Rapid Whole Genome Sequencing (rWGS): Improves Patient Outcomes; Generates an ROI for Children's Hospitals; Increasing Coverage by Payors and Medicaid

Michael Vishnevetsky
SVP, Business Development,
Fabric Genomics,
Oakland, CA

Today’s Agenda

- Introduction to Fabric Genomics
- Whole Genome Sequencing (WGS) review
- Impact of WGS in the NICU
- How can Fabric AI help me?
- Ultra Rapid WGS case study
- Reimbursement landscape

Fabric Genomics

Our mission

To make genomics-driven medicine a reality by leveraging AI to

- **Facilitate scalability of testing**
- **Enhance accuracy and turn-around times**
- **Provide affordable solutions**

Bay-area based in Oakland, CA

Mendelian diseases are a leading cause of NICU admission, mortality, & healthcare costs

Rare Disease

- ~10,000 currently known single locus genetic diseases
- >50% rare diseases impact children

NICU

- ~400,000 US NICU admissions per annum, costing >$17B per annum
- 30% of admission to NICU are due to genetic conditions
- ~40% infant death in ICU are associated with single locus variants

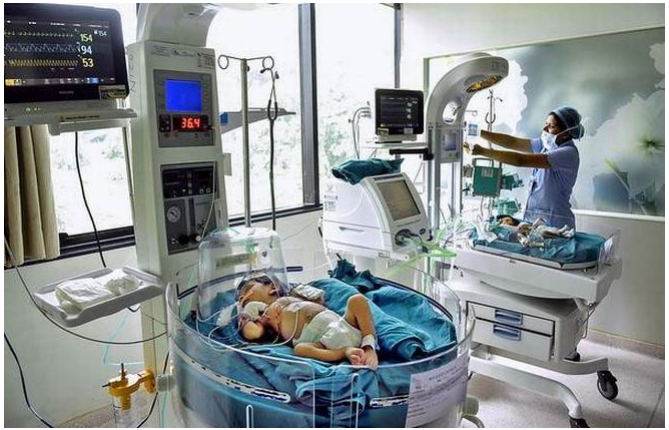
Treatment

- Nearly 900 disorders caused by a single gene are known to be treatable

Kingsmore et al. 2024 - https://doi.org/10.1038/s41525-024-00404-0

Need for Rapid WGS Diagnosis in the NICU

- Genetic diseases are common the NICU setting
  - Structural birth defects (3-5%)
  - Inborn errors of metabolism (0.5%)
  - Neurodevelopmental disorders (3%)
  - Aneuploidy (0.3%)
- Leading cause of mortality in NICU and PICU*
- Disease progression can be rapid in infants
  - Fast turnaround essential to impact management
  - *Speed matters*



* Smit el at, 2019; Willing et al, 2015.

Whole Genome Sequencing (WGS) workflow

DNA purification

- Specimen: blood, saliva or buccal
- Purify DNA with commercial kits
- QC

Library Prep

- Adapter ligation
- Size selection
- QC

Sequencing & variant calling

- Sequencing on long or short-reads
- Read alignment
- Variant calling

Interpretation

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- Variants classified
- Variants prioritized
- Report generated

Report sign out

- Report is reviewed and signed out by a qualified medical director

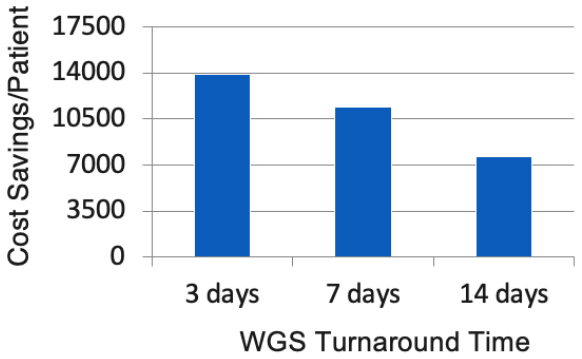
3 days (ultra-rapid)

7 days (rapid)

Faster WGS equates to better care and cost savings in NICU

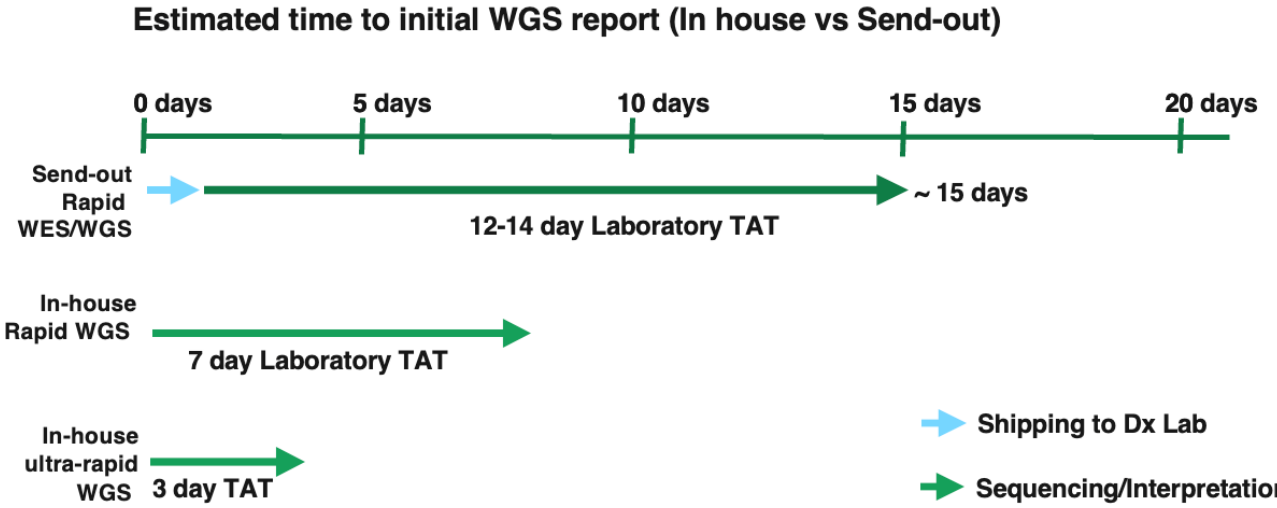
- **Diagnosis is critical for understanding prognosis, optimizing treatment, and estimating recurrence risks**
  - The faster the molecular Dx, the greater impact on care / costs
  - The time to act is short: NICU stays average 14-21 day
  - Maximal cost savings of $14,000 per child if rapid WGS is completed within 3 days

Test	Study Size	Dx Rate	Change in Management
15 day WES/WGS	894	37%	38%
3.6 day WGS	35	49%	58%



Dimmock, et al. AJHG 2020,2021

In-house (*on-site*) testing offers increased benefits



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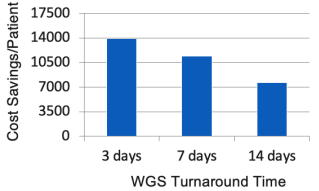


Dimmock, et al. AJHG 2020,2021

Both send out and In house testing result in change in management and reduced costs, but faster is better

Figure credit, S. Meyn, U. Wisconsin, ACMG Presentation 2024

Benefits to bringing whole genome testing in-house

Patients

- Control of turn around time
- Especially for NICU cases
- Improved diagnostic yields than send outs with dynamic analysis/reporting
- Iterative phenotyping
- Periodic reanalysis

Hospital/healthcare system

- Lower cost
- Track test utilization
- ‘Own’ patient data for research

Fabric Genomics products and services for whole genome sequencing (WGS)

Next-Gen Sequencing | Secondary Analysis | Interpretation | Reporting

Alignment | Variant Calling | Annotation & Analysis | Gene Interpretation | Systems Integration | Clinical Reporting

Fabric Enterprise Software

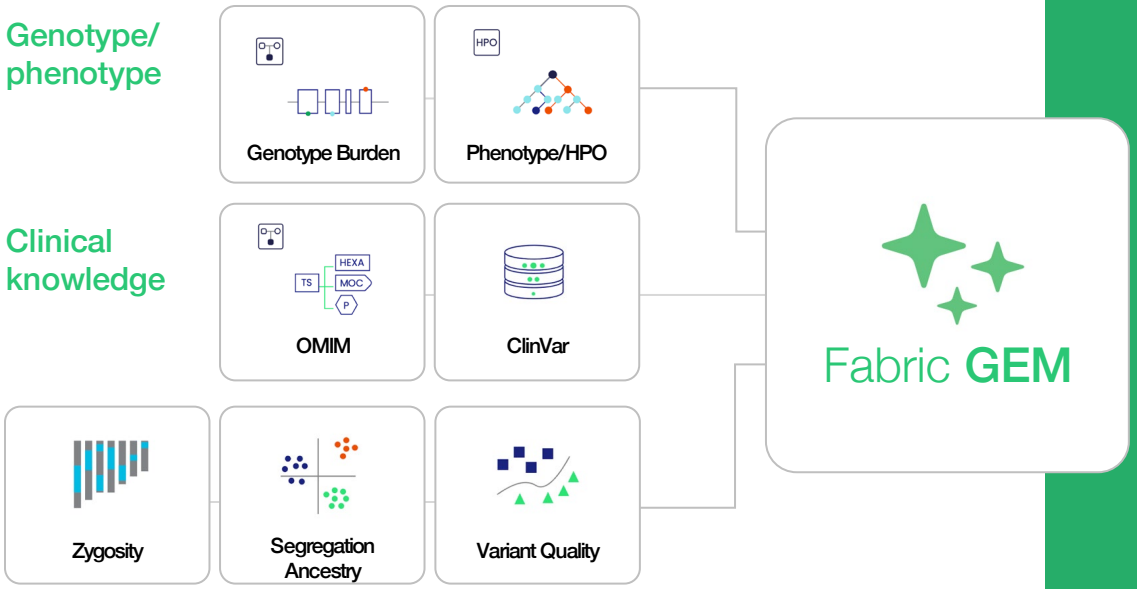
AI-driven Clinical Software that transforms raw genome sequence data Into high-quality, clinically meaningful insights

Fabric Clinical Services

Expert interpretation services using Fabric Enterprise software
CLIA CAP accredited

CLIA compliant HIPAA compliant ISO 27001 certified

Fabric GEM is an AI-based gene prioritization algorithm that considers multiple data sources



- Prioritizes putative causal variants
- Integrated analysis includes SNVs, indels, CNVs, SVs
- Explainable AI for genomes or exomes

Time saved can be spent on scaling samples and harder cases

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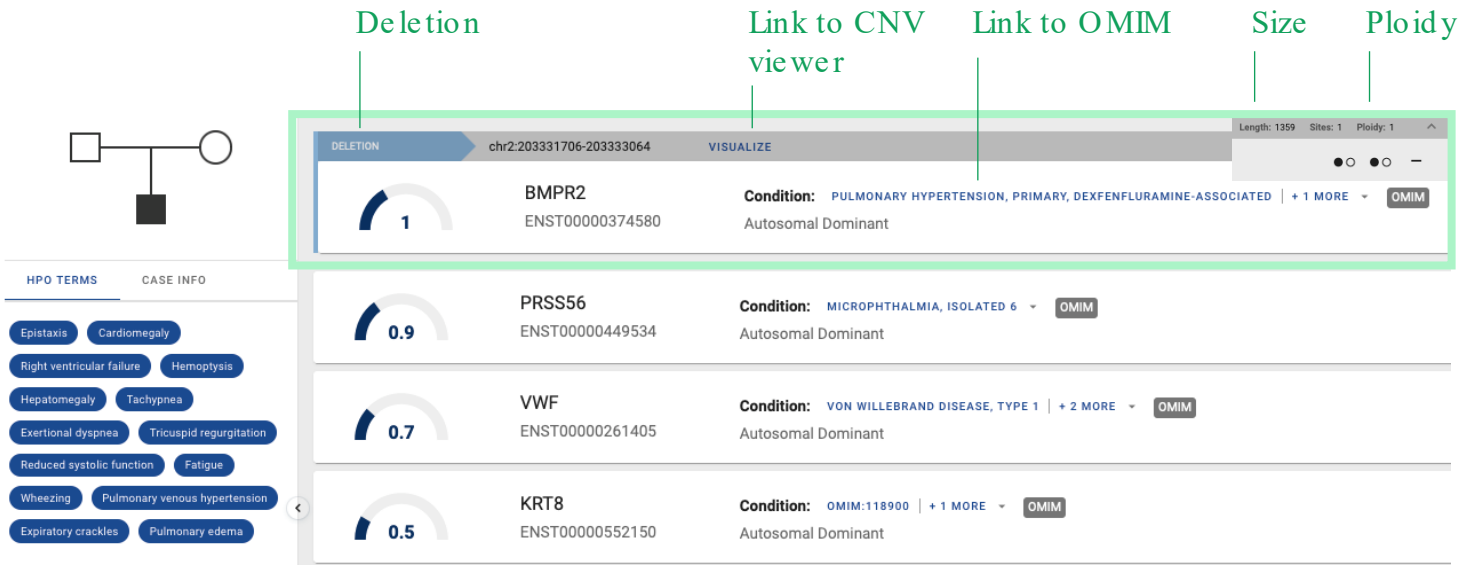
Fabric prioritizes variants including SNVs and CNVs from WGS data



Fabric provides physician-ready clinical reports from WGS data

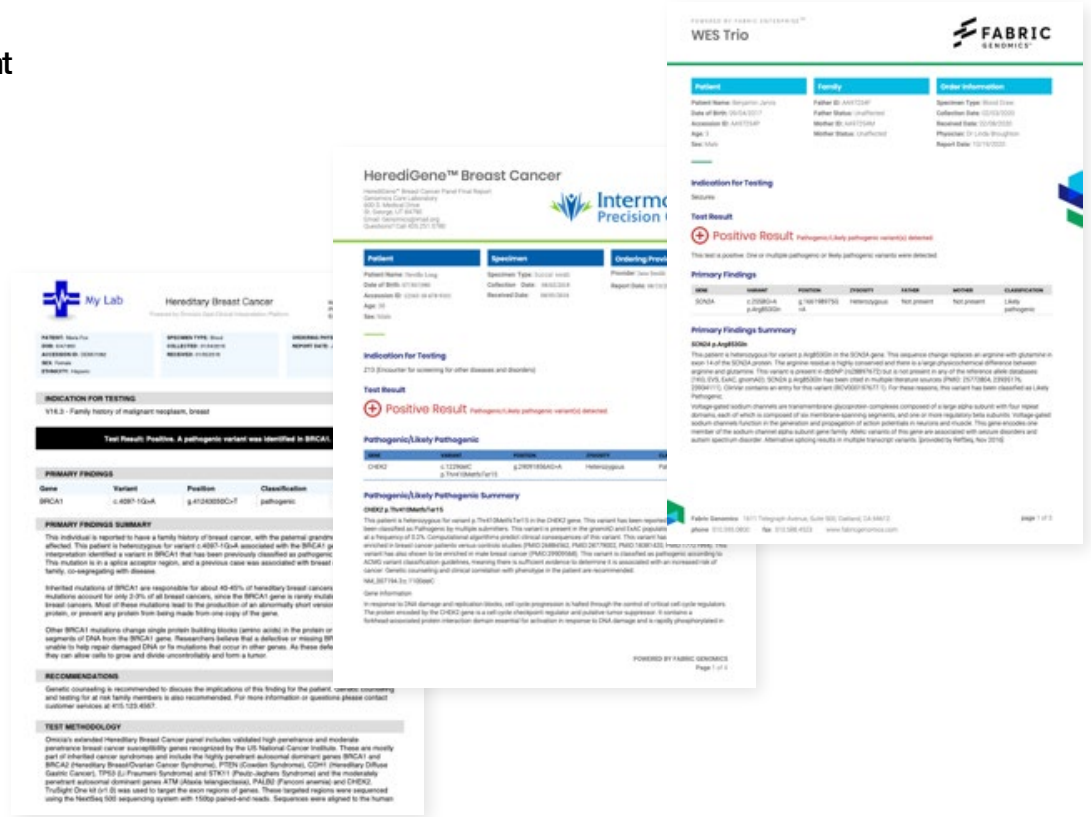
Fabric can generate comprehensive patient reports across multiple assays

Personalize reports with patient guides

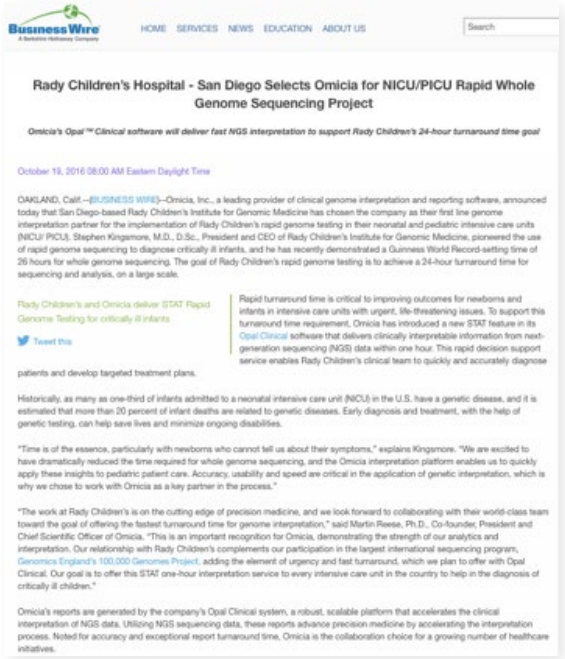
Display detailed clinical curation results

Generate comprehensive reports

Flexible delivery options



Case study: Rady Children's Hospital STAT pediatric clinical genome



Business Wire

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Rady Children's Hospital - San Diego Selects Omicia for NICU/PICU Rapid Whole Genome Sequencing Project

Omicia's Opal™ Clinical software will deliver fast NGS interpretation to support Rady Children's 24-hour turnaround time goal

October 19, 2016 08:00 AM Eastern Daylight Time

OAKLAND, Calif.--(BUSINESS WIRE)--Omicia, Inc., a leading provider of clinical genome interpretation and reporting software, announced today that San Diego-based Rady Children's Institute for Genomic Medicine has chosen the company as their first line genome interpretation partner for the implementation of Rady Children's rapid genome testing in their neonatal and pediatric intensive care units (NICU/ PICU). Stephen Kingsmore, M.D., D.Sc., President and CEO of Rady Children's Institute for Genomic Medicine, pioneered the use of rapid genome sequencing to diagnose critically ill infants, and he has recently demonstrated a Guinness World Record-setting time of 26 hours for whole genome sequencing. The goal of Rady Children's rapid genome testing is to achieve a 24-hour turnaround time for sequencing and analysis, on a large scale.

Rady Children's and Omicia deliver STAT Rapid Genome Testing for critically ill infants

Tweet this

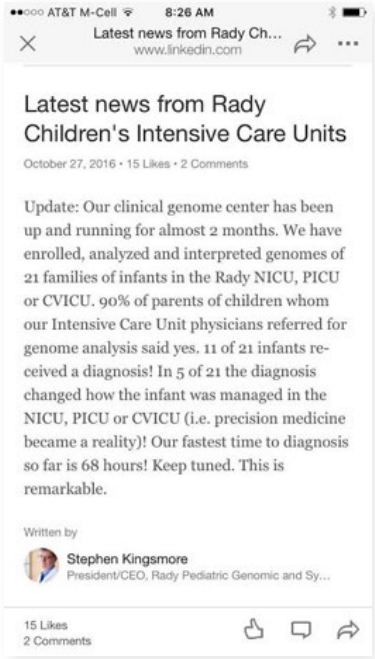
Rapid turnaround time is critical to improving outcomes for newborns and infants in intensive care units with urgent, life-threatening issues. To support this turnaround time requirement, Omicia has introduced a new STAT feature in its Opal Clinical software that delivers clinically interpretable information from next-generation sequencing (NGS) data within one hour. This rapid decision support service enables Rady Children's clinical team to quickly and accurately diagnose patients and develop targeted treatment plans.

Historically, as many as one-third of infants admitted to a neonatal intensive care unit (NICU) in the U.S. have a genetic disease, and it is estimated that more than 20 percent of infant deaths are related to genetic diseases. Early diagnosis and treatment, with the help of genetic testing, can help save lives and minimize ongoing disabilities.

"Time is of the essence, particularly with newborns who cannot tell us about their symptoms," explains Kingsmore. "We are excited to have dramatically reduced the time required for whole genome sequencing, and the Omicia 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 Omicia as a key partner in the process."

"The work at Rady Children's is on the cutting edge of precision medicine, and we look forward to collaborating with their world-class team toward the goal of offering the fastest turnaround time for genome interpretation," said Martin Reese, Ph.D., Co-founder, President and Chief Scientific Officer of Omicia. "This is an important recognition for Omicia, demonstrating the strength of our analytics and interpretation. Our relationship with Rady Children's complements our participation in the largest international sequencing program, Genomics England's 100,000 Genomes Project, adding the element of urgency and fast turnaround, which we plan to offer with Opal Clinical. Our goal is to offer this STAT one-hour interpretation service to every intensive care unit in the country to help in the diagnosis of critically ill children."

Omicia's reports are generated by the company's Opal Clinical system, a robust, scalable platform that accelerates the clinical interpretation of NGS data. Utilizing NGS sequencing data, these reports advance precision medicine by accelerating the interpretation process. Noted for accuracy and exceptional report turnaround time, Omicia is the collaboration choice for a growing number of healthcare initiatives.



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Latest news from Rady Ch...
www.linkedin.com

Latest news from Rady Children's Intensive Care Units

October 27, 2016 • 15 Likes • 2 Comments

Update: Our clinical genome center has been up and running for almost 2 months. We have enrolled, analyzed and interpreted genomes of 21 families of infants in the Rady NICU, PICU or CVICU. 90% of parents of children whom our Intensive Care Unit physicians referred for genome analysis said yes. 11 of 21 infants received a diagnosis! In 5 of 21 the diagnosis changed how the infant was managed in the NICU, PICU or CVICU (i.e. precision medicine became a reality)! Our fastest time to diagnosis so far is 68 hours! Keep tuned. This is remarkable.

Written by

Stephen Kingsmore
President/CEO, Rady Pediatric Genomic and Sy...

15 Likes
2 Comments

THE JOURNAL OF PRECISION MEDICINE

NEWS

Dr. Stephen Kingsmore – A Vision for Transforming Medicine with Rapid Genome Sequencing (Part 1)

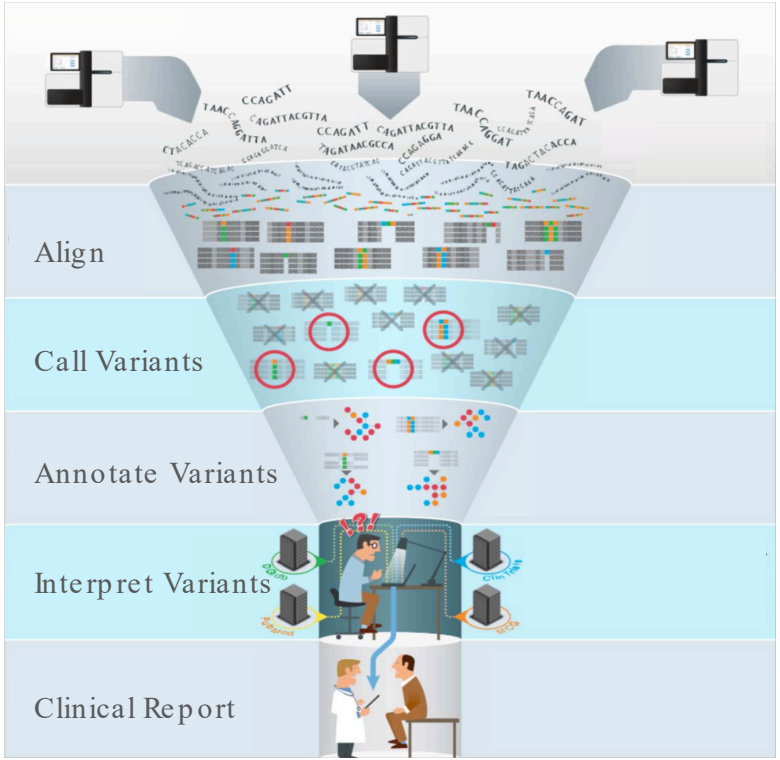
Dr. Stephen Kingsmore – A Vision for Transforming Medicine with Rapid Genome Sequencing (Part 1)

PRECISION MEDICINE LEADERS SUMMIT

SAVE the DATE

40–52%
Diagnosis rate

Ultra Rapid genome interpretation workflow



Adapted from: Good, B. M., Ainscough, B. J., McMichael, J. F., Su, A. I. & Griffith, O. L. Organizing knowledge to enable personalization of medicine in cancer. Genome Biology 15, 438 (2014).

Turn Around Time

	Industry Std.	Fabric/Rady rWGS	
Align	26-72 h	16-24 h	
Call Variants	2-8 h	0.5 h	
Annotate Variants	>1 h	0.25 h	
Interpret Variants	>2 h	<1 h	
Clinical Report	10-48 h	<1 h	Days → Minutes
	3-6 h	<2 h	
Total:	2-6+ days	21-33 h	

Rady Children's Institute Genomic Medicine®

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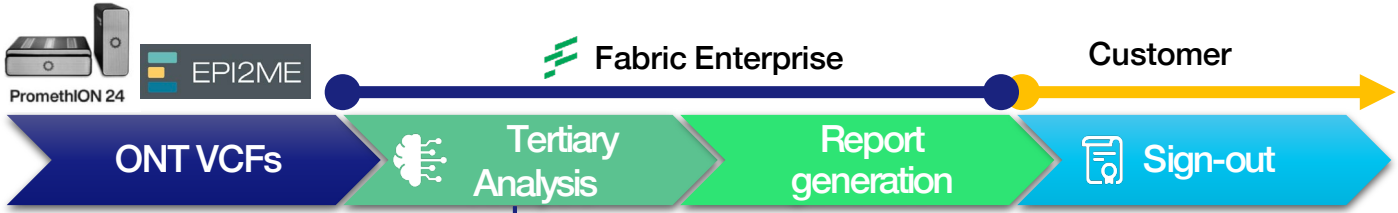
Fabric Genomics and ONT: A new decentralized AI-driven solution for rapid NICU testing



Fabric Enterprise Software performs

Annotation	Variant Prioritization	Variant Classification	Report Generation
• Annotation of all types of variants (SNVs, CNVs, SVs) with Fabric Enterprise	*Fabric GEM* • AI-driven tool speeds up interpretation by reducing gene review to an average of 2 genes per case • Rare Disease Diagnostic WGS/WES	*Fabric ACE* • Automatic variant classification following ACMG guidelines • Hereditary panels including virtual panels from WES/WGS	• White-labeled reporting and customizable lab workflows • Detailed clinical curation • Options for automated delivery

<2 hrs

HIPAA COMPLIANT

ISO 27001

A complete and accessible long-read solution for rWGS

ONT PromethION **EPI2ME** **Fabric Enterprise software** HIPAA and ISO 27001 certified

Sequencing

- Sample prep
- Sequencing

Variant Calling

- Variant alignment
- Variant calling

Variant Prioritization and Classification

- Fabric GEM AI
- Fabric ACE: automated variant classifications

Custom Reports

- Custom Reports per Customer Specifications
- Integration with customer systems

PromethION Project Packs are structured as a reagent purchase with an instrument included.
This enables users wishing to get started with PromethION to do so with minimal commitment.

Long-Read rWGS results from ACMG 2024

Clinical cohort: 9 trios from the UW UDP (3 “positive controls” + 6 undiagnosed after NGS WES/WGS)

Results:

All positive controls detected

Variants types tested:
2 point mutations
1 large deletion

Case	Result	Variants	Associated condition
11	**Positive**	15q11-q13 del	Prader-Willi syndrome
10	Inconclusive	NDUFAF6 p.Asn162IlefsTer27 DARS2 c.492+2T>C	Mitochondrial complex I deficiency Leukoencephalopathy
9	**Positive**	PMM2 p.Phe119Leu PMM2 p.Phe157Ser	Congenital disorder of glycosylation
8	**Positive**	EMC1 p.Pro582Arg	Cerebellar atrophy, visual impairment, and psychomotor delay
7	Inconclusive	BLM p.Leu394GlyfsTer23	Bloom syndrome
6	Negative	Negative	
5	Negative	Negative	
4	Negative	Negative	
3	Inconclusive	ADGRV1 p.Asn319LysfsTer6 ARSA p.Pro428Leu	Usher syndrome Metachromatic leukodystrophy

Data from: S. Meyn, U. Wisconsin, ACMG Presentation 2024

Prader-Willi case study from ACMG 2024

Fabric Trio #11: Prader-Willi Syndrome

9 year old boy with neonatal hypotonia, failure to thrive, developmental delays, sleep apnea, cryptorchidism, submucous cleft palate, high myopia, prognathia, scoliosis

Fabric GEM analysis: 8.5 Mb pathogenic deletion encompassing the 15q11.2-15q13.1 critical region for Prader Willi syndrome

Report generated

POWERED BY FABRIC ENTERPRISE™

FABRIC GENOMICS®

Patient	Specimen	Ordering Physician

Patient Name:

Accession ID:
UDP_rapid_03042024_11-1

Sex: Male

Report Date: Not yet approved

Test Result

Positive Result Pathogenic/Likely pathogenic variant(s) detected.

Result Summary:

This individual is heterozygous for a deletion encompassing 15q11.2-q13.1. Disease-causing variants in this gene are associated with Prader-Willi syndrome, which is consistent with this individual's reported clinical features.

Primary Findings

GENES	VARIANT	SIZE	ZYGOSITY/CNV COPY NUMBER	CLASSIFICATION
26 Genes	chr15:23500001-32000000,del	8.5 MB	Heterozygous	Pathogenic

8.5 MB DEL chr15:23500001-32000000

Variant Description:
A Pathogenic 8.5 **MB DEL** chr15:23500001-32000000 was detected.
This single copy loss of a 8.5 Mb genomic fragment spans cytoband 15q11.2-q13.1 (chr5:23500001-32000000) and encompasses many genes including the **UBE3A, SNRPN, MAGEL2, MKRN3,** and **SNURF** genes. This variant is not present in gnomAD or DGV databases. This variant has 66% overlap with a 5.6 Mb copy number deletion variant (chr15:22876632-28557186) which is classified as pathogenic and has been associated with 15q11.2-q13.1 deletion syndrome in ClinGen database (Variant ID: nssv1184533). Several similar-sized copy number deletion variants overlapping with 15q11.2-q13.1 have been reported as pathogenic or likely pathogenic in individuals with the clinical features of Prader-Willi syndrome/Angelman syndrome in **DECIPHER** (Patient ID: 290887, 331346, 288738, 368668) and also in ClinVar (Variation IDs: 57194, 1180527, 441725, 441569, 151256, 58599, 151262, 153993). According to the ClinGen dosage sensitivity calculation, there is sufficient evidence of dosage pathogenicity associated with haploinsufficiency of this region (ClinGen: ISCA-37404). Copy number deletion variants encompassing 15q11-q13 region exhibit parent-of-origin effect. Paternal deletion encompassing this region causes Prader-Willi syndrome, while maternal deletion variants encompassing this region causes Angelman syndrome. These variants are usually de-novo; however, rare familial transmission has also been reported (OMIM: 14993551). These data were assessed using the ACMG/ClinGen copy number variant interpretation guidelines. In summary, there is sufficient evidence to classify this variant as Pathogenic for the autosomal dominant 15q11.2-q13.1 deletion syndrome.

Fabric Genomics
436 14th St, Suite 1300, Oakland, CA 94612
(510) 595-0800 || fabricgenomics.com

Fabric and Broad Clinical Labs partner to deliver $1,000 sample to report CLIA whole genome sequencing service

CLIA sequencing at Broad Clinical Labs

Interpretation by Fabric Clinical

Review and report sign-out by Broad Clinical Labs

Dr. Heidi Rehm, Ph.D.

Institute Member, Co-director of the Program in Medical and Population Genetics

Shana White, MS, CGC

Sr. Director, Fabric Genomics

FABRIC GENOMICS + BROAD CLINICAL LABS

Elevate your large-scale programs in rare disease and population screening with trusted partners in sequencing and interpretation.

FABRIC GENOMICS

Reimbursement for rapid WGS is already established in the UK

Pediatricians in the National Health Service (NHS) in England and Wales can order a rapid diagnostic genome for any child that they suspect may benefit.

News

World-first national genetic testing service to deliver rapid life-saving checks for babies and kids

12 October 2022

Children and young people | Genomics

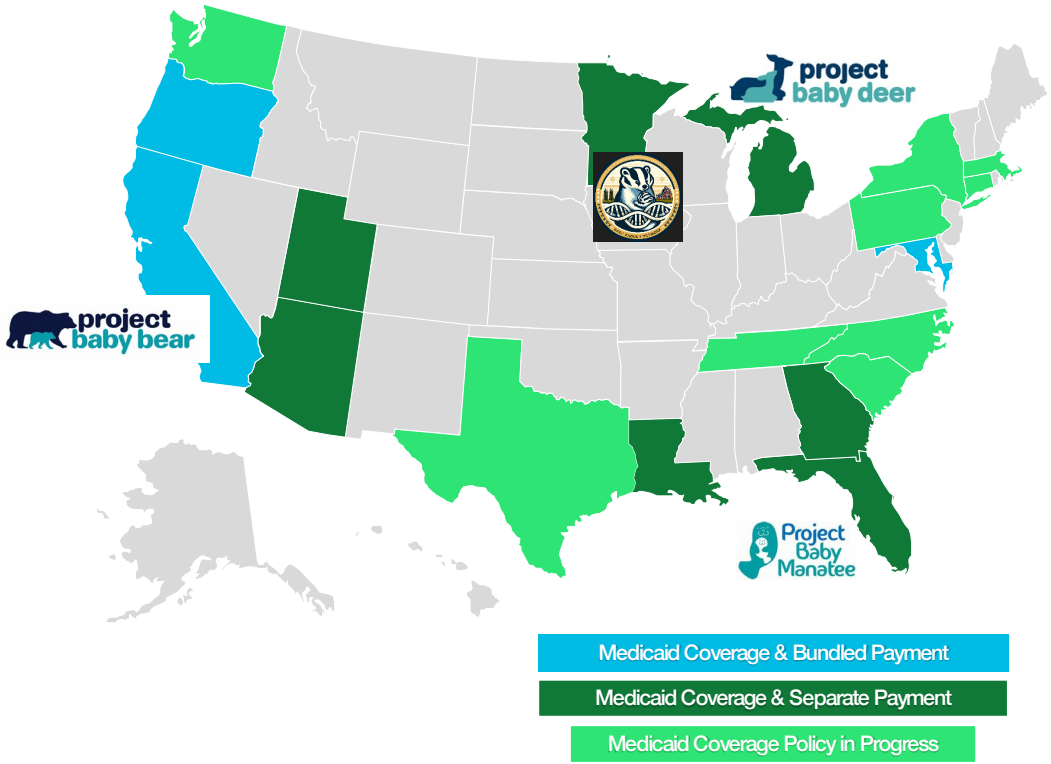
The NHS will be able to diagnose and potentially save the lives of thousands of severely ill children and babies — within days rather than weeks — with a world-first national genetic testing service launching today.

Australia studying a national approach to rapid WGS

Rapid genome sequencing helps save hundreds of critically ill babies

More than 400 children have taken part in a rapid whole-genome sequencing trial at every children's hospital in Australia. With results in less than three days, many of the participants have quickly been diagnosed with rare genetic conditions and received appropriate treatment

Insurance Landscape for rWGS in the USA



Current as of January 2024

Coloring in the map

Improving access to rWGS through medical and payment policy

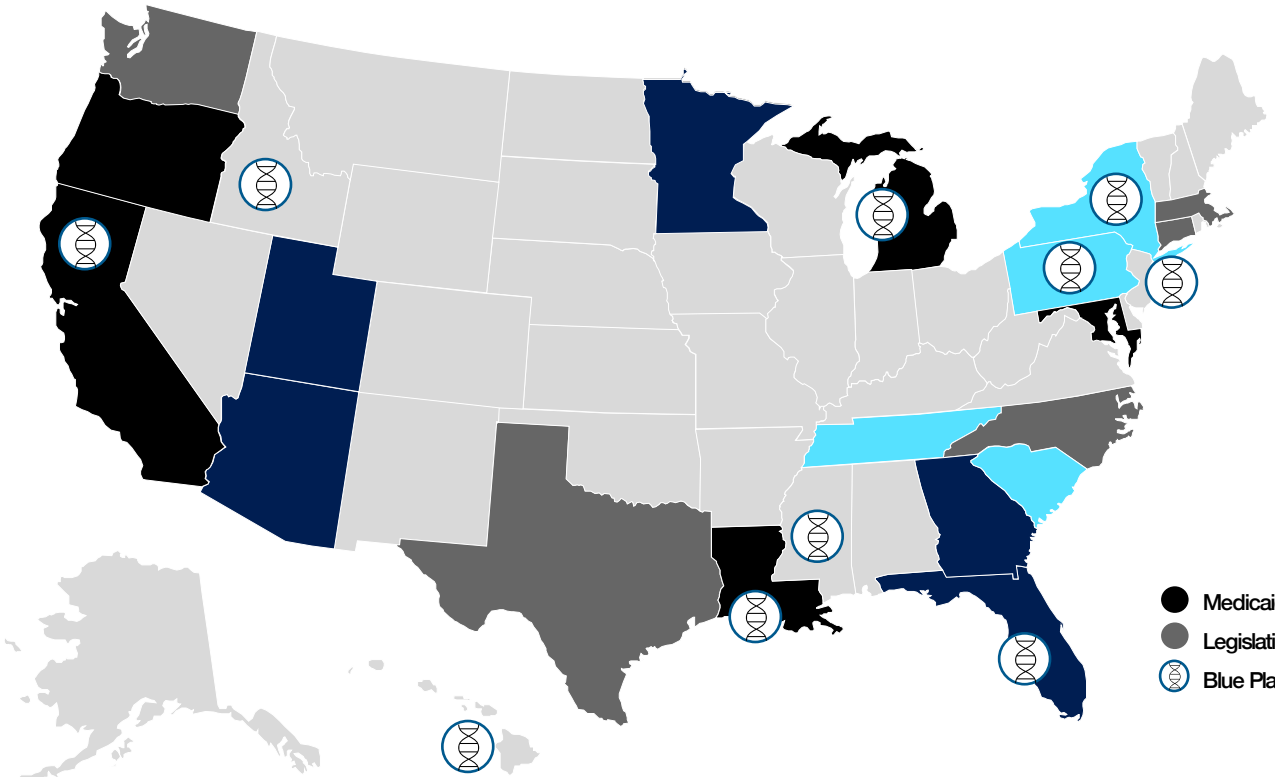
MEDICAID

- 10 State Medicaid programs now cover rWGS
  - Paid within DRG: CA, MD, OR
  - Separately Payable: AZ (3-year pilot), FL, GA, LA, MI, MN, UT
- Additional state-based advocacy initiatives underway

COMMERCIAL

- Blue Cross Blue Shield: 11 plans in 9 states provide rWGS coverage
- 1 State (Louisiana) mandates all health plans cover rWGS
- Cigna: Coverage of Whole Exome and Whole Genome Sequencing – Patient must meet clinical criteria. (Effective: Jan 15, 2023)
- United HealthCare: Coverage of Whole Exome and Whole Genome – currently only applies to outpatient or post-discharge from hospital. (Effective: April 1, 2023)
- Evicore: updated clinical guidance to declare rWGS medically necessary for certain clinical indications.

Insurance Landscape for rWGS



Separately Payable & Effective Medicaid

Arizona, Florida, Georgia (expected) Michigan, Minnesota, Louisiana, Utah (expected)

States with Favorable Blues:

- CA, ID, HI, MI, MS, LA, FL, NJ, NY, FEP (national)

National Carriers with Outpatient WGS Coverage

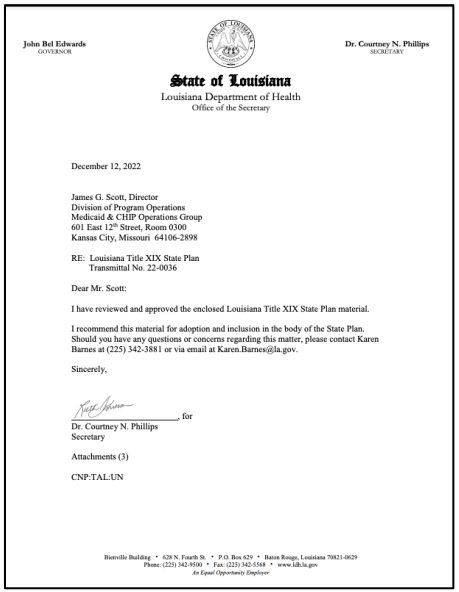
- United Healthcare Group
- Cigna

Medicaid Policies – Rapid Whole Genome Sequencing

State	Effective Date	Separate Payment	High-Level Clinical Criteria	Detailed Clinical Criteria	Authorization
Arizona	October 31, 2023	Yes	≤ 1 year of age, intensive care unit or high acuity pediatric unit	AHCCCS Reimbursement for Rapid Whole Genome Sequencing (rWGS)	Required. Provider requests expedited review or post-delivery of care retroactive authorization (akin to emergency services)
California	January 1, 2022	No	≤ 1 year of age, intensive care	No additional criteria	None
Florida	January 1, 2024	Yes	≤ 20 years of age, intensive care unit or high acuity pediatric unit	Florida Medicaid Health Care Alert | December 20, 2023 Medicaid Reimbursement for Rapid Whole Genome Sequencing	*Not yet specified*
Georgia	January 1, 2024	*TBD*	*Not yet specified*	*Not yet specified*	*TBD - Working with GA Medicaid*
Louisiana	August 1, 2022	Yes	≤ 1 year of age, intensive care unit or pediatric unit	MCO Manual | Rapid Whole Genome Sequencing of Critically Ill Infants	Authorization required to receive reimbursement
Maryland	January 1, 2022	No	≤ 1 year of age, intensive care or recently discharged from NICU	MD Department of Health Whole Genome Sequencing Clinical Criteria	Prior Authorization - Unclear if it can be submitted retroactively
Michigan	September 1, 2021	Yes	≤ 1 year of age, intensive care	MSA 21-33 Coverage of Rapid Whole Genome Sequencing (rWGS) Testing	Authorization may be submitted retroactively
Minnesota	April 1, 2022	Yes	Infant or child, intensive care unit	MN DHS Laboratory and Pathology Services	None for 0094U
Oregon	January 1, 2022	No	≤ 1 year of age, intensive care	Oregon Prioritized List of Health Services	None
Utah	November 1, 2023	Yes	≤ 1 year of age, intensive care unit or other intensive care unit	Section 8-12.10.4 Next Generation Sequencing	Authorization may be submitted retroactively

Reimbursement for rWGS in Louisiana

Covered by Medicaid[1]



John Bel Edwards
GOVERNOR

Dr. Courtney N. Phillips
SECRETARY

State of Louisiana
Louisiana Department of Health
Office of the Secretary

December 12, 2022

James G. Scott, Director
Division of Program Operations
Medicaid & CHIP Operations Group
601 East 12th Street, Room 0300
Kansas City, Missouri 64106-2898

RE: Louisiana Title XIX State Plan
Transmittal No. 22-0036

Dear Mr. Scott:

I have reviewed and approved the enclosed Louisiana Title XIX State Plan material.

I recommend this material for adoption and inclusion in the body of the State Plan. Should you have any questions or concerns regarding this matter, please contact Karen Barnes at (225) 342-3881 or via email at Karen.Barnes@la.gov.

Sincerely,

_____, for
Dr. Courtney N. Phillips
Secretary

Attachments (3)

CNP:TAL:UN

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Whole Exome and Whole Genome Sequencing for Diagnosis of Genetic Disorders

Policy # 00389
Original Effective Date: 11/20/2013
Current Effective Date: 08/01/2023

Applies to all products administered or underwritten by Blue Cross and Blue Shield of Louisiana and its subsidiary, HMO Louisiana, Inc. (collectively referred to as the "Company"), unless otherwise provided in the applicable contract. Medical technology is constantly evolving, and we reserve the right to review and update Medical Policy periodically.

Genetic Testing of Critically Ill Infants

Effective for dates of service on or after January 1, 2023, hospitals shall receive reimbursement for rapid whole genome sequencing testing, in addition to the hospital per diem payment for the inpatient stay.

[1]https://ldh.la.gov/assets/medicaid/StatePlan/Amend2022/22-0036/22-0036CMSSubmittal.pdf

Summary

NICU

~400,000 US NICU admissions per annum, costing >$17B per year

~40% infant death in ICU are associated with single locus variants

rWGS

Both in-house and send out testing equated with increased change in management and cost savings per child

3 day rWGS Can save $14,000 per child and change management in 56% of cases

Reimbursement

Private Payors covering rWGS are increasing

7 states have Medicaid coverage policy and reimbursement rate for inpatient RGS separate from the Diagnosis Related Group (DRG) payment

Long-reads

Oxford Nanopore (ONT) can help you get started with an instrument for rWGS with minimal commitment

Fabric

Can help you with rapid Whole Genome Sequencing with Interpretation Software or Full-Service Interpretation Services

Fabric is the solution of choice for genomics leaders around the world

"We chose Fabric to develop and implement our clinical WGS offerings because it is the only solution that allows for scalability and is unparalleled in the market."

Dr. Heidi Rehm,

Co-director of the Program in Medical and Population Genetics, Broad Institute of Harvard & MIT

BROAD CLINICAL LABS

"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

Rady Children's Institute Genomic Medicine

eurofins · RANDOX · Intermountain Healthcare · Cleveland Clinic · Cincinnati Children's · e-lab · HEALTH University of Utah · Genomics england

Quest Diagnostics · Children's Hospital Colorado · Ann & Robert H. Lurie Children's Hospital of Chicago · Providence · labcorp · Roche · RAINBOW GENOMICS · VANDERBILT UNIVERSITY

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Transforming Healthcare through AI-Driven Clinical Genomic Insights