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Rady Children's Institute for Genomic Medicine

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# Delivering Rapid Whole Genome Reports for NICU Cases with Fabric Enterprise

> "Time is of the essence, particularly with newborns who cannot tell us about their symptoms. We are excited to have dramatically reduced the time required for whole genome sequencing, and the Fabric Clinical interpretation platform enables us to quickly apply these insights to pediatric patient care. Accuracy, usability and speed are critical in the application of genetic interpretation, which is why we chose to work with [Fabric Genomics] as a key partner in the process."

**Dr. Stephen Kingsmore**
President and CEO, Rady Children's Institute for Genomic Medicine

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**Shimul Chowdhury PhD.**
Clinical Lab Director, Rady Children's Institute for Genomic Medicine

Rady Children's Institute for Genomic Medicine (Rady Children's) was established in 2014 in San Diego, CA, with a goal to "enable the prevention, identification, treatment and ultimately cure of childhood diseases through genomics and systems medicine research." Stephen Kingsmore, M.D., D.Sc., Rady Children's President and CEO, has built a world-class program for rapid sequencing and diagnosis of childhood genetic diseases. Dr. Kingsmore's goal is to go from blood sample to genetic results and clinical report, in under 24 hours. This rapid turnaround time is particularly important in the Newborn Intensive Care Unit (NICU) and Pediatric Intensive Care Unit (PICU) where children are critically ill, and each day without a diagnosis can be life-threatening and lead to catastrophic costs. A night in the NICU can cost more than $8,000 dollars, which poses a significant burden for both patients and full-risk health systems.

Dr. Kingsmore and his team decided to pursue whole genome sequencing (WGS) because it provides the most complete genetic picture of a critically ill child. In the past, sequencing was expensive, however with the introduction of new technologies, the cost of sequencing a single whole genome or whole exome is now much lower. When dealing with critically-ill newborns and children, rapid diagnosis and treatment can save lives. In fact, whole genome sequencing can be faster and more cost effective than multiple, hypothesis-driven panel tests performed over a period of weeks or months.

Two in 25 newborns are admitted to the NICU, and up to a third of these NICU patients have genetic diseases.[1] Rapid diagnosis and treatment can have a significant positive impact on survival, long-term health outcomes, and treatment costs.

Rady Children's has recently published their results from Project Baby Bear, proving, convincingly, that WGS improved the health of critically ill newborns while reducing cost. Project Baby Bear was launched with $2 million dollars in California state funding and provided WGS to 178 acutely sick newborns enrolled in Medi-Cal at intensive care units at five hospitals: Children's Hospital Orange County, Rady Children's Hospital-San Diego, UC Davis Children's Hospital in Sacramento, UCSF Benioff Children's Hospital in Oakland, and Valley Children's Hospital in Madera. Of the 178, 55 (31%) had their care changed based on the diagnosis.

The net effect was that children in the program spent 513 fewer days in the hospital than acutely ill babies who didn't receive WGS. They also had 11 fewer major surgeries, as well as 16 fewer invasive diagnostic tests. With an average savings of ~3 hospital days per child, it is clear how this can be a net saving since hospital days and major procedures are the primary drivers of healthcare costs.

## Rady Children's Clinical Genome Center

The Rady Children's Institute for Genomic Medicine brings together a team of world experts with a singular vision: making genomic medicine fast, facile and fully integrated into the daily standard of care for all children who are ill. Under the direction of Stephen Kingsmore, M.D., D.Sc., who pioneered rapid whole genome sequencing for childhood genetic diseases, the Institute is working hand-in-hand with Rady Children's Hospital-San Diego to be able to predict, pre-empt and more effectively treat a myriad of childhood diseases.[2]

### Fabric GEM – Near instant identification of causative variants

In order to meet the time-critical needs of Rady Children's patients in the NICU and PICU, Fabric Genomics™ in collaboration with Rady Institute for Genomic Medicine developed a novel AI algorithm for genome interpretation Fabric GEM which is unlocking diagnostic yields better than previously imagined. The software makes the data sources and logic fully transparent to the clinician allowing for high diagnostic confidence without the need to review pages of results. This accuracy enables a whole new level of speed and throughput of interpretation to be achieved. Fabric customers can expect a "time to causative variant" of minutes for whole genomes in rare disease

### Looking Forward

Rady Children's is committed to making whole genome sequencing the standard of care for pediatrics in clinical practice. In addition, Rady Children's vision expands beyond the NICU and PICU, with plans to expand its rapid genome service to neuro-oncology and other patients. Rady Children's and Fabric Genomics are partnering to achieve a goal of a 24-hour genome service, from sample to clinical report.

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Dr. Kingsmore has launched the leading pediatric whole genome service with a goal of 24-hour turnaround time for preliminary diagnoses. The Rady Children's team chose Fabric Genomics' clinical interpretation and clinical reporting product to support their turnaround time requirements. Fabrics Genomics' solution for NICU/PICU delivers clinical insights for whole genomes within 1 hour, including comprehensive annotation for all variants, as well as the ranking of disease-causing candidates using proprietary algorithms.

## Fabric Enterprise™

Fabric Enterprise is a comprehensive, secure and scalable platform that accelerates raw data analysis, annotation, interpretation and clinical reporting of next generation sequencing (NGS) data. Fabrics Genomics' solution for NICU/PICU, a powerful component of Fabric Enterprise, incorporates an ultra-fast annotation engine with the most up-to-date annotations from the world's leading public and proprietary reference databases. Fabric Enterprise is an optimal solution for triaging candidates: the best-in-class AI complemented with filtering tools allows labs to accelerate the identification of the most likely disease-causing variants based on impact and relationship to phenotype.

Fabric Enterprise's integrated reporting tools enable Rady Children's to quickly generate actionable reports from interpreted variant data. Additionally, Fabric Enterprise components can be easily integrated with any electronic medical record (EMR) platform using its application programming interface (API).

## Rady Achieves Rapid, High Confidence Diagnoses with Fabric Genomics

Because Rady Children's patients are critically-ill newborns and children, it is imperative that urgent patient genomic data is interpreted as quickly as possible and with high confidence. In Project Baby Bear, 43% of patients received a genetic diagnosis. These diagnoses are enabled and accelerated through Fabric's AI. In a retrospective study using the Fabric's newly introduced AI, Fabric GEM, 106 whole-genome cases from sick children in the NICU previously diagnosed by Stephen Kingsmore's expert team, in 88% of these cases, the causative variant was ranked first by Fabric GEM, and in 95% of cases, that variant was in the top 5.

An example of how the Fabric Platform helped alter a patient's life comes from a case of a 3-day-old infant with seizures since birth. First-line treatments of Levetiracetam, Phenobarbital, then Lorazepam were ineffective. Through Rady Children's rapid genome sequencing program, the infant received a provisional diagnosis in 68 hours, where a KCNQ2 mutation was identified, and Ohtahara Syndrome (OS) was diagnosed. For a KCNQ2 mutation, Carbamazepine and Phenytoin are the recommended. Rady Children's team, using the insights from Fabric Enterprise, quickly changed to the appropriate seizure medication. In addition to controlling seizures, diagnosis using rapid WGS and interpretation significantly reduced the cost of care and limited the risk of related neurodevelopmental impairment.

By contrast, another OS patient's genome was not sequenced until ~8 weeks after birth; the infant was hospitalized for 2 months, with hospital costs more than $150,000 greater than a genome case and diagnosed only later after a targeted panel test. "Early recognition of KCNQ2 encephalopathy followed by the most appropriate and effective treatment may be important for reducing the neurodevelopmental impairment associated with the disorder."[3]

1. JAMA Pediatr. 2015; 169(9):855-862, doi: 10.1001/jamapediatrics.2015.1305
2. https://www.rchsd.org/programs-services/rady-childrens-institute-for-genomic-medicine/
3. Pisano et al. Epilepsia 2015 56:685-91

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## Update: Rady develops world's fastest WGS-based diagnosis workflow

Since this case study was released in 2017, Rady Children's continues to guide medical intervention to neonatal and pediatric intensive care (NICU/PICU) patients while also striving to push the boundaries of rapid diagnostics to deliver preliminary genetic results within 24 hours of collecting a blood sample. Fabric Enterprise is integrated into Rady Children's standard variant analysis and data interpretation workflow, combining sequencing data with phenotypic data from patient records to rank genes based on pathogenicity and identify the genetic variants responsible for genetic disease.

As of March 2019, the team had completed testing and interpretation of more than 750 children's genomes. One-third of the children tested received a genetic diagnosis, with 25 percent of those benefiting from an immediate change in clinical care based on their diagnosis.

In April 2019, the Rady Children's team published a study in the journal Science Translational Medicine that details the assembly of an experimental, ultra-high-throughput genome sequencing workflow that combines many of the recent advances in rapid library prep and DNA sequencing instrumentation plus the AI-driven bioinformatics of Fabric Enterprise to quickly identify meaningful variants from the genomic dataset.

The team also broke the world record for delivering a fully sequenced and interpreted patient genome in **less than 20 hours**. "This new method opens the door to increasing the use of genome sequencing as a first-line diagnostic test for babies with cryptic conditions," says Dr. Kingsmore. "Our ultimate goal is to expand access to make rapid whole genome sequencing available to any child who needs it. This life-saving technology should be standard of care in every pediatric and neonatal intensive care unit in the nation."

1. JAMA Pediatr. 2015; 169(9):855-862, doi: 10.1001/jamapediatrics.2015.1305
2. https://www.rchsd.org/programs-services/rady-childrens-institute-for-genomic-medicine/
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