edico genome

2017

White Paper

Precision Medicine for Newborns by 26-Hour Whole Genome Sequencing

Ultra-Rapid NGS Analysis in Neonatal Intensive Care Units and Pediatric Intensive Care Units

Rady Children's Institute Genomic Medicine

EDICO GENOME | 3344 North Torrey Pines Court, Plaza Level - La Jolla, California 92037

"Diagnosing acutely ill babies is a race against the clock, which is why it's so essential for physicians to have access to technology that will provide answers faster and help set the course of treatment."

Stephen Kingsmore, M.D. D.Sc.

President and CEO, Rady Children's Institute for Genomic Medicine

Precision Medicine for Newborns by 26-Hour Whole Genome Sequencing

Abstract

Genetic diseases, of which there are >5000, are the leading cause of death in infants, especially in Neonatal Intensive Care Units (NICU) and Pediatric Intensive Care Units (PICU). The gateway to precision medicine and improved outcomes in NICUs/PICUs is a rapid genetic diagnosis. Diagnosis by standard methods, including whole genome sequencing (WGS), is too slow to guide NICU/PICU management. Edico Genome, Rady Children's Institute for Genomic Medicine, and Illumina Inc. have developed scalable infrastructure to enable widespread deployment of ultra-rapid diagnosis of genetic diseases in NICUs and PICUs.

First described in "A 26-hour system of highly sensitive WGS for emergency management of genetic diseases" in September 2015, this infrastructure has now been improved and implemented at Rady Children's Hospital – San Diego. Among the first 48 Rady Children's Hospital infants tested, 23 received diagnoses and 16 had a substantial change in NICU/PICU treatment. We are currently equipping other children's hospitals to emulate these results. Rapid diagnostic WGS has the potential to transform the care of infants in NICUs and PICUs around the world.

Introduction

Of 4 million births in the US per year, approximately 15% are admitted as infants to a NICU or PICU for management of an acute medical condition, and 2 – 6% (80,000 – 240,000) to a regional NICU/PICU. Given the high incidence of genetic diseases, up to one half of babies (40,000 – 120,000) admitted to a regional NICU in the United States may benefit from WGS. More than 20% of infant deaths are caused by genetic illnesses. Whole genome sequencing (WGS) and whole exome sequencing (WES) are effective methods for diagnosis of genetic diseases. However, they are too slow to have clinical utility in acute care, such as in diagnosis of genetic diseases in very ill infants where there is often a very narrow time window to guide interventions. Newborn screening with return of results within the first ten days of life, identifies over five thousand infants per year with a newborn screening conditions. However, newborn screening is only currently available for about 60 genetic diseases and there is variability in the number and types of conditions listed on each state's newborn screen panel, as is determined by the state's public health department. Ultra-rapid WGS, together with ultra-rapid tools for phenotype extraction, primary, secondary and tertiary analysis and clinical reporting, allows a diagnosis to be made in as little as 26 hours,

"This ultra-rapid NICU testing is the first clinical application of the DRAGEN platform. IT's not enough for one institute to implement this technology though. This testing needs to be scaled for easy use by NICUs around the world."

Pieter van Rooyen, Ph.D.

CEO and Founder, Edico Genome

and covers the vast majority of the 5000 known genetic diseases. Return of diagnostic results in a setting that includes physician mentoring by expert physicians can have profound impact on patient management and outcomes.

"Rapid diagnosis of critically ill newborns is no longer an academic exercise, it's a reality for critically ill newborns admitted to the NICU and PICU at Rady Children's Hospital. The information we receive from this rapid and comprehensive testing is already helping our medical teams make treatment decisions and impacting the lives of these babies and their families," said Dr. Stephen Kingsmore, President and CEO of Rady Children's Institute for Genomic Medicine.

Dr. Kingsmore's work at Children's Mercy Kansas City on the 26-Hour Genome, as published in the journal of Genome Medicine, inspired his relocation to Rady Children's Hospital to pioneer the Institute for Genomic Medicine. Rady's Children's Hospital is the largest children's hospital in California based on admissions and is situated in a city home to over 800 biotech companies, making it an ideal location to launch an institute around rapid genomic testing and consequent precision treatment. Dr. Kingsmore's focus at Rady Children's Hospital is on developing the clinical research infrastructure for accelerated translation of research discoveries – such as rapid diagnostic WGS - into prevention, diagnosis, treatment and improved outcomes for childhood genetic diseases. The work that Dr. Stephen Kingsmore did on the 26-Hour Genome together with Illumina and Edico Genome earned a Guinness World Record for Fastest Genetic Diagnosis.

Solution

Rady Children's Hospital – San Diego and Edico Genome have partnered to create an ultra-rapid platform and infrastructure at Rady Children's Institute of Genomic Medicine. Rady Children's Hospital began providing whole genome sequencing in July 2016 with clinical interpretation in a clinically enlightening, timely and highly accurate manner to critically ill children. Utilizing Edico Genome's DRAGEN, the world's first bio-IT processor designed to rapidly accelerate the analysis of genomic data while maintaining high accuracy, this ultra-rapid method allows the simultaneous evaluation of nearly all 5000 known genetic diseases in a single test.

The ultra-rapid method is both a compute and storage solution and is part of a two-phase broader impact vision. First, our goal is for Rady to become an ultra-rapid medical sequencing center and hub for all children's genome sequencing, thereby enabling children's hospitals without sequencers or adequate funds and resources to outsource their patient's samples and data to Rady Children's Institute for sequencing and ultra-rapid analysis.

Dr. Stephen Kingsmore is the official title holder of the Guinness World Records® designation for Fastest Genetic diagnosis, which he accomplished by successfully diagnosing critically ill newborns in just 26 hours, as published in the journal Genome Medicine. The feat was made possible by several time-shrinking technologies, including Edico Genome's genomic data-crunching computer chip, DRAGEN, and one of Illumina's high-throughput sequencing instruments.

"There are ways that we can make investments on other people's behalf, and then share with them the protocols, methods, and software that they can deploy locally," said Dr. Kingsmore. "That's our goal, initially for 4 other children's hospitals, and then scaling to 1500 across North America."

As part of that genome center, Edico has implemented the analysis and storage infrastructure, along with Illumina's HiSeq sequencing instruments, to support and continue scaling this vision. In the near-term the genome center will positively impact all children in four Southern California counties (San Diego, Imperial, Riverside and Orange). The far broader impact is replicating what is being done at Rady in an appliance format that can be implemented at any hospital around the country, all connected via a secure data sharing cloud.

The NICU and PICU are the ideal location to start using the ultra-rapid diagnostic technology because of the high burden of genetic disease, most rapid rates of disease progression – minutes matter there – and because the cost of NICU and PICU care is already very high per day relative to the cost of WGS. Thus, the NICU and PICU are locations where the technology is likely to be most cost-effective and have highest clinical utility in the short term. NICUs and PICUs at separate institutions have a high degree of collaboration, particularly with regard to quality improvement projects and implementation of new best practices, and this will greatly facilitate broad adoption.

Details/Results

Of 116 infants at Rady Children's Hospital referred for rapid medical WGS since July 2016, 58 have been enrolled (representing 95% of families approached for consent). At present, 48 families have completed testing and results have been reported. 23 infants (48%) received a molecular diagnosis. Among those, 14 (70%) received substantive changes in their care. We have had infants with metabolic disorders who were among the youngest in the world to be started on targeted therapeutics for that disease or started on metabolically optimized diets. For infants with seizures, we have been able to recommend specific antiepileptic treatments that target the underpinning neurologic mechanism of disease, resulting in seizures stopping within days rather than within months. For an infant with heart failure and another with liver failure, we were able to rule out diseases which were a contra-indication to heart and liver transplant, respectively. Without such information, an infant may be at too high risk for transplant or may not survive transplant.

For another infant with liver disease we provided a diagnosis that resulted in cancellation of a surgery that would have had 60% risk of

"Imagine if your child was born with a disease but no one could identify what was wrong or what treatment was needed. Further imagine a medical odyssey of repeated tests spanning months, even years, with no answers. We have demonstrated that genomic sequencing can provide these answers! For a few, a diagnosis offers new hope of disease-specific treatment. For many, it is the end of the diagnostic nightmare."

Stephen Kingsmore, M.D. D.Sc.

CEO and President, Rady Children's Institute for Genomic Medicine

mortality. For an infant with hypoglycemia we were able to recommend a specialized, curative surgery, shortening the duration of hypoglycemia (and NICU stay) by one month. In one infant who had been in the NICU for six months with many problems, the diagnosis was of a uniformly fatal genetic disease, and that result helped allow the physicians and parents to reach decisions about palliative care. In almost all cases unnecessary treatments and tests are discontinued or avoided. In almost all cases we are able to provide genetic and reproductive counseling for families. For most parents the diagnosis is a definitive answer which ends a period of waiting, alleviates guilt, and enables parents to start to make plans for the future. Another child with cardiac arrest was diagnosed with CPVT, permitting targeted treatment with an antiarrhythmic prior to surgical implantation of a defibrillator. Two infants tested to date were patients at NICUs at other children's hospitals in the US, and a DNA sample and a medical record extract were rapidly shipped to Rady Children's Hospital to allow the diagnosis to be made. One of these infants had a very poor prognosis without transplant. There was concern that this child may have a disorder not amendable to transplant, placing the parents at inappropriate risk as donors of a living related transplant. A diagnosis was made in 43 hours, and the infant received a transplant. The sooner a definitive diagnosis is made, the less potential for inappropriate treatment and unmitigated disease progression.

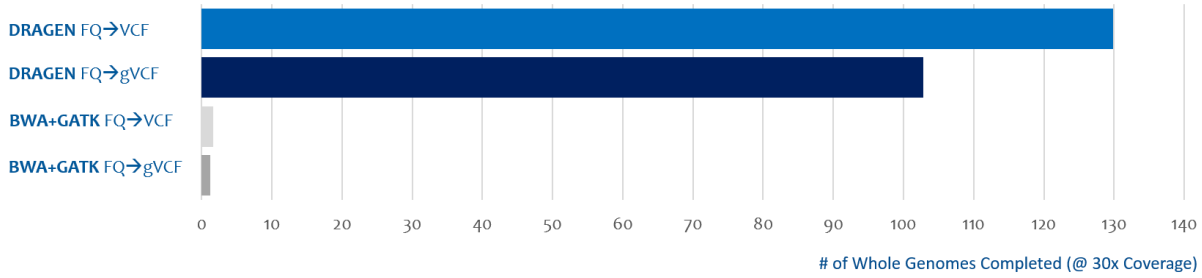
The total cost of rapid, diagnostic, whole genome sequencing, together with confirmatory testing of results and reporting is approximately $7000. This is a reduction from about $10,000 one year ago, largely due to efficiencies of scale and lower sequencing costs with the Illumina HiSeq 4000. With the introduction of the NovaSeq platform, improvements in sample preparation, and additional development of the DRAGEN technology we anticipate further decreases in cost and turnaround time in the coming year, together with at least a 10% gain in rate of diagnosis associated with rapid structural variant detection.

The key enabling technology to reduce the time of the 26-Hour Genome was the DRAGEN Platform based on the World's first Bio-IT Processor. The DRAGEN (Dynamic Read Analysis for Genomics) Platform uses a field-programmable gate array (FPGA) to provide hardware-accelerated implementations of all of the most widely used types of NGS workflows such as Genome/Exome, Cancer, Transcriptome/RNA-seq, Microbiome/Metagenome, Epigenome and Joint-Genotyping/Population-Calling.

Edico Genome's computing platform accelerates whole genome data analysis from hours to minutes, while maintaining high accuracy and reducing costs, enabling clinicians and researchers to reveal answers more quickly. The platform is available for virtual or onsite ultra-rapid analysis of next-generation sequencing data. This hybrid-cloud technology provides users with the flexibility to securely share data and scale up to the cloud during times of high capacity and return to onsite analysis when demand is reduced.

DRAGEN Speed and Accuracy Charts

DRAGEN Ultra-Rapid Analysis: # Genomes Sequenced in 48 Hours*



DRAGEN Speed: Single Sample Pipeline*

Dataset	Pipeline Configuration	DRAGEN	BWA + GATK-HC	DRAGEN Speed Up
SRA056922 NA12878 @ 30x	FASTQ to VCF	0:22:11	30:20:20	~82X
	FASTQ to gVCF	0:28:31	36:53:29	~78X
Garvan Lane1 NA12878 @ 37x	BCL to VCF	0:26:28	32:18:25	~73X
	BCL to gVCF	0:29:27	38:51:34	~79X

DRAGEN Speed: Multi-Sample Pipeline*

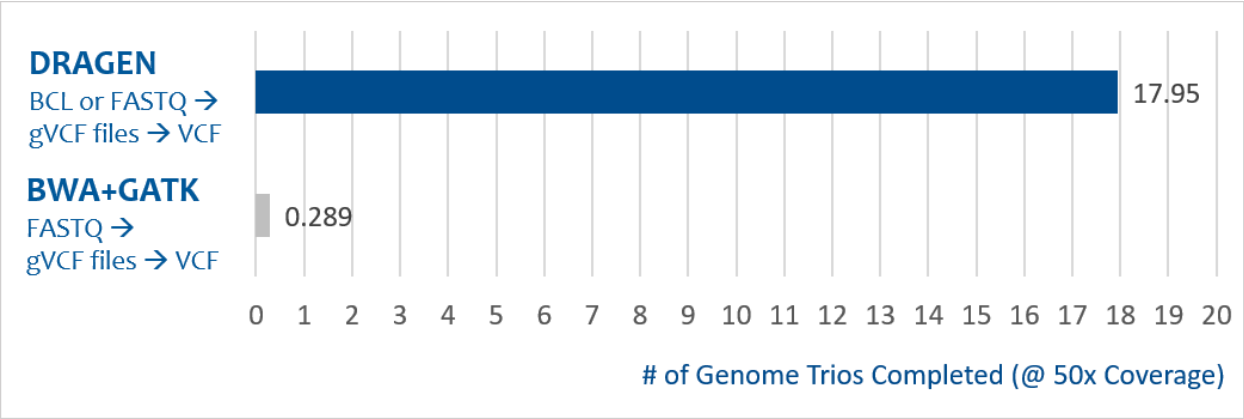
Processing of 12 Samples	DRAGEN	Bcl2fastq + BWA + GATK-HC	DRAGEN Speed Up
BCL to FASTQs to VCFs	4:21:43	279:02:36	~70X
BCL to VCFs	3:26:49	N/A**	N/A**

DRAGEN Accuracy: Single and Multi-Sample Pipelines*

Accuracy	Pipeline	True-Pos	False-Pos	False-Neg	Precision	Sensitivity	F-Measure
SNP + INDEL Combined	DRAGEN	3230927	20398	55603	99.37%	98.31%	98.84%
	BWA-MEM + GATK	3233756	21402	55834	99.34%	98.30%	98.82%
SNP Only	DRAGEN	2859895	7624	25434	99.73%	99.12%	99.43%
	BWA-MEM + GATK	2862995	8511	25593	99.70%	99.11%	99.41%
INDEL Only	DRAGEN	371032	12774	30169	96.67%	92.48%	94.53%
	BWA-MEM + GATK	370761	12891	30241	96.64%	92.46%	94.50%

*All DRAGEN results are compared against BWA-MEM 0.7.12 + GATK 3.1 running on comparable servers.

DRAGEN Ultra-Rapid Analysis: # Platinum Genome Trios Genotyped in 48 Hours



DRAGEN Speeds: Joint Genotyping Pipeline

Pipeline	DRAGEN	BWA-MEM + GATK-HC	DRAGEN Speed Up
Platinum Genomes Trio @ 50x coverage + Joint Genotyping	2:40:46	166:45:00	69X

DRAGEN Accuracy: Joint Genotyping Pipeline

Accuracy	SNP+INDEL Combined	True-Pos	False-Pos	False-Neg	Precision	Sensitivity	F-Measure
SNP + INDEL Combined	DRAGEN	3284846	15741	22590	99.5%	99.3%	99.4%
	BWA-MEM + GATK	3288002	22168	22867	99.3%	99.3%	99.3%
SNP Only	DRAGEN	2874110	11407	16078	99.6%	99.4%	99.5%
	BWA-MEM + GATK	2876319	17191	16320	99.4%	99.4%	99.4%
INDEL Only	DRAGEN	410736	4334	6512	99.0%	98.4%	98.7%
	BWA-MEM + GATK	411683	4977	6547	98.8%	98.4%	98.6%

*All DRAGEN results are compared against BWA-MEM 0.7.12 + GATK 3.1 running on comparable servers.

"When each of your experiments produces a trillion base pairs, you end up finding a company like Edico Genome a lot faster than you otherwise might… it is very clear that you can do high quality, high speed mapping using DRAGEN and it is quite possible that it is simply the best thing out there. You would simply not do CPU-based alignment – it would be silly."

Erez Lieberman Aiden

Ph.D., Baylor College of Medicine & Rice University

Business Benefits

The primary ROI for making a rapid diagnosis in a NICU/PICU infant is measured in Quality Adjusted Life Years saved (QALYs). Given current US life expectancy, each infant's live saved yields ~70 QALYs. In a recently terminated randomized controlled trial of rapid whole genome sequencing versus standard tests in critically ill infants, the rate of neonatal (day of life 28) molecular diagnosis was 22% by rapid WGS, and 0% in infants receiving standard tests, including NGS panel tests and WES (p=0.0048)(Kingsmore et al, in preparation). As yet, only one published case series has examined QALYs, yielding an admittedly soft value of 2.5 QALYs per NICU/PICU infant tested. We estimate that offering testing of all at-need NICU and PICU infants in the US (~40,000), would save ~80,000 QALYs per year.

The secondary ROI is other measures of clinical utility, such as minimizing morbidity and maximizing quality of life for the infant and family. This was discussed above. The tertiary ROI is overall reduction in healthcare cost during the first year of life. Healthcare economic data is being generated at present. However, the average cost per day of hospitalization in a regional NICU or PICU is in excess of $3000.

Conclusions

NICU and PICU care is amongst the most effective in healthcare when the prognosis is good, both as measured by QALYs saved and cost per QALY. Equally, when the prognosis is poor, adoption of palliative care may minimize infant suffering, and a definitive diagnosis mayprovide profound long term psychosocial benefits for parents and siblings. These include alleviation of anxiety, depression, prolonged grief, and posttraumatic stress disorder. Therefore, timely establishment of an etiologic diagnosis in a NICU or PICU infant with a likely genetic disease is critically important for effective treatment (precision medicine), and for full parental participation in clinical decision making.

Rapid diagnostic WGS has the potential to transform the care of infants in NICUs and PICUs around the world. Timely diagnoses of NICU and PICU infants with genetic diseases would enable institution of optimal precision medicine. Unnecessary, empiric testing, procedures and treatments would be avoided. Parental guilt and anxiety would be lessened. Early, complete ascertainment of infants with specific genetic diseases would make some conditions tractable for new drug development. An ultimate goal would be for genetic diseases to no longer by the leading cause of infant mortality, NICU mortality and PICU mortality.

References

1. Berg JS, Agrawal PB, Bailey DB Jr, Beggs AH, Brenner SE, Brower AM, Cakici JA, Ceyhan-Birsoy O, Chan K, Chen F, Currier RJ, Dukhovny D, Green RC, Harris-Wai J, Holm IA, Iglesias B, Joseph G, Kingsmore SF, Koenig BA, Kwok PY, Lantos J, Leeder SJ, Lewis MA, McGuire AL, Milko LV, Mooney SD, Parad RB, Pereira S, Petrikin J, Powell BC, Powell CM, Puck JM, Rehm HL, Risch N, Roche M, Shieh JT, Veeraraghavan N, Watson MS, Willig L, Yu TW, Urv T, Wise AL. Newborn Sequencing in Genomic Medicine and Public Health. ***Pediatrics***. 2017 Jan 17. pii: e20162252. doi: 10.1542/peds.2016-2252.
2. Noll AC, Miller NA, Smith LD, Yoo B, Fiedler S, Cooley LD, Willig LK, Petrikin JE, Cakici J, Lesko J, Newton A, Detherage K, Thiffault I, Saunders CJ, Emily G Farrow EG Kingsmore SF. Clinical detection of deletion structural variants in whole-genome sequences. ***npj Genomic Medicine*** 2016 1, 16026.
3. Twist GP, Gaedigk A, Miller NA, Farrow EG, Willig LK, Dinwiddie DL, Petrikin JE, Soden SE, Herd S, Gibson M, Cakici J, Riffel AK, Leeder SJ, Dinakarpandian D, Kingsmore SF. Constellation: a tool for rapid, automated phenotype assignment of a highly polymorphic pharmacogene, CYP2D6, from whole-genome sequences. ***npg Genomic Medicine*** 2016 1:15007.
4. Brenner SE, Kingsmore S, Mooney SD, Nussbaum R, Puck J. USE OF GENOME DATA IN NEWBORNS AS Smith LD, Willig LK, Kingsmore SF. Whole-Exome Sequencing and Whole-Genome Sequencing in Critically Ill Neonates Suspected to Have Single-Gene Disorders. ***Cold Spring Harb Perspect Med.*** 2015 Dec 18. pii: a023168.
5. Kingsmore SF. Newborn testing and screening by whole genome sequencing. ***Genet Med.*** 2015 Dec 17. doi: 10.1038/gim.2015.172.
6. Petrikin J, Willig LK, Smith LD, Kingsmore SF. Rapid Whole Genome Sequencing and Precision Neonatology. ***Semin Perinatol.*** 2015 Dec;39(8):623-31.
7. Miller NA, Farrow EG, Gibson M, Willig LK, Twist G, Yoo B, Marrs T, Corder S, Krivohlavek L, Walter A, Petrikin JE, Saunders CJ, Thiffault I, Soden SE, Smith LD, Dinwiddie DL, Herd S, Cakici JA, Catreux S, Ruehle M, Kingsmore SF. A 26-hour system of highly sensitive whole genome sequencing for emergency management of genetic diseases. ***Genome Med***. 2015 Sep 30;7(1):100.
8. Kingsmore SF, Petrikin J, Willig LK, Guest E. Emergency medical genomes: a breakthrough application of precision medicine. ***Genome Med***. 2015 Jul 30;7(1):82.
9. Willig LK, Petrikin JE, Smith LD, Saunders CJ, Thiffault I, Miller NA, Soden SE, Cakici JA, Herd SM, Twist G, Noll A, Creed M; Alba PM, Carpenter SL, Clements MA, Fischer RT, Hays JA, Kilbride H, McDonough RJ, Rosterman JL, Tsai SL, Zellmer L, Farrow EG, Kingsmore SF. Diagnostic and Clinical Findings among Critically Ill Infants Receiving Rapid Whole Genome Sequencing for Identification of Mendelian Disorders. ***Lancet Respir Med.*** 2015 May;3(5):377-87.
10. "About Newborn Screening Screening Facts." Screening Facts | Baby's First Test | Newborn Screening | Baby Health. N.p., 2016. Web. 20 Mar. 2017.

DRAGEN™