined med school wasn't her desired path, but she knew she wanted to work in the medical field, so she changed her major to psychology.

When she graduated in 2019, she decided to explore different career options in medicine, and because she had an interest in genetics, on a whim she registered to attend RCIGM's Frontiers in Newborn Genomic Medicine Conference. There, Peckham met Lisa Salz, a genetic counselor with the Institute. Salz shared a lot of information about her work with Peckham, who grew even more interested as she learned more. "She was just the best," says Peckham. "She actually asked if I wanted to intern at the Institute over the summer and just get a feel for the position and see if it's something I would want to pursue."

The COVID-19 pandemic cut Peckham's internship short after just six months, but that was long enough to become inspired working alongside Salz and her colleague Jerica Lenberg. "Just getting the hands-on experience at Rady Children's and watching them with their day-to-day … I loved how they interacted with patients and wrote up reports and explained it to patients," says Peckham. "So, it was just something I knew I wanted to do. I was like, 'How do I get there?'"

Salz and Lenberg encouraged Peckham and helped her identify genetics education programs to apply to. Peckham was admitted to the Keck Graduate Institute in the Claremont area, and she earned her master's in human genetics and genomic data analytics in May 2022.

> I love Rady Children's. I love all the work they do," she says. "I could see myself one day taking on more of a patient-facing role. That's definitely something I may consider in the future."
>
> Amy Peckham

Because genomics is such a growing field, Peckham immediately had several job opportunities available to her. She chose a position as a genomic variant scientist with a diagnostics company, which offered her an opportunity she's really excited about. Not only is it a remote-work situation, but she also gets to work on analyzing and interpreting DNA data for the company's hereditary cancer panel. "My brother was actually treated at Rady when he was about eight years old for Burkitt lymphoma," says Peckham, "so that was something that kind of drove me towards the cancer side."

For now, Peckam is happy working remotely and interpreting genetic data for cancer, and she's glad to be growing her experience where she is. But she doesn't rule out eventually working in a different sort of position. "I love Rady Children's. I love all the work they do," she says. "I could see myself one day taking on more of a patient-facing role. That's definitely something I may consider in the future."

> I'm proud of what we've accomplished in this first year of BeginNGS® because genetic diseases are among the leading causes of severe illness and death in children. Hundreds of these genetic diseases have effective treatments, but families typically undergo years of medical testing before a diagnosis is reached and treatment is started. We want to right this wrong."

Stephen Kingsmore, MD, DSc

TRANSFORMING THE FUTURE WITH

Innovation

INNOVATION

Through innovative research and clinical care, RCIGM aims to achieve its vision by developing cutting-edge programs, tools and collaborations to advance science and make a meaningful impact on millions of children's lives.

The Institute is a pioneer and leader in the effort to establish whole genome sequencing as the new standard of care in newborn screening, having started the BeginNGS® platform development in FY22. **We are thrilled to have made impressive progress in growing this innovative program in FY23** (see pages 83-85).

A critical part of BeginNGS is deciding which diseases or conditions are important to include on a screening test for healthy newborns. Our team turned to the GTRx® system as the model tool to identify conditions for which there are viable treatment options for patients. GTRx stands for Gene-to-Treatment, which a cross-functional team including bioinformaticians, medical geneticists, partners from Alexion and many others built and launched in FY21. Ever since, the team has continued to develop this proprietary automated tool to guide pediatricians in diagnosing genetic diseases and managing care for their patients in intensive care units (see pages 86-87).

> I think we are at an inflection point of enthusiasm, collaboration and feasibility now. Genomics will become a component of newborn screening in the future."
>
> Charlotte Hobbs, MD, PhD

Also, in FY23, RCIGM became part of innovative national and international collaborations, most notably the International Consortium on Newborn Sequencing (ICoNS). Institute President and CEO Dr. Stephen Kingsmore is one of the founding members of ICoNS, which introduced itself and its mission to the world at the inaugural *International Conference on Newborn Sequencing* held in Boston in October of 2022.

ICoNs is an alliance of genomic scientists and stakeholders who share a vision of responsibly implementing newborn sequencing to predict treatable disease in babies and intervene before symptoms begin. Their mission is to inform the public health application of newborn sequencing by harmonizing research efforts, scientific evidence and best practices.

Until the formation of ICoNS, researchers from around the globe have been independently studying the implementation of newborn sequencing. The founding members convened ICoNS to accelerate that process by bringing these experts together to share knowledge, exchange ideas and establish a common vision for newborn sequencing as a health tool.

The organization has already grown to more than 30 contributing partners. Dr. Kingsmore remains a part of the ICoNS Steering Committee, the governing body of project leaders focused on concentrating all of the world's research on newborn genomics into one unified effort to improve public health for all.

Dr. Charlotte Hobbs, RCIGM's Chief Research and Clinical Management Officer, attended the inaugural ICoNS conference and was impressed with the caliber of expertise and passion gathered all in one place. She recalls the first time she heard someone at a conference ask, "When will we begin screening all newborns?" was around 2008. "And now here we are, 15 years later, and it's becoming a real thing that we're all working on together. I think we are at an inflection point of enthusiasm, collaboration and feasibility now," she says. "Genomics will become a component of newborn screening in the future."

BeginNGS®:

Innovating to Transform the Future of Newborn Screening

In 2016, RCIGM started using whole genome sequencing (WGS) to identify genetic diseases in critically ill babies at Rady Children's Hospital as quickly as possible. After several years, Institute leaders came to realize there was a higher genetic disease burden in this fragile population than they previously understood. At the same time, the cost to perform WGS and the time to get results had both dramatically decreased. Science and technology had advanced to a point where it could be feasible to use WGS to complement the existing and highly effective public health program of newborn screening (NBS), which identifies a few serious childhood diseases that have effective therapies.

The current standard NBS tests for a range of between 31 and 76 conditions (which varies by state). RCIGM leaders felt sure that, if implemented for all newborns, NBS-by-WGS could screen for hundreds more actionable genetic conditions and could save lives and prevent suffering for tens of thousands more children each year.

To more quickly turn this idea into standard of care, in July of 2022, RCIGM launched the BeginNGS initiative. There are two components of BeginNGS. The first component is the BeginNGS NBS-by-WGS Platform. This unique precision-medicine-delivery platform is predicated on genome sequencing and artificial intelligence for consented screening of newborns. RCIGM and technical collaborators designed the platform to screen infants for approximately 700 known, treatable genetic diseases to allow medical professionals to identify treatment options at or before symptom onset. It also includes guidance on confirmatory testing and management and provides genetic disease screening and management information across the lifespan.

The second component is the BeginNGS Program, which consists of activities designed to advance NBS-by-WGS as a standard of care for all newborns. Program priorities and activities are developed in collaboration with members of the BeginNGS Consortium, a group of public/private experts assembled to address the various complexities of rare disease screening and treatment. The consortium includes representation from patient advocacy groups and the biomedical ecosystem, who collectively provide strategic and technical expertise.

In July 2023, the Institute celebrated the program's first anniversary having achieved several important milestones.

Screening

Screening newborns for ~400 genetic diseases with known treatment options using rWGS

Diagnostic Report

Diagnosing rare disease earlier

RPM Rapid Precision Medicine™ Treatment

Employing Genome-to-Treatment (GTRx®) to provide immediate treatment guidelines to clinicians

BeginNGS

NEWBORN GENOMIC SEQUENCING

to end the diagnostic odyssey

In FY23, the Institute completed development of version 1 of the BeginNGS® platform, which encompasses 388 diseases, and, while research grade, had excellent sensitivity and specificity in a retrospective analysis of the genomic data of over 450,000 adults and critically ill infants who had previously received WGS. **Results of the version 1 study were published in the *American Journal of Human Genetics* in late summer 2022** (see page 42 for a more detailed description of this paper).

Version 2 of the BeginNGS Platform began development in 2023. It will include 411 treatable, genetic disorders and will be clinically validated in the future. The BeginNGS consortium program activities during 2023 included a retrospective clinical study similar to that performed with Version 1 and an exploratory prospective clinical trial in children admitted to the Rady Children's Hospital NICU but who are not suspected to have an underlying genetic disease. The results of these studies will be published in FY24. Version 2 of the BeginNGS Platform and Phase 2 of the BeginNGS Program are focused on preparing for a large, prospective, adaptive clinical trial of BeginNGS that will start in FY24.

Throughout the year, **the RCIGM team continued to recruit and build the BeginNGS Consortium and ended FY23 with a total of 23 members**. The members of the Consortium have contributed nearly $2.2 million to fund BeginNGS program activities. The group met in April 2023 and agreed to focus on three key areas of BeginNGS: clinical trial data stewardship, BeginNGS cost effectiveness and reimbursement, and family and patient advocacy. These stakeholders are committed to providing thought leadership through their active involvement in collaborative working groups that focus on solving the challenges of establishing WGS for newborns as a standard of care. Successful implementation of the next phases of BeginNGS activities require scaling the program.

In addition to growing the BeginNGS Consortium, **RCIGM was a founding member of the International Conference on Newborn Sequencing** (see page 82 for more on ICoNS).

"I'm proud of what we've accomplished in this first year of BeginNGS because genetic diseases are among the leading causes of severe illness and death in children. Hundreds of these genetic diseases have effective treatments, but families typically undergo years of medical testing before a diagnosis is reached and treatment is started. We want to right this wrong," says Stephen Kingsmore, MD, DSc, president and CEO of Rady Children's Institute for Genomic Medicine. "Finding a way for children to receive effective treatment before they have any symptoms of disease isn't an easy problem to solve, and we're extremely grateful for the support of each of the founding partners who are working with us towards this urgent goal."

Dozens attended a BeginNGS Consortium meeting held the day before RCIGM's annual Frontiers in Pediatric Genomic Medicine Conference in April 2023.

GTRx®

An Innovative Tool to Inform Clinicians in Caring for Children

In addition to innovation, two other facets of RCIGM's operating model are advancing care delivery and educating the public. Together, these three facets converge with GTRx, a proprietary software system that the Institute developed with Alexion Pharmaceuticals in FY21 and continues to enhance.

GTRx, which stands for Genome-to-Treatment, is RCIGM's unique online system that helps guide pediatricians in managing care for children in intensive care units who have newly diagnosed genetic diseases.

A detailed explanation of the process to develop GTRx appeared for the first time in a scientific publication early in FY23. **The paper, "An automated 13.5-hour system for scalable diagnosis and acute management guidance for genetic diseases," was published in *Nature Communications* in July of 2022.**

The Institute's team, in conjunction with Alexion, developed the technical functionality and interface for the tool. Dr. Laurie Smith oversees the Institute team that vets every disorder and treatment before it is uploaded into the system (see facing page). **Through the end of FY23, Smith and the rest of the GTRx team had added information on more than 500 diseases and 1,800 treatments to GTRx**.

Using the technological backbone of GTRx, in FY23 the Institute's bioinformatics and GTRx teams began creating a parallel platform for use with the BeginNGS newborn screening program. The difference is that the conditions included in the BeginNGS platform have to meet strict criteria for universal screening. BeginNGS diseases must be severe, have onset in early childhood, be detected by WGS, and have available, effective treatments and confirmatory tests. To create this new system, Smith and her team reviewed each GTRx entry again using these criteria, and only retained 388 diseases, with their associated treatments and confirmatory tests, that met these criteria.

Because knowledge of genetic diseases and available treatments continually change with time, **in FY23, Smith and her team launched a re-review to update every condition and treatment in the database**. The re-review ensures information on the conditions are up to date. "The first time through, the publications we reviewed were only through 2018. So now we're doing 2019 to 2023," says Smith. "And we've found that a lot has changed for several of them. There are new gene therapies for several diseases that were untreatable before."

The re-reviews wrapped up in the late summer of 2023, and the team has turned its focus to adding at least 50 new conditions to the GTRx database for FY24. In addition to adding new conditions identified by experts within RCIGM, the team has solicited nominations from BeginNGS Consortium members.

Meet the GTRx Head Curator: Laurie Smith, MD, PhD

Aside from the challenge to build the technical functionality of the GTRx platform, RCIGM leaders knew it would be a monumental task to populate its database with useful, accurate and up-to-date information. So, the Institute's President and CEO Dr. Stephen Kingsmore contacted **Dr. Laurie Smith**, a former colleague from his time working in Kansas City. Smith, a biochemical geneticist who is board-certified in clinical genetics, had recently retired, and Kingsmore knew her expertise would be a valuable asset to the team responsible for populating the GTRx database.

A self-professed workaholic, Smith agreed to come out of retirement to help with the project.

When Smith describes how GTRx works for a user, it's clear she's gratified by the work her team has done. "It tells you what the disease is, what other conditions can be associated with it, how often you can see it, tells you if you need to call a specialist right away, if there's something you should or shouldn't do, like, don't do anesthesia or don't let the patient fast. And then it goes through recommended treatments, when they should be started," she explains. "And then it has the summary so you can read that. It's really beautiful."

Smith's goal is to conduct a complete re-review of all conditions in GTRx and the BeginNGS screening every six months. "Genetics is always changing. There's always going to be new literature to look up, new treatments available," she says. When the team discovers new information, they'll update the databases to reflect the latest knowledge. "I can tell you that six months from now, a gene variant of uncertain significance might be reclassified as pathogenic or likely pathogenic," says Smith, "so it's always going to be a work in progress. It's never going to stop."

In addition to Smith, there are three others at RCIGM who work part time adding content and keeping it fresh. External partner Rancho Biosciences also contributes assistance with searching the literature. Every new condition added has a primary reviewer and a secondary reviewer, and it takes an average of three hours to manually curate all the necessary information to add one new condition to the database.

One of the things Smith loves most about her job is its potential to help many people, so she takes the quality and usability of the content very seriously. She spends a good deal of time fine-tuning content with the rest of the team, auditing condition descriptions to ensure everything is correct and checking that sources of information are properly cited. "I have reviewed every single gene on GTRx and BeginNGS," Smith says, "because the buck stops with me. So you're darn tootin' right, I'm gonna make sure that it's the best it can be."

> Individual commitment to a group effort — that is what makes a team work, a company work, a society work, a civilization work."
>
> Vince Lombardi

TRANSFORMING THE FUTURE WITH

Generous Support

GENEROUS SUPPORT

Legendary American football coach Vince Lombardi once said, “Individual commitment to a group effort — that is what makes a team work, a company work, a society work, a civilization work.”

It’s what makes Rady Children’s Institute for Genomic Medicine work, too. RCIGM’s continued growth and achievements aren’t solely due to the hard work and dedication of our employees and investigators. Our organization is thriving also thanks to the commitment of passionate individuals who are invested in the success of our mission.

We are grateful to the many people who so generously share their time and talent, volunteering as critical advisors and advocates on our Board of Directors and Scientific Advisory Board (see pages 92-93 and 69). RCIGM has evolved its operations and developed many strong relationships thanks to the guidance and feedback they have offered and the doors they have opened.

One example of this valuable support in FY23 came from **Justin Gover** who joined RCIGM’s board in the fall of 2022. Given his extensive leadership experience in the biotech field and his background as CEO and founder of GW Pharmaceuticals, Gover expressed keen interest in our collaborations with industry partners. This interest led to a series of discussions with RCIGM Chief Strategy and Innovation Officer Wendy Benson and her team. During the Frontiers Conference in April, Justin connected with fellow board member **Kitty Mackey** and suggested scheduling a half-day working session with Wendy’s team to advance the pharma research collaboration work. Wendy added **Diego Miralles** to create an even more diverse and interactive brainstorming session. Our board members’ active engagement in these discussions has been instrumental in the ongoing development of our value proposition and the continued increase in the number of projects in the pipeline.

In addition to being thankful for this passionate advocacy, we are tremendously grateful for philanthropic support from many individuals, families and grant-making organizations. Without their commitment, the Institute simply would not exist. The Rady Family’s generous investment in founding RCIGM led the charge to make a transformational impact in pediatric health. And many others have followed their example because they want to help to jump-start innovation and accelerate progress in pediatric medical research. They want to bridge critical funding gaps that hinder bold ideas from moving forward. Indeed, nearly a decade later, the Institute has made a huge impact for critically ill children across the country and throughout the world.

In FY23, with assistance from our board members, our colleagues in the RCHSD Foundation engaged six new prospective donors. They also submitted proposals for six new grants. And the Institute received two new grants totaling $128,000 from Danher Foundation and SENSE Foundation Brussels to support the Precision Medicine Clinic and BeginNGS. **In total, philanthropic support for the Institute from all sources in FY23 totaled $557,000.** Philanthropy will continue to be a game-changer for the future of pediatric genomic medicine.

The Gift of Giving:

Q&A with Donor and Board Member Ken Buechler, PhD

Ken Buechler is a generous supporter of RCIGM and has served as a board member since 2017. Here he answers a few questions regarding his involvement with the Institute.

Q: How did you initially get involved with the Institute?

A: I got involved with the Institute because of David Hale [chair of RCIGM's Board of Directors], who I've known for more than 30 years. We saw each other at a Salk Institute benefit, and he asked if I might be interested in joining the board.

Q: And what was your thought process in deciding whether joining the board would be worthy of your time?

A: In the beginning, I didn't know much about the role of being on the board, but I knew what Rady Children's does – obviously it's a children's hospital. And we all have children in common because everyone of us was a child once, and you know, it's lucky for us that we made it through. I have five kids, so children are very important for me. Their health is the most important. So, from that perspective, it was an easy sell for me.

Q: Do you personally know anyone who has had to deal with a rare-disease diagnostic odyssey or treatment odyssey? And how does that color your perspective?

A: No, I don't. I have to say, I'm very lucky to have all healthy family members – all my brothers and sisters, and all of my family has been healthy. We've been fortunate that none of us has been touched by childhood illnesses or even illness as adults for that matter.

Q: You've been a member of the board and a donor to the Institute for more than five years now. What about the organization continues to appeal to you and keeps you engaged?

A: It's really an honor to be part of this organization because, in many cases, it actually gives babies the gift of life. Some of these newborn babies wouldn't live without the treatment they get thanks to the rapid diagnoses they receive. In other cases, the Institute can offer children a better quality of life by understanding the particular condition they have. So being a part of that, somewhat indirectly helping give life to these children or making their lives better – I think that's remarkable. If I can help in that endeavor in any way, then I feel really good about that. It almost feels a little selfish on my part… I get the opportunity to help other people, and that's what I enjoy.

Q: You have so many options for where you could direct your philanthropy. What is it about the Institute that inspired you to make it a primary focus of your charitable giving?

A: Well, in addition to being able to support an organization that helps children and babies, the fact that they're advancing science and research is definitely a driving factor for me. It's another motivator because I'm a science guy – my career was devoted to science. For most of my life, I was in different kinds of diagnostics, then genomic science, and we did very similar work – saving lives through rapid diagnosis of acute conditions like heart attacks, drug overdose, heart failure and those sorts of conditions. The Institute has really outstanding scientists and leaders, and it's such a pleasure to work with my fellow board members. So, of course helping the children is the main driver, but even just the science itself is very exciting and fun. It keeps you really interested because there's always something new that's coming out.

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We gratefully recognize the following officers and members of the RCIGM Board of Directors for their dedicated service and generous contributions in FY23:

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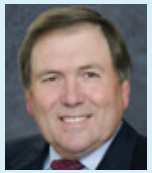
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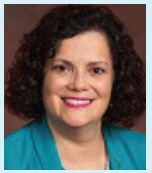
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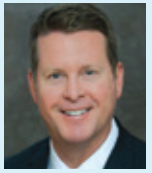
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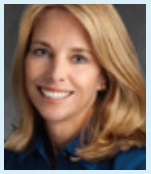
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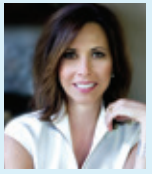
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