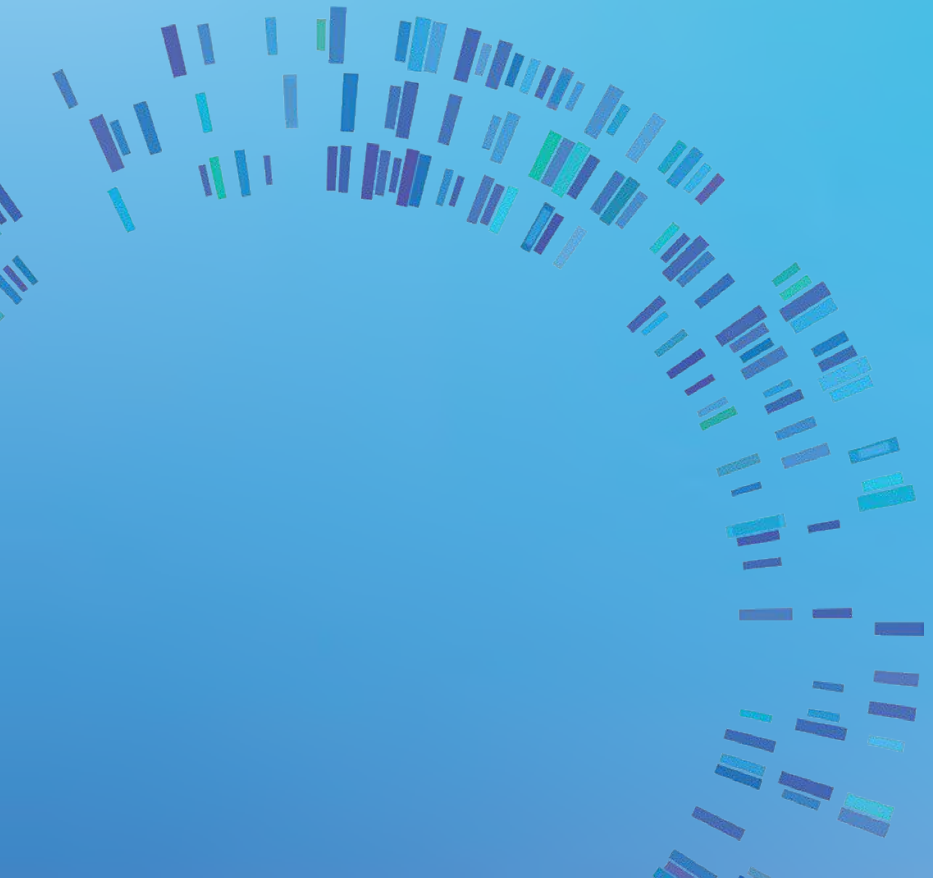
Sequence of Hope

Rady Children's Institute Genomic Medicine®

Highlights from the Year 2022 Impact Report



A Letter from the President & CEO

Dear Friends,

At Rady Children's Institute for Genomic Medicine, innovation in pediatric medicine is fueled by philanthropy. Donor support established our Institute and assembled a team of world-class scientists, researchers and clinicians focused on preventing, diagnosing and treating childhood disease.

I'm proud to say we are doing all of this and more. This report shares with you the impact that we are making collectively in bringing life-changing genomic medicine to advance child health with highlights of key accomplishments from FY22.

Thank you for being a vital part of our work. I look forward to all that we can accomplish together in the years to come.

Sincerely,

Stephen F. Kingsmore, MD, DSc

Who We Are

Genetic diseases are the leading cause of death in infants. Without prompt and precise diagnosis, families face the anxiety of delayed decisions and ineffective treatments. This leads to needless loss of life and suffering for families.

Established in 2015, Rady Children's Institute for Genomic Medicine leapt onto the scene to take on the daunting task of preventing and ending the diagnostic odyssey.

We are focused on making an immediate impact on the sickest children and babies.

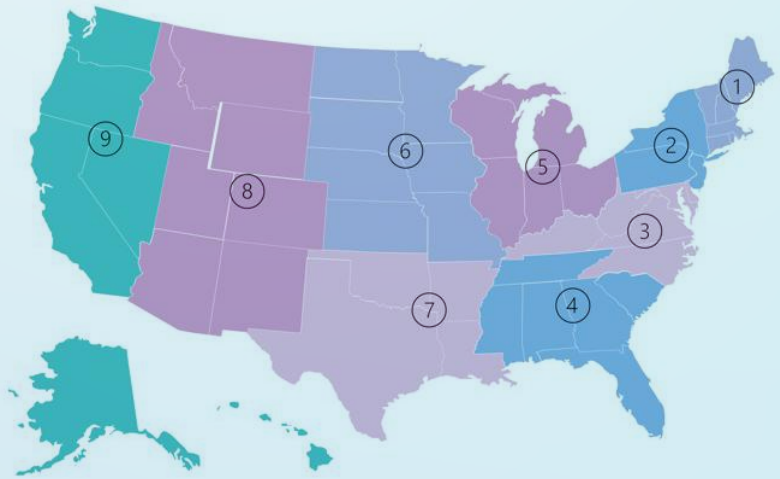
Through our system of rapid Whole Genome Sequencing™ and clinical decision support, illnesses are diagnosed early, answers are delivered rapidly and medical treatments are targeted accurately.

Seeing the tremendous impact being made for children in San Diego, we committed to scaling this technology to children's hospitals nationwide.

RCIGM Partner Network

At the close of FY22, the RCIGM partner network consisted of 83 partners in 27 US states, and two countries outside the US.

Total Unique Ordering Providers by Region Since RCIGM Inception (2015)



- 0-9 Providers
- 10-29 Providers
- 30-59 Providers
- 60-99 Providers
- 100+ Providers

All-time ordering through July 2022
Numbered regions defined as American Hospital Association regions
https://www.ahvrp.org/sites/default/files/aha-regional-map.pdf

Sebastiana Manuel

From the day Sebastiana Manuel was born, her tiny body was wracked by seizures. She didn't eat. She would twist her neck and scream. Her family knew something was wrong but didn't know exactly what. Doctors at her north county birth hospital also were unable to pinpoint a cause of the seizures. They sent Sebastiana to the neonatal intensive care unit at Rady Children's Hospital where the mystery deepened. Not only was the cause of her seizures unclear, but traditional antiseizure medicine did not work.

Sebastiana was also too sleepy to eat, and, for any newborn, frequent feedings are critical. There was no time to lose. Fortunately, Sebastiana had been transferred to Rady Children's, where doctors can access advanced technology that offers a shortcut to a precise answer. On day two of Sebastiana's life, research scientists at Rady Children's Institute for Genomic Medicine extracted her DNA from a vial of her blood and sequenced her entire genome. Four days later, the sequencing pinpointed Sebastiana's exact diagnosis: Ohtahara syndrome with KCNQ2 mutation.

The diagnosis is rare and almost always is associated with developmental delay and severe neurological damage. About half the children with the syndrome do not reach their second birthday. But Sebastiana improved quickly after doctors adjusted her medication based on the newfound diagnosis.

While she has a few physical complications and developmental delays associated with the seizures she had as a baby, Sebastiana has made great progress in therapy. Today, she is a happy kindergartner. Her mother, Dolores, says Sebastiana is a helpful and imaginative girl – she loves helping clean up after dinner and pretending she's Anna from the movie *Frozen*. She has equine therapy once a week and adores horses. She also enjoys singing and drawing and loves to read a book every single night.

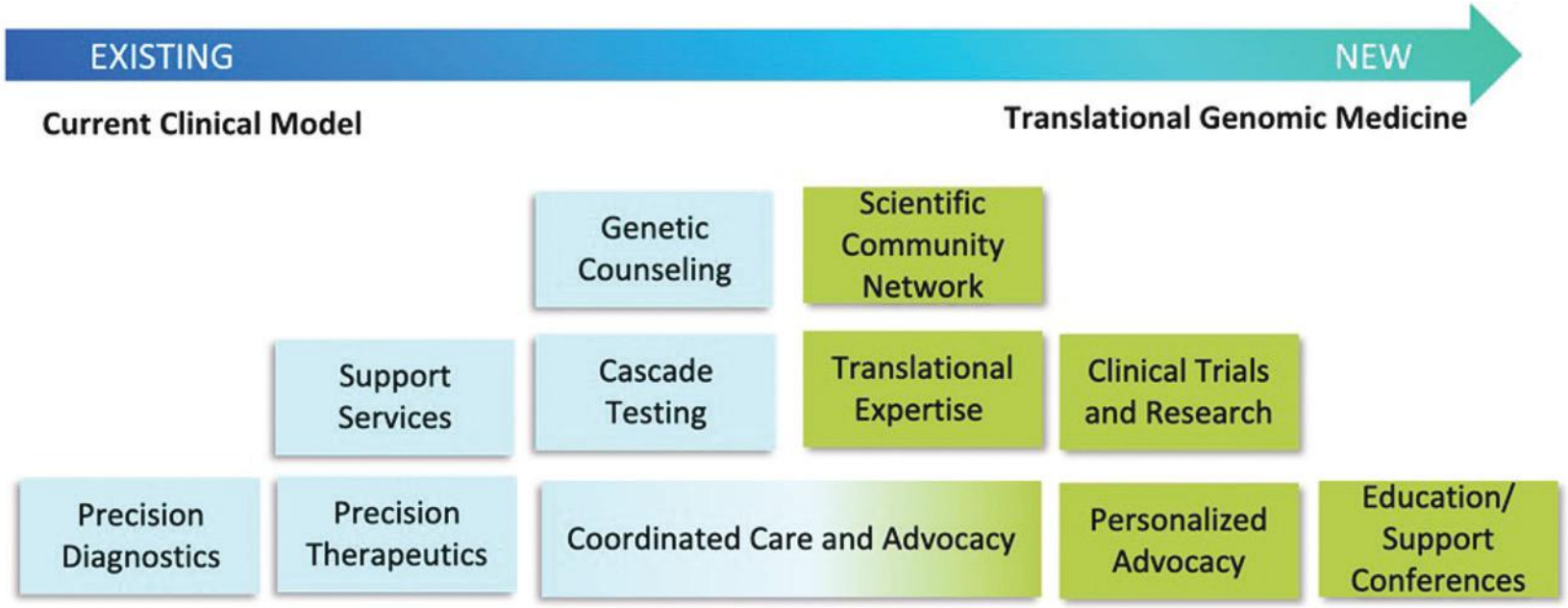
Dolores is deeply grateful to Dr. Stephen Kingsmore and all the other providers who have helped Sebastiana. "To see her start kindergarten, after worrying she might not live or may have to be in a hospital her whole life," she says, "it's just the best feeling in the world."

The Precision Medicine Clinic: Partnering with Families on the Rare Disease Journey

Many families dealing with rare undiagnosed genetic diseases endure long diagnostic odysseys before they finally identify the cause of their child's illness – test after test, year after year, while their child's health deteriorates.

The mission of the Precision Medicine Clinic is to partner with patients who have suspected or diagnosed rare or ultra-rare genetic disorders, and their families, throughout their disease journey. Our partnership begins with a molecular diagnosis and bridges the gap between diagnosis and treatment, even when no effective treatment exists. The clinic leverages multi-disciplinary deep phenotyping, genome sequencing, independent data curation and research collaborations for children with undiagnosed neurological disorders and/or other ultra-rare disorders. A long-term aspiration is to develop a novel therapeutics program for ultra-rare disorders.

FY22 was the third year for the clinic, and we continue to expand operations to help more families and develop more knowledge.



Precision Medicine Clinic

Kristen Wigby, MD, FACMG

Physician Investigator, Rady Children's Institute for Genomic Medicine

Clinical geneticist and dysmorphologist, Rady Children's Hospital-San Diego

Assistant Professor, Department of Pediatrics, University of California San Diego

Dr. Wigby has been with RCIGM for five years – one year as a research fellow and four years as a physician investigator and UCSD faculty. Before joining RCIGM,she was a fellow in clinical genetics and dysmorphology at UCSD, excited to learn about whole genome sequencing and its applications to healthcare.

I am passionate about helping parents find answers for their child's rare disease and coming alongside them on their rare disease journey. This drives my research to improve identification and diagnosis of children with rare diseases, study the natural history of these conditions, and collaborate with scientists to advance understanding of rare diseases and develop effective therapies."

Dr. Wigby on what drives her passion for research

Discovery research and training of future physicians to provide genomic-informed care is a key priority for RCIGM. In FY22 the Institute advanced 10 important research projects and published 17 articles in highly regarded scientific journals. The following spotlights a couple of outstanding initiatives:

The Conrad Prebys Foundation Grant to Fund Innovative Study

The Conrad Prebys Foundation, through the generous donation from the late Conrad Prebys, funds various endeavors within San Diego to further the health and wellbeing of the local community. In March 2022, The Conrad Prebys Foundation awarded RCIGM a $1.2 million research grant.

This grant will fund an innovative study that **Dr. Charlotte Hobbs**, Dr. Erica Sanford Kobayashi, Dr. Matthew Bainbridge, Dr. Kristen Wigby and multiple colleagues designed to evaluate:

1) **Machine learning and natural language processing** to select patients for first-tier rapid whole genome sequencing (rWGS), and;
2) **Long-read and RNA sequencing** to increase the diagnostic yield.

The investigators hypothesize that physicians will increase the number of patients they select for first-tier rWGS by utilizing a clinical decision support tool. Parents whose children are admitted to the Neonatal Intensive Care Unit (NICU) at Rady Children's Hospital will be informed about the study and asked to provide consent. The study will test innovative technology integrating natural-language processing (NLP) and machine learning to provide an electronic clinical decision support tool to support physicians when selecting patients for rWGS.

In addition to rWGS and NLP, new molecular techniques will be implemented in the study allowing for long-read sequencing and RNA fibroblast sequencing, with the intent to diagnose more infants. The study seeks to enroll 120 patients over a 12-month period.

> I finished pediatric residency before the first human genome was sequenced. At that time, **it was beyond my wildest imagination that someday I would have the opportunity to bring together my experience and skills to join an extraordinary team combining science and medicine to improve the health of babies and children for generations to come.**"

Charlotte A. Hobbs, MD, PhD
Vice President, Research and Clinical Management at RCIGM

Aaron D. Besterman, MD

Physician Investigator, Rady Children's Institute for Genomic Medicine

Health Sciences Assistant Clinical Professor, Department of Psychiatry, University of California San Diego

Attending Psychiatrist, Child and Adolescent Psychiatry Intensive Services, Rady Children's Hospital-San Diego

Dr. Besterman has been with RCIGM for two years. He completed his adult psychiatry training at UCSF and then a child and adolescent psychiatry fellowship and postdoctoral research fellowship in medical genetics at UCLA. In FY22, Dr. Besterman was focused on the following projects:

Understanding Mental Health Crises in Youth with Intellectual and Developmental Disabilities

The goal of this project is to better understand why some children with intellectual and development disabilities have mental health crises. Researchers will attempt to identify medical, genetic, psychological and social factors that may predispose these children to mental health crises. The long-term goal is to identify those youth at highest risk for mental health crises early on and intervene ahead of time.

Multiomic Diagnostics in Child and Adolescent Psychosis

The goal of this project is to explore the clinical benefit of genomic and proteomic testing in the diagnostic evaluation of youth in their first episode of psychosis. In 15 psychiatrically hospitalized youth with psychosis, researchers will perform whole genome sequencing to identify rare genetic changes known to be associated with schizophrenia. Also, in collaboration with Dr. Christopher Bartley at the NIH, researchers will perform 'PHIP-seq' analysis to identify known and new brain autoantibodies that can cause psychotic symptoms. This study will help inform the best diagnostic approach for youth with new psychotic symptoms.

Key project accomplishments in FY22:

Understanding Mental Health Crises in Youth with Intellectual and Developmental Disabilities

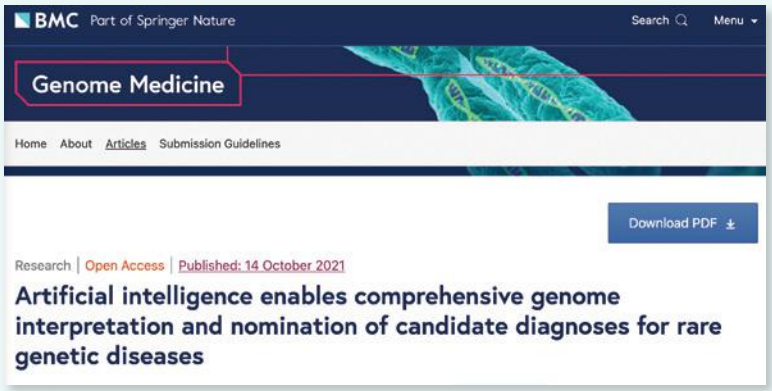
- **Submitted** K23 Career Development Award Application to the National Institute of Mental Health.
- **Enrollment started** in fall 2022.

Multiomic Diagnostics in Child and Adolescent Psychosis

- **Obtained** pilot funding from the UCSD Academy of Clinician Scholars.
- **Enrollment started** in fall 2022.

Genomic Medicine Research: Highlights of Published Manuscripts

Part of our mission is to broadly share knowledge to ultimately help more children with rare diseases. One way we accomplish this goal is to publish research findings in scientific publications. In FY22, RCIGM researchers had 50 manuscripts accepted for publication in scientific journals. Seventeen had an impact factor greater than 10. Here we feature two especially impactful manuscripts published in FY22:



De La Vega FM, Chowdhury S, Moore B, Frise E, McCarthy J, Hernandez EJ, Wong T, James K, Guidugli L, Agrawal PB, Genetti CA, Brownstein CA, Beggs AH, Löscher BS, Franke A, Boone B, Levy SE, Õunap K, Pajusalu S, Huentelman M, Ramsey K, Naymik M, Narayanan V, Veeraraghavan N, Billings P, Reese MG, Yandell M, Kingsmore SF.

Genome Med. 2021 Oct 14;13:153.

Chai G, Szenker-Ravi E, Chung C, Li Z, Wang L, Khatoo M, Marshall T, Jiang N, Yang X, McEvoy-Venneri J, Stanley V, Anzenberg P, Lang N, Wazny V, Yu J, Virshup DM, Nygaard R, Mancia F, Merdzanic R, Toralles MBP, Pitanga PML, Puri RD, Hernan R, Chung WK, Bertoli-Avella AM, Al-Sannaa N, Zaki MS, Willert K, Reversade B, Gleeson JG

N Engl J Med. 2021 Sep 30;385:1292-1301.

Fitz Kettler

In June 2019, just 36 hours after Christina and Daniel Kettler arrived home from the hospital with their new baby, Fitz, their pediatrician called with bad news. A newborn screening test revealed Fitz had a rare genetic condition called Severe Combined Immunodeficiency (SCID), commonly known as “bubble boy disease.” The prognosis was devastating. Babies with SCID have no immune system and often do not reach their first birthday.

Fitz was admitted to Rady Children’s right away, and, when he was just 10 days old, doctors ordered whole genome sequencing. The test, completed within just 92 hours, pinpointed the exact type of SCID Fitz had: Artemis-deficient SCID (ART-SCID), one of about 20 variations of the disorder. Having a precise diagnosis was crucial to making life-saving treatment decisions. In this case, knowing the specific variant of SCID meant Fitz was eligible for a gene therapy clinical trial at UCSF Benioff Children’s Hospital in San Francisco.

Over the course of four months, doctors extracted Fitz’s stem cells, injected them with a corrected copy of the flawed gene that causes SCID, then infused the cells back into his body. The new cells provided instructions for his body to develop a healthy immune system.

Thanks to the gene therapy, Fitz’s immune system rebounded. This medical science trailblazer is now an active, happy and curious 3-year-old, who recently welcomed a baby sister. The Kettlers are deeply grateful to RCIGM for the role it has played in Fitz’s life. “There’s moments when we think back and even imagine what it would look like if there was no rapid genome sequencing, if there was no gene therapy trial,” says Daniel. “We could have very well ended up in a different place.”

Information Management, Bioinformatics and Genomics

Team's Expertise:

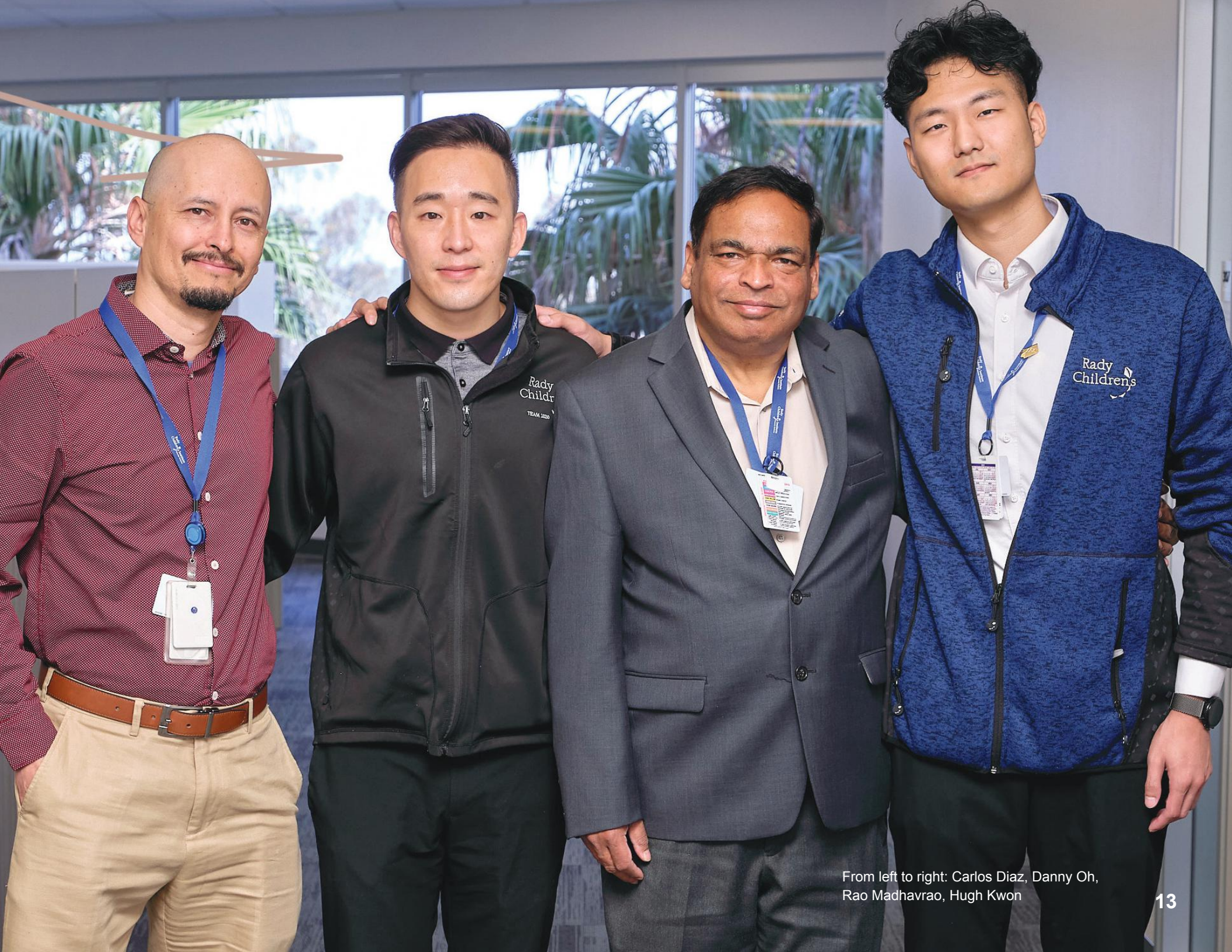
The Information Management, Bioinformatics and Genomics department comprises 12 professionals and contractors with expertise in bioinformatics, laboratory information management system application, software development and scalable data services for genomic and phenotypic data.

This group continues to serve a broad and deep role at RCIGM, developing innovative approaches and solutions to manage the huge amount of data our wet lab produces daily, as well as the pipelines the Interpretation and Reporting teams require for their analysis. In FY22, RCIGM invested in virtual desktops to avoid numerous crashes due to limited memory/storage with the large data sets.

This team also evaluates technological advances across the field to identify tools to optimize work across the Institute. In FY22, they initiated a new relationship with TileDB Inc., leveraging their unique and universal data engine, which allows work in complex data sets at global scale.

The team manages the continuous upgrades and maintenance of the RCIGM portal, which continues to be a significant asset for customer ordering, communication and tracking, as well as generating information required for productivity, efficiency and CAP/CLIA compliance. Interfaces between the portal and other tools may create additional opportunities for automation, reducing the risk for manual errors. The team is working closely with ClinOps and other teams for additional system enhancements and quality improvements.

The team's areas of focus included informatics, cybersecurity, data analytics and supporting the newborn sequencing initiative. This included reprocessing more than 4,000 samples with a new pipeline (Human Reference Genome v38) and identifying more than 30,000 variants with pathogenic and likely pathogenic designations. Working closely with technology partners, the team also helped evaluate more than 450,000 UK biobank samples in the prototype development efforts.



From left to right: Carlos Diaz, Danny Oh, Rao Madhavrao, Hugh Kwon

By rewriting the beginning, we can help families end their diagnostic and therapeutic odysseys **so they can fill their stories with hope.**”

Dr. Stephen Kingsmore

BeginNGS

NEWBORN GENOMIC SEQUENCING

to end the diagnostic odyssey

BeginNGS

Rapid whole genome sequencing (rWGS) has the potential to eliminate the diagnostic and therapeutic odysseys for many children with rare genetic diseases. Being able to identify babies with rare but treatable genetic conditions early, before symptom onset, provides the opportunity in some cases to intervene to prevent morbidity and mortality.

In recent years, there has been an increase in the number of genetic diseases identified and in the number of cell, gene and RNA therapies available coming to the market to treat these genetic conditions. Additionally, rWGS has increased in speed, diagnostic performance and scalability. These advances make it an opportune time to accelerate patient access to precision medicine by adding rWGS for newborns and evaluating the impact(s) to existing newborn screening protocols.

This innovative approach to screen primarily healthy newborns is highly synergistic with RCIGM's diagnostic rWGS franchise. The Institute's board of directors made it a priority to develop a prototype for such a program in FY22.

In FY22, RCIGM made significant progress proving the technical feasibility of a program to screen newborns using rWGS. The program is called BeginNGS (pronounced "beginnings") and stands for Begin Newborn Genomic Sequencing. The Institute's vision is for BeginNGS to become a new, additional standard of care for newborn screening across the globe.

The Potential of Newborn Screening by rWGS: A Case Study

An 8-month-old child presented to the ICU with partial paralysis suggestive of a stroke (hemiparesis), concern for brain bleeding (hemorrhage/hematoma) and elevated lactic acid in the blood stream. Neuroimaging suggested the child had an abnormal formation of brain vessels (vascular malformation), which can cause fatal brain hemorrhaging.

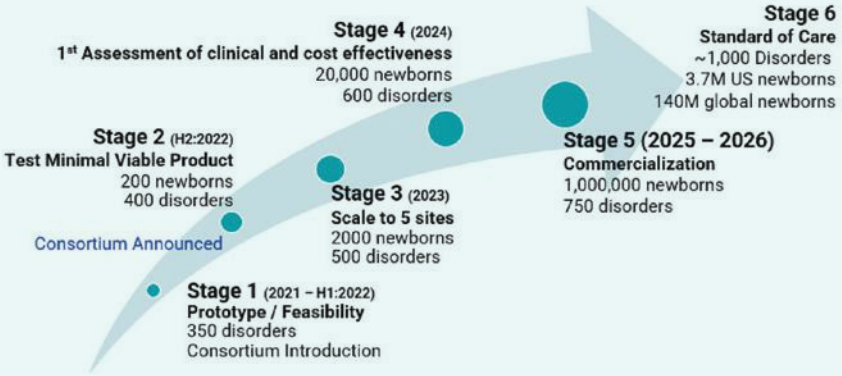
The child underwent brain surgery to relieve bleeding and obtain biopsy; however, biopsy showed no evidence of vascular malformations. Shortly after, rapid whole genome sequencing (rWGS) found a mutation in the F13A1 gene, and with confirmatory tests the child was diagnosed with a form of hemophilia called Factor XIIIA deficiency, which impairs the blood's ability to clot. Fortunately, the diagnosis allowed for targeted treatment with recombinant FXIIIA therapy.

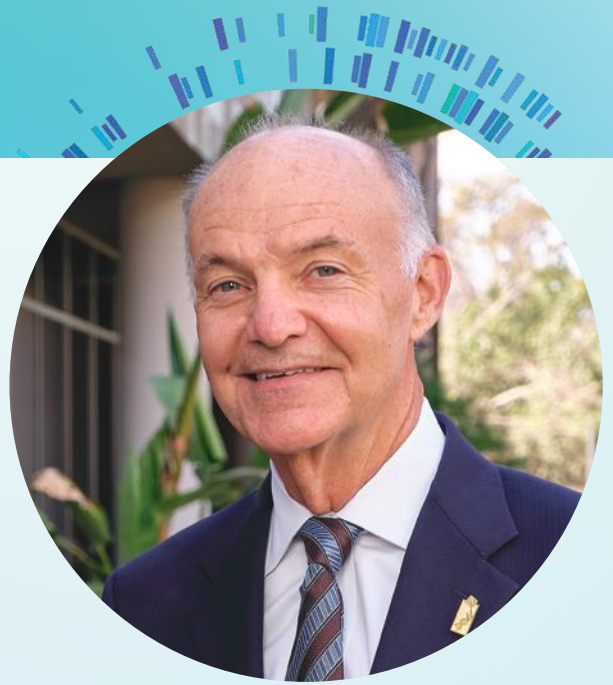
Factor XIIIA deficiency will be a condition included on the BeginNGS test. Had this child been diagnosed at birth using the BeginNGS test, he would have been prophylactically started on the recommended treatment. This prophylactic treatment likely would have avoided the hemorrhagic stroke and brain surgery.

Objective: Screen One Million Newborns

The BeginNGS initiative aims to catalyze the sequencing of one million newborns to screen for actionable genetic conditions at birth. Project implementation will scale in stages over the next several years to achieve key milestones. The Institute has completed Stage 1.

The Institute's long-term vision is to see BeginNGS as a new, additional standard of care to screen for approximately 1,000 rare conditions in more than 140 million newborns around the world.





His imperative was, **'Get out there and make kids healthier,'** and that's what [this] initiative is about."

Donald Kearns, then President & CEO of Rady Children's Hospital, speaking in 2015 about Ernest Rady's $120 million gift to launch RCIGM

Endowing the David F. Hale Chair in Pediatric Genomic Medicine

To honor David's legacy and immense impact at Rady Children's, our board members and community leaders came together to endow the David F. Hale Chair in Pediatric Genomic Medicine, with Stephen Kingsmore, MD, DSc, as the inaugural chairholder.

Endowed chairs are one of the highest honors that an institution can bestow – a mark of career accomplishments and vote of confidence in a faculty member's future work and vision. An endowed chair gives a recipient funding, freedom and flexibility to pursue promising ideas, to prioritize mentoring, and to be a leader on a national and international stage.

Having a named chair means that the faculty member also is associated with the distinguished namesake in perpetuity. By endowing this chair, David Hale's name will forever be associated with the incredible work at RICGM and its global impact.

David Hale with Dr. Stephen Kingsmore,
David F. Hale Chair in Pediatric Genomic Medicine

The Role of Philanthropy at RCIGM

Philanthropy drives innovation. It was the visionary investment of the Rady Family that established the Rady Children's Institute for Genomic Medicine. The Conrad Prebys Foundation's grant is a promise to continue advances in pediatric genomic medicine. Endowed chairs and fellowships enable the Institute to attract and retain brilliant scientists and clinicians. Many other contributions from donors fund sequencing, partnership building and discrete research projects. Because of these generous gifts, pediatric genomic medicine has become a reality.

Thanks to you, we are providing new hope and better outcomes to children and families in San Diego and around the globe.

For more information or to continue your support of this work, please contact

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radygenomics.org

"Opening up access to excellent care for all San Diego children and families is a priority for The Conrad Prebys Foundation. **We are pleased to support this work and the excellent care Rady Children's Hospital provides.**"

Grant Oliphant, CEO, The Conrad Prebys Foundation

Rady Children's Institute
Genomic Medicine®