Accurate and Rapid Genome Interpretation – in clinical care

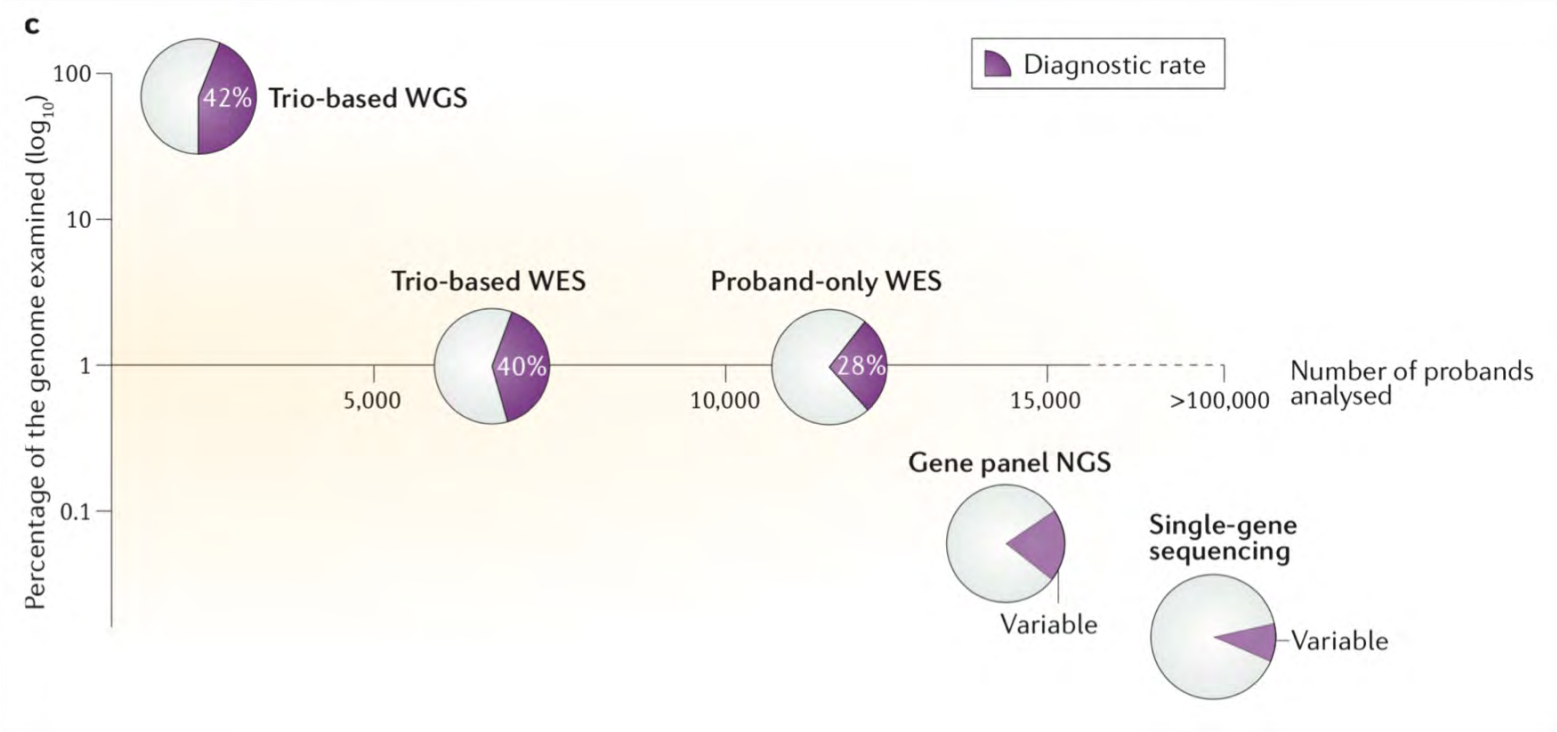
Martin Reese, Ph.D.
Founder and CEO

FABRIC GENOMICS™

Overview

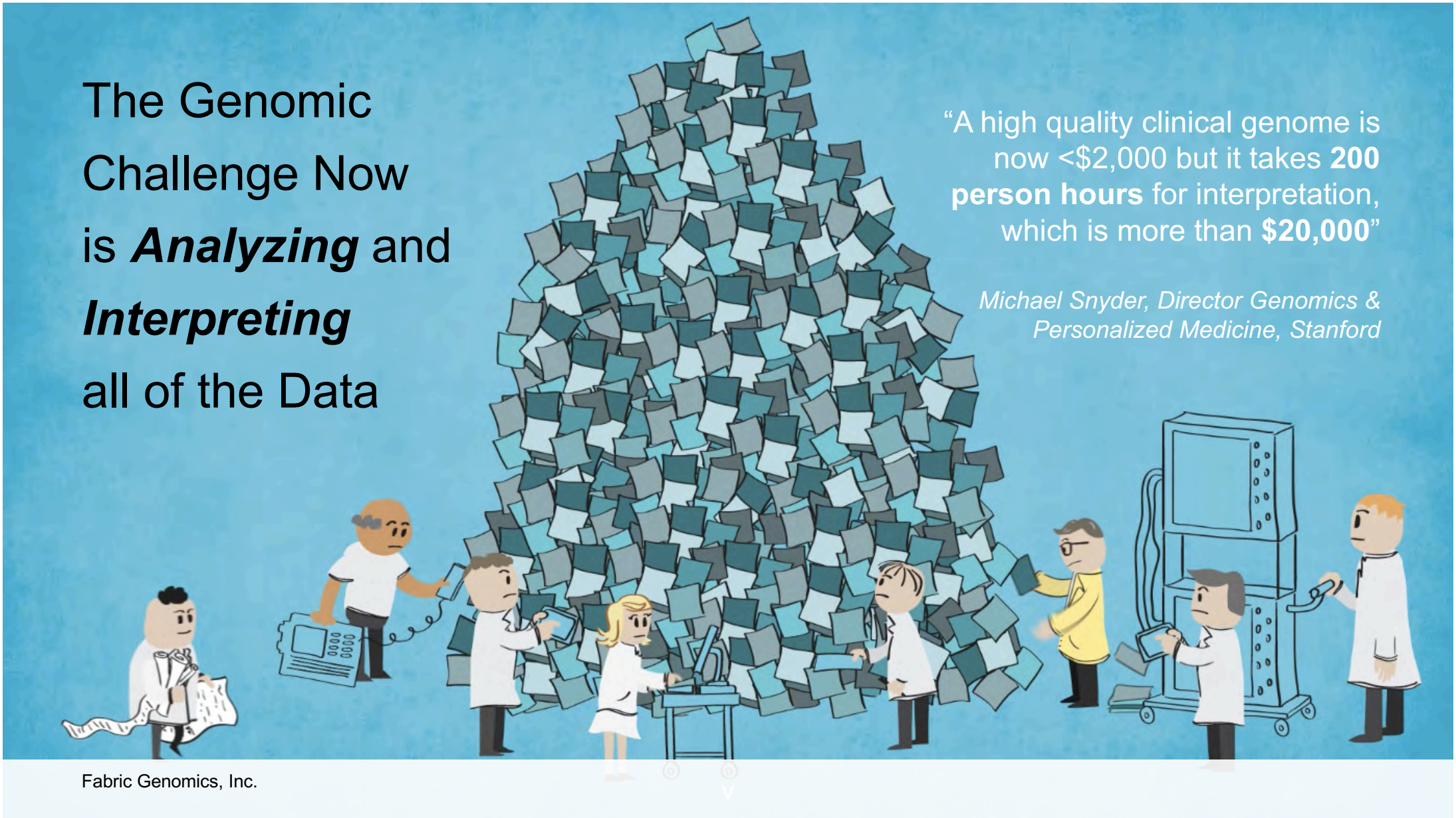
- What is genome variant interpretation?
- Optimized variant ranking VAAST/Phevor - ready to scale
  - For Clinical Diagnostics and Gene Discovery on a population scale
- Collaborative clinical variant sharing for improved diagnosis
- Two clinical genomics examples
  - Undiagnosed genetic disease patients – Genomics England 100,000 Genome Project
  - First line diagnosis for NICU/ICU babies –Rady's Children Hospital (Dr. Kingsmore)

Diagnostic rate of genetic diseases



Wright, C. F., FitzPatrick, D. R. & Firth, H. V. Paediatric genomics: diagnosing rare disease in children. *Nature Publishing Group* **10,** 1–16 (2018).

The Genomic Challenge Now is ***Analyzing*** and ***Interpreting*** all of the Data

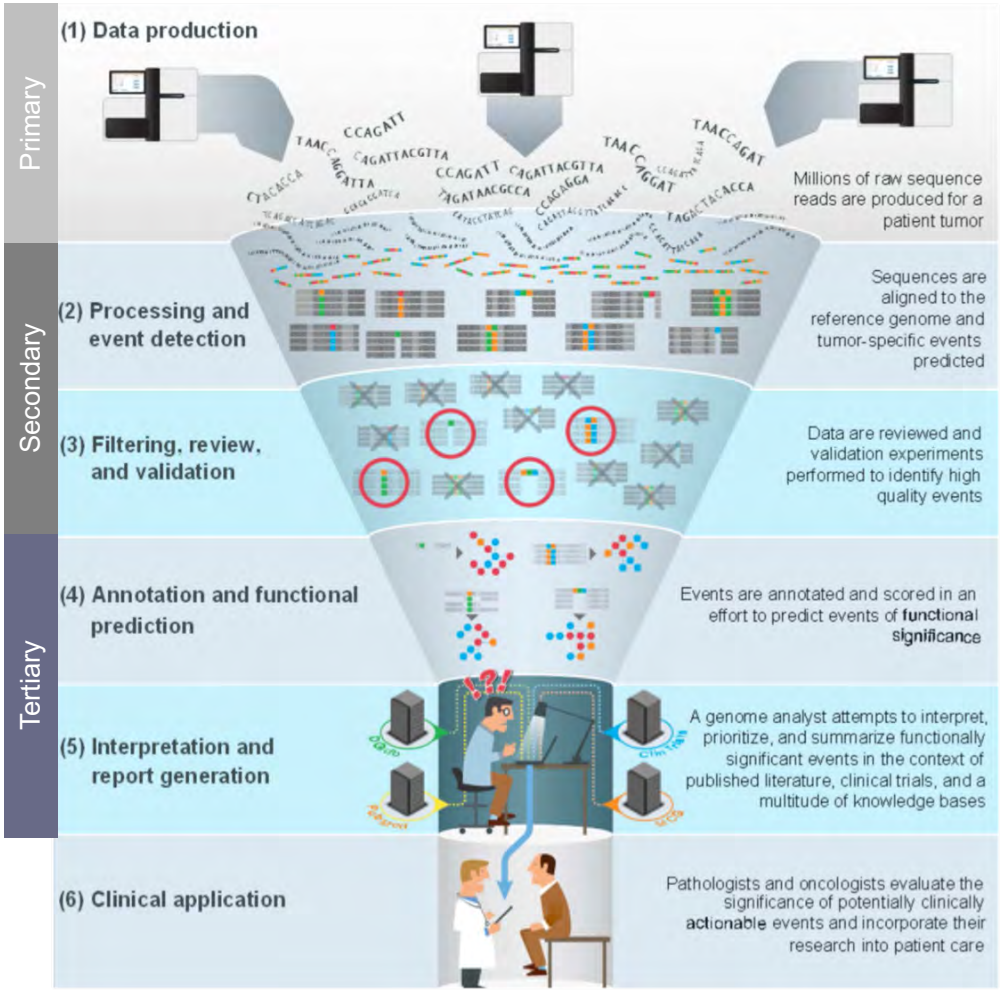


"A high quality clinical genome is now <$2,000 but it takes **200 person hours** for interpretation, which is more than **$20,000**"

Michael Snyder, Director Genomics & Personalized Medicine, Stanford

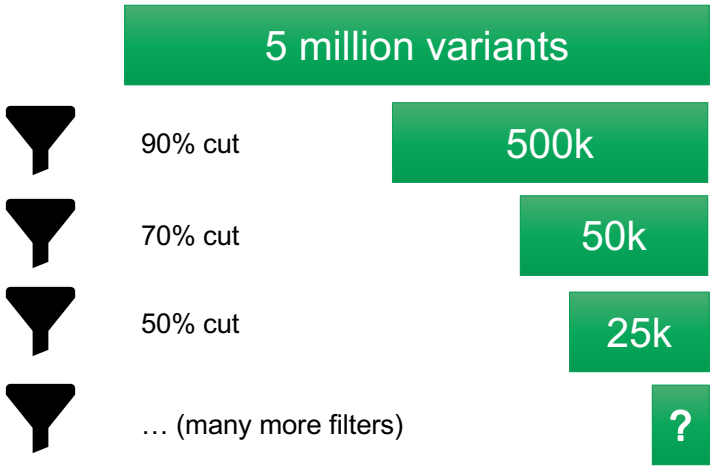
Variant Interpretation

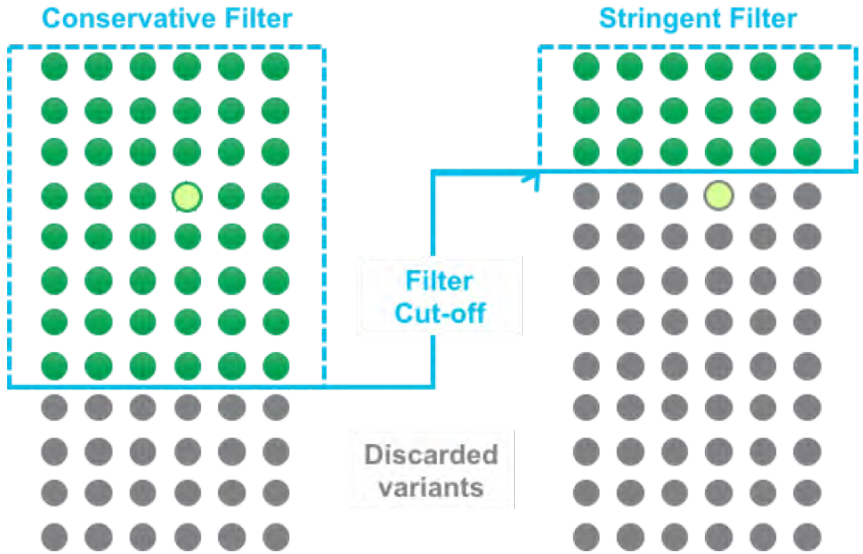
- How do we find the variants important for the disease or phenotype of the patient(s)?
- How do we find the important variants quickly, reliably, and reproducible?
- How do we find the important variants at scale?



WGS/WES uncovers a huge amount of information
Which findings actually matter?

Conventional Analysis - Filtering





100s of unranked variants to review

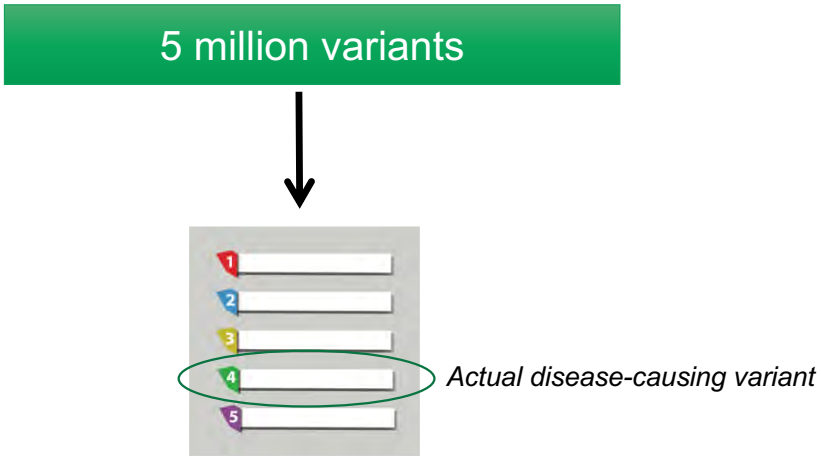
Limit Throughput

Drive Costs

Can easily spend days interpreting un-prioritized candidates for a single case

Alternative Variant Prioritization: Automatization without filtering caveats

Algorithm-Driven Prioritization



Result: Specific ranked list of variants to review
Diagnostic candidate consistently near top

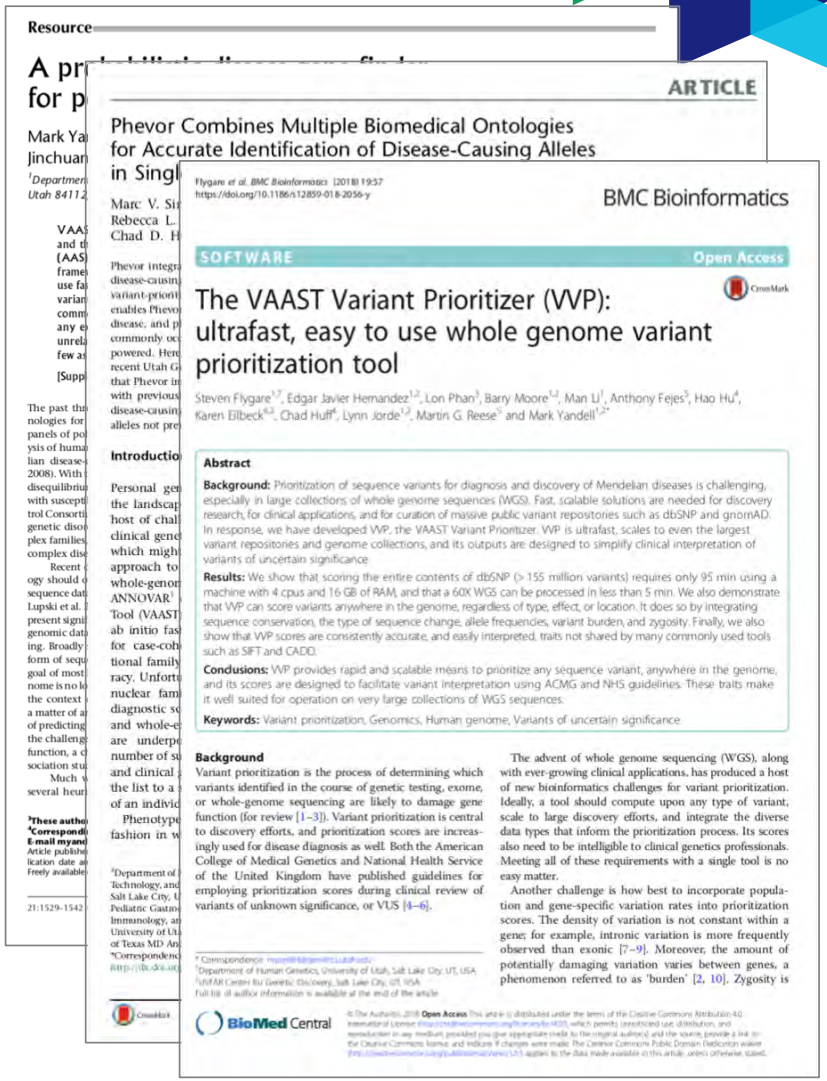
- Combine **phenotype**, **disease** and **genotype** information for **phenotype driven prioritization**
- harmonize information across hundreds of sources
- Algorithmic methods provide complementary data points

VAAST-Phevor Algorithms for Variant Prioritization

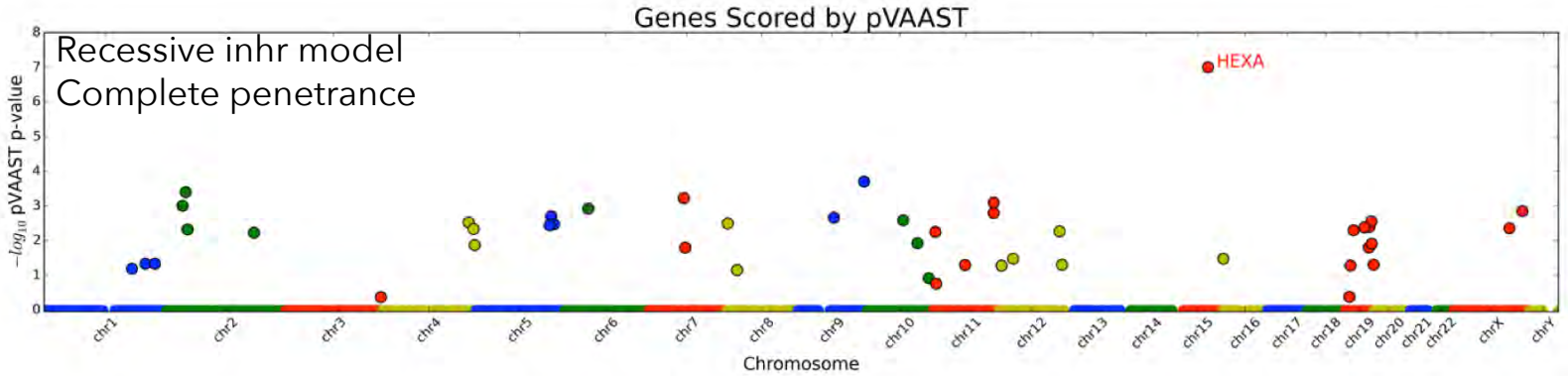
Peer-Reviewed and Clinically Validated

- **VAAST:** Evaluate and rank **every variant** based on **effect**, **conservation** and **frequency**
- **Phevor:** Re-prioritize variants based on patient's **phenotype**
- **Validated, Published** and **Clinically Proven** for **phenotype driven genome-wide** variant prioritization

VAAST-Phevor has been shown to consistently elevate the causative variant to the top

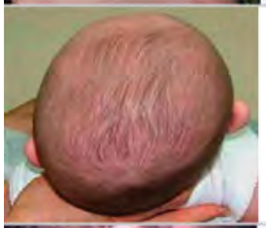
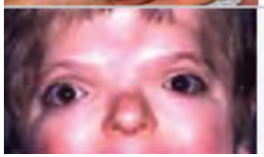


VAAST, Families and Disease



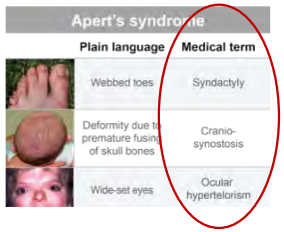
A family with a Tay-Sachs affected child

Patient phenotype (symptoms) are big clues

	Plain language	Medical term
	Webbed toes	Syndactyly
	Deformity due to premature fusing of skull bones	Cranio-synostosis
	Wide-set eyes	Ocular hypertelorism

Phevor Combines Phenotype and Genotype

Phenotype description



VAAST

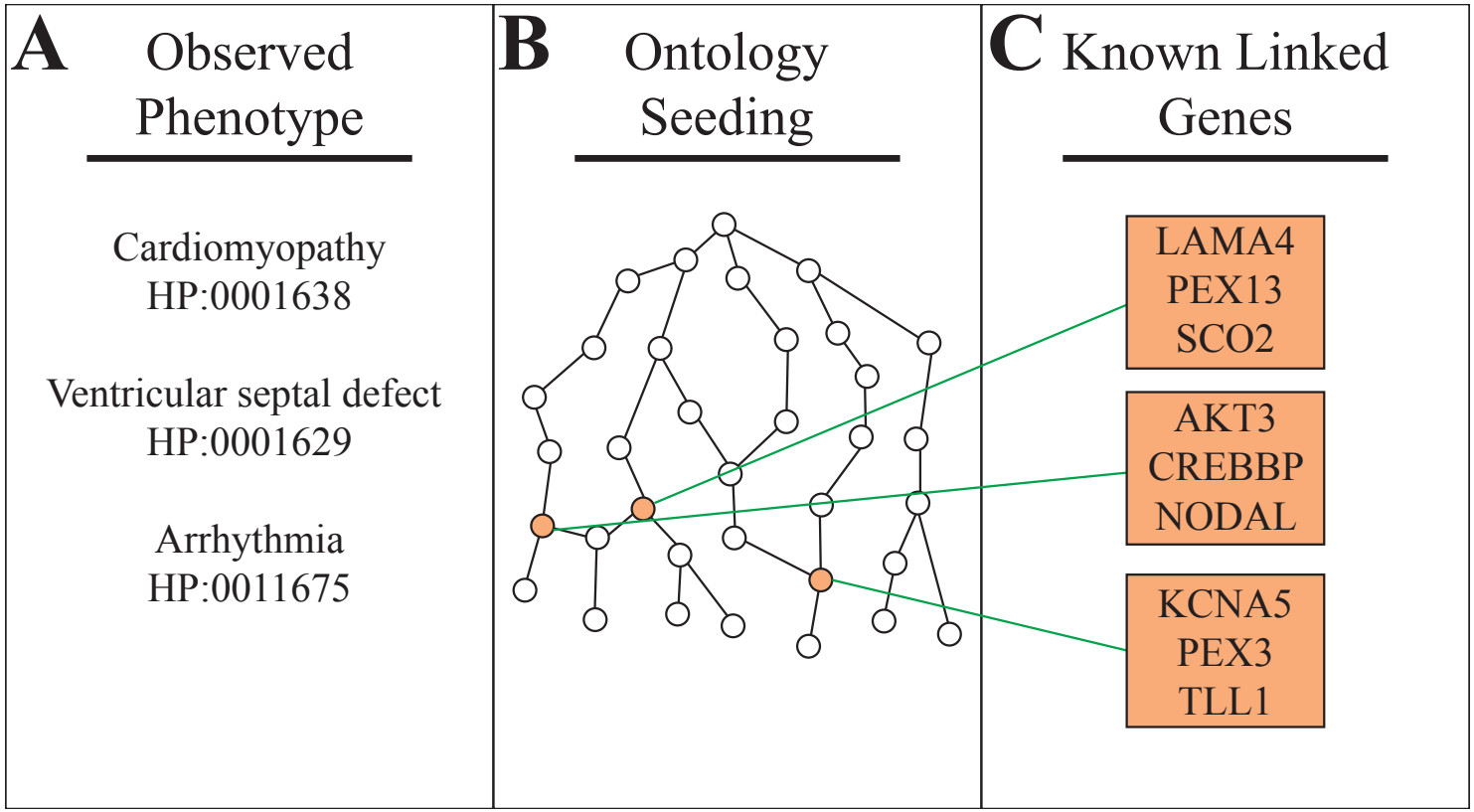
PHENOTYPE DRIVEN VARIANT ONTOLOGICAL RE-RANKING TOOL
PHEVOR

Improved power to identify causative variants

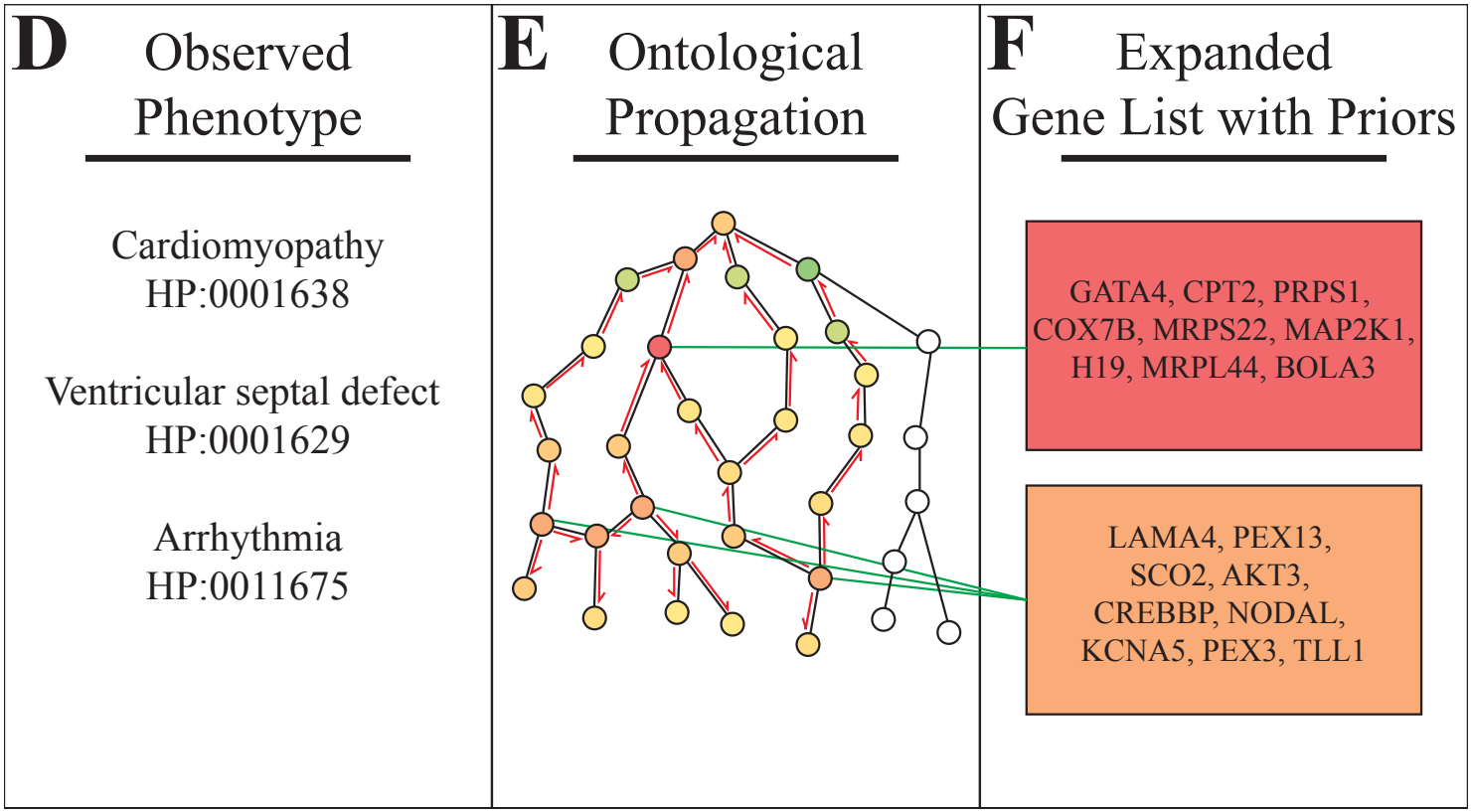
Phevor Combines Multiple Biomedical Ontologies for Accurate Identification of Disease-Causing Alleles in Single Individuals and Small Nuclear Families. Singleton M., Guthery SL., Voelkerding KV., *et al.*, Reese MG., Jorde LB., Huff CD., Yandell M. (2014) . Am J Hum Genet. **2014 Apr 3**; 94(4):599-610.

THE UNIVERSITY OF UTAH

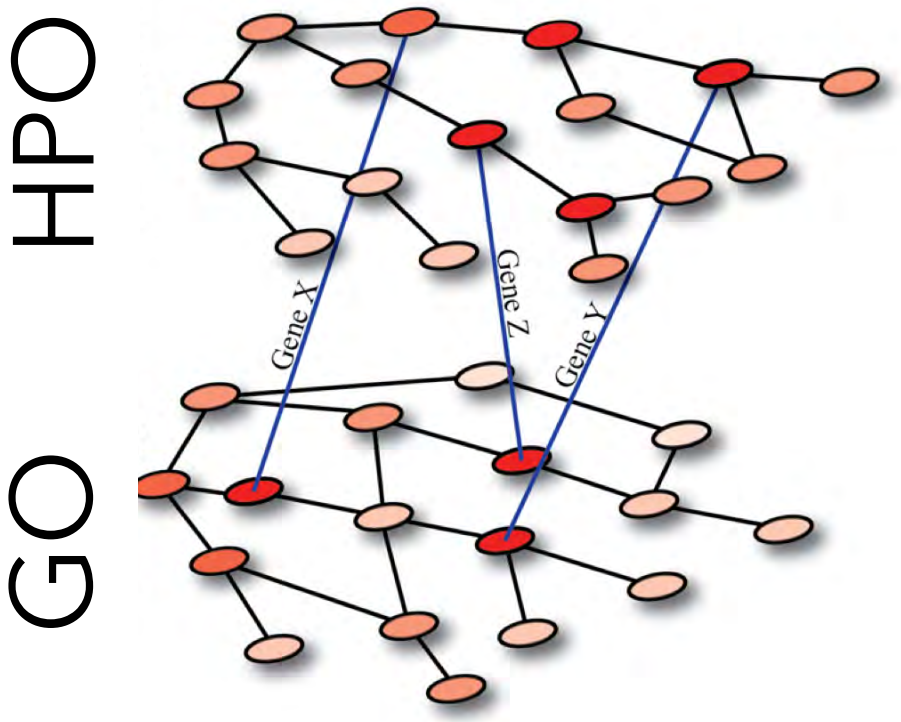
How Phevor Works (seeding)



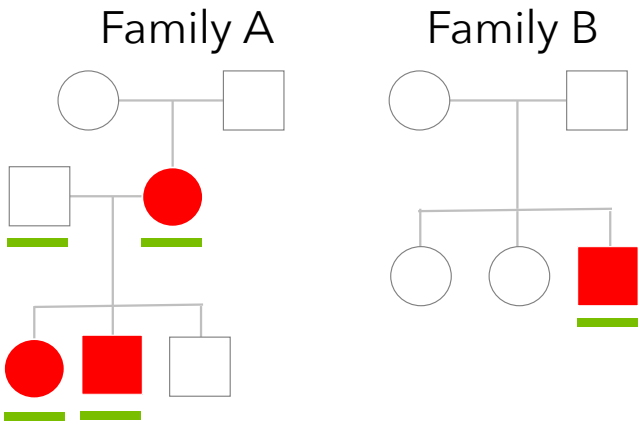
How Phevor Works (seeding)



How Phevor Works (combining ontologies)



Common Variable Immune disease (CVID)



Phenotype

Recurrent infections (HPO:0002719)

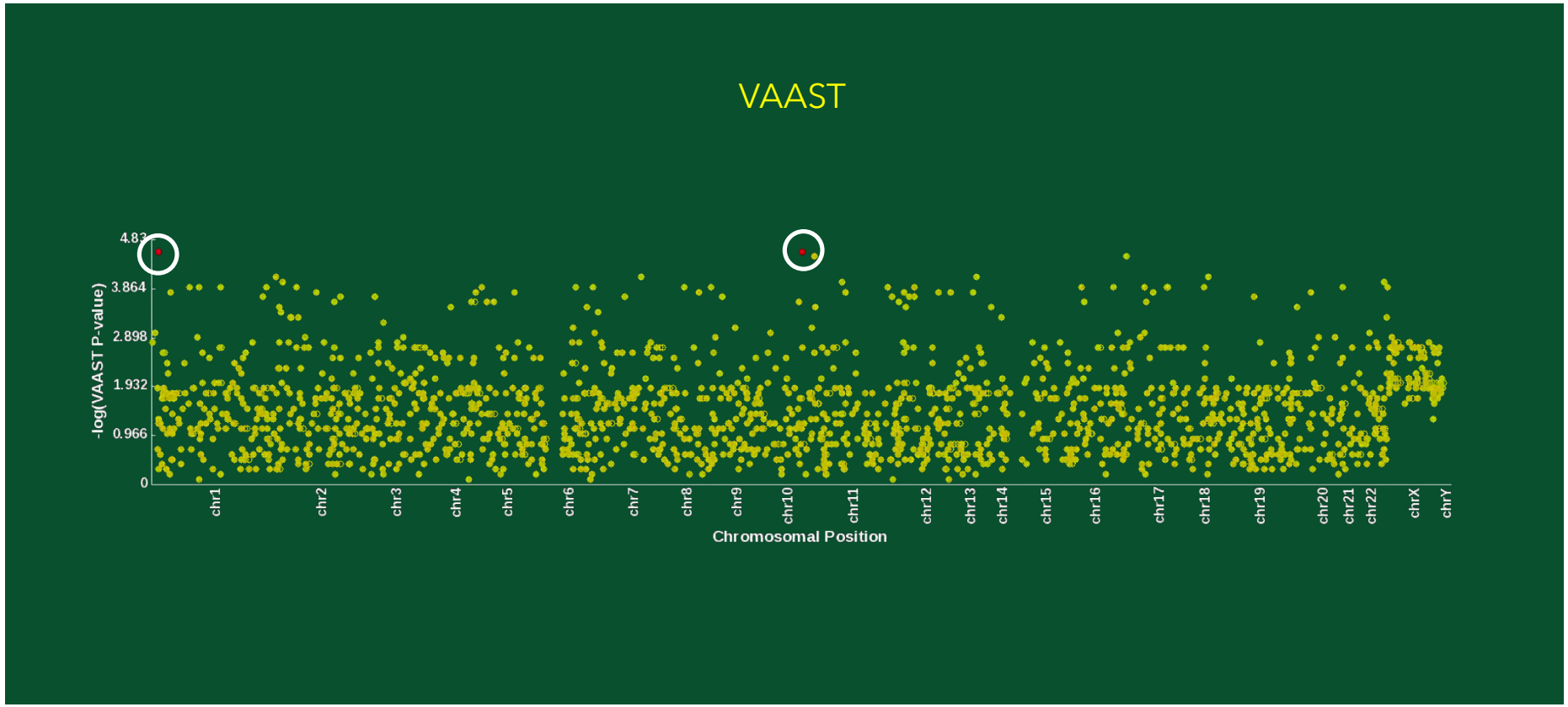
Abnormality of Humoral immunity (HPO:0005368)

affected

unaffected

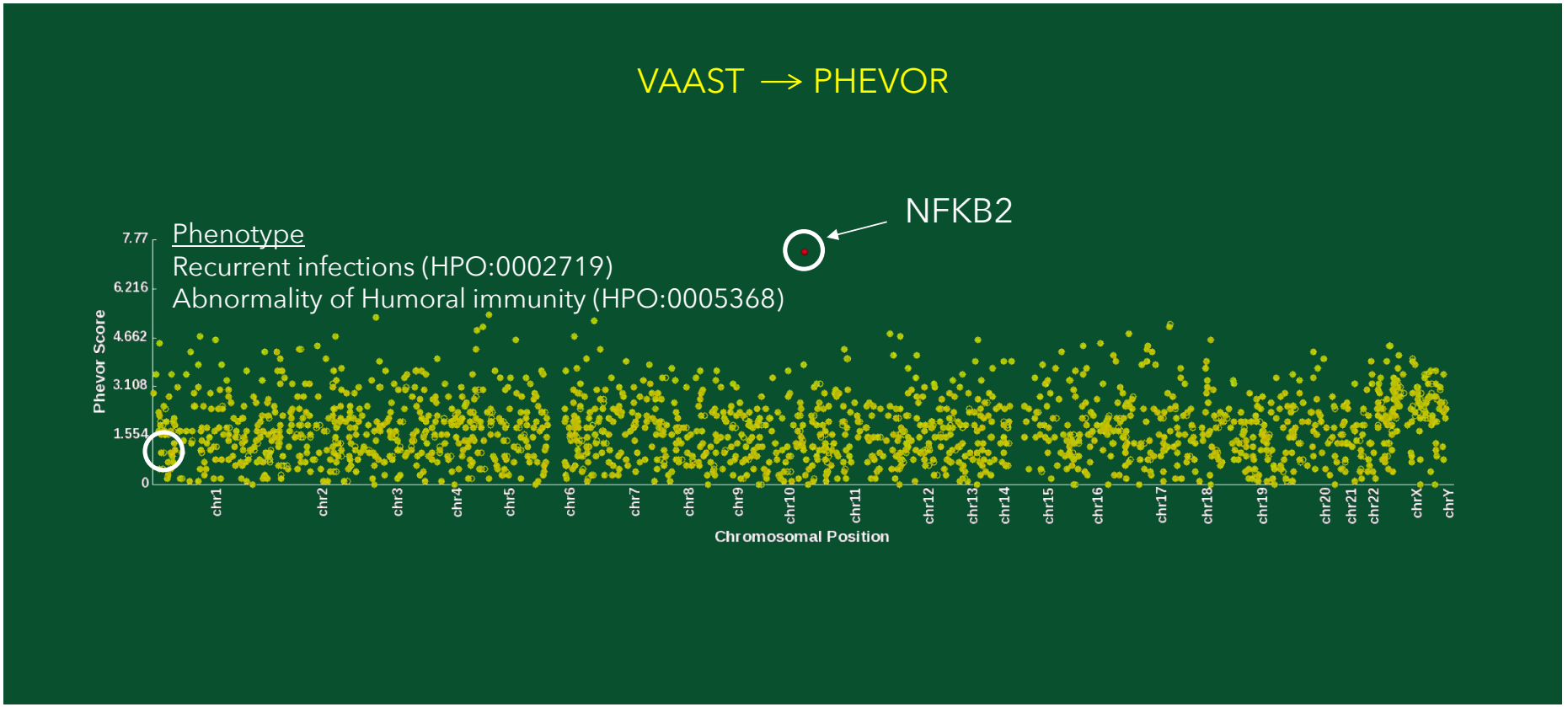
exome sequenced

A Family with Common Variable Immune disease (CVID)



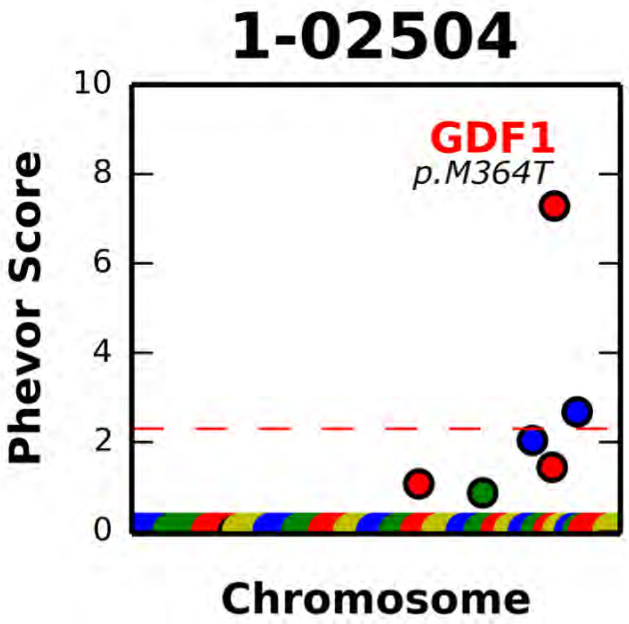
K. Chen MD, EM. Coonrod PhD, A. Kumanovics, K. Voelkerding MD, et al.

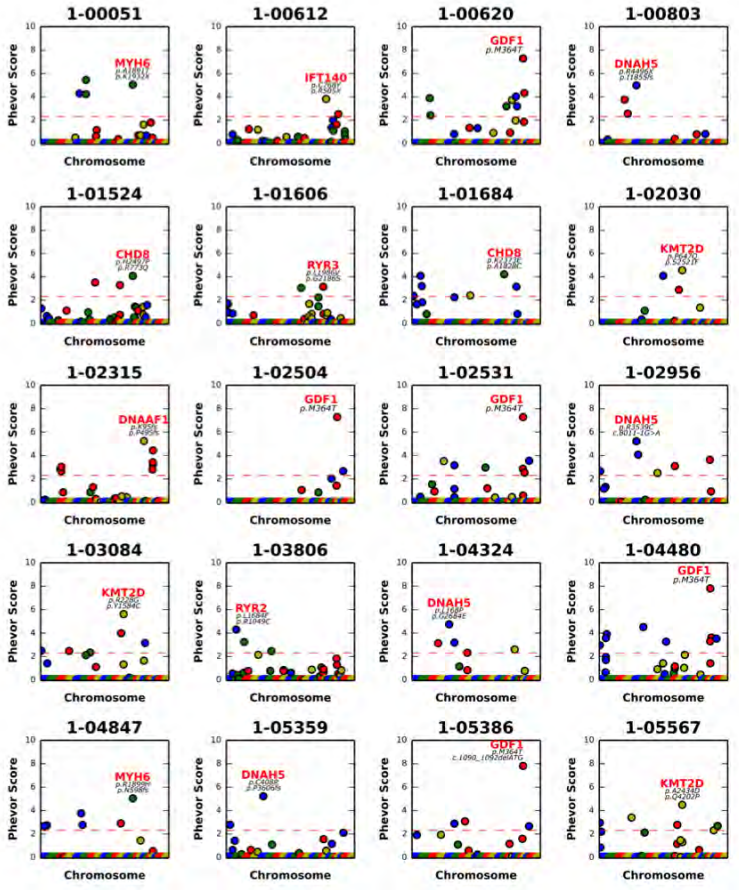
A Family with Common Variable Immune disease (CVID)



K. Chen MD, EM. Coonrod PhD, A. Kumanovics, K. Voelkerding MD, et al.

Selected *Recessive* Congenital Heart disease genes identified with VAAST & PHEVOR in a cohort of *2,871 congenital heart disease probands* *





*Jin SC., Homsy J. et al. *Contribution of rare transmitted and de novo variants among 2,871 congenital heart disease probands*. Submitted.

USTAR Center for Genetic Discovery

Country Sequencing Program

Genomics England & 100,000 Genomes Project

Genomics england

Goal:

Sequence 100,000 whole genomes to discover and diagnose the genetic basis for rare disease and cancer

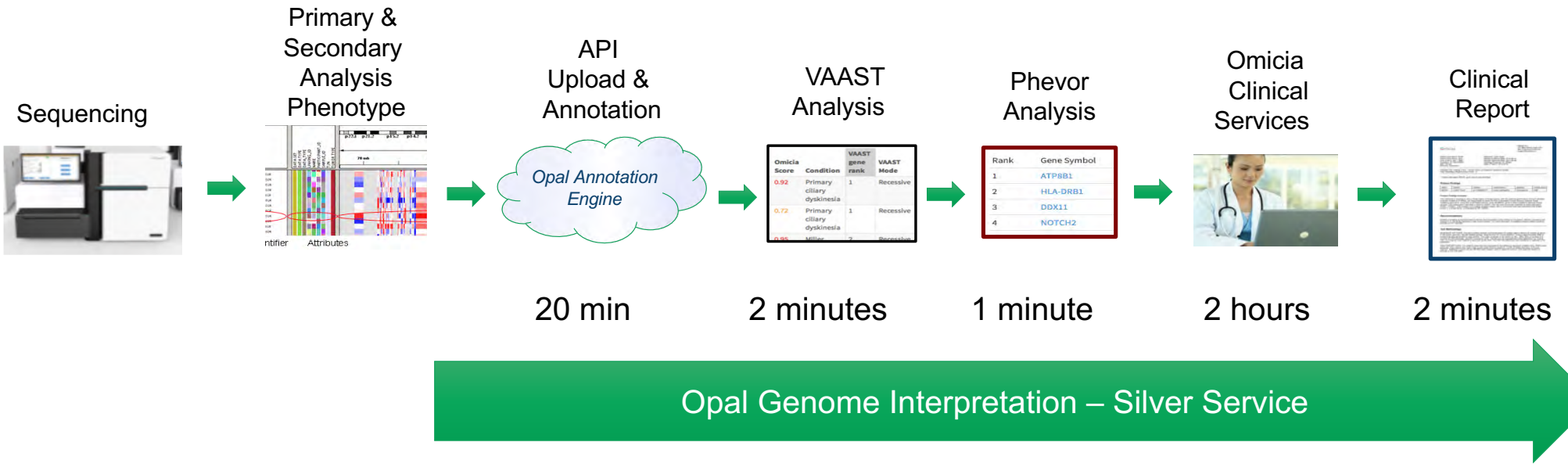
NHS Foundation Trust NHS

The UK's 100,000 Genomes Project

is the largest initiative of its kind in the world. It is ground-breaking ….and is establishing protocols and standards that will be applied across the entire healthcare system.

SIR JOHN CHISOLM,
EXECUTIVE CHAIR
OF GENOMICS ENGLAND

Fabric Delivers Automated, Intelligent Interpretation Workflows



Performance highlights:

1st
Company to deliver clinical reports
(*April, 2016*)

1,900+
Cases returned as of February 2018

40.8%
Disease causing candidate yield[1]
(industry average: 29%)[2]

Initial WGS interpretation
< 2 hours

53.3%
Candidates identified by Phevor-VAAST as Top hit[1]

Genomics england

Delivering reports to multiple main program sites

[1]Identified disease-causing candidates in first 609 cases. Babcock et al, *Increased Yield of Clinically Relevant Candidates in the UK 100,000 Genomes Project Using Opal™ Clinical for Hereditary Disease*. Poster session presented at: ACMG; 2017 Mar 21-25; Phoenix, AZ.

[2]"The success rate of 29 percent, which is about twofold higher of conventional genetic evaluations for such patients, makes WES a reasonable diagnostic approach for patients on a diagnostic odyssey" says Dr. Lazaridis, Mayo Clinic, Individualized Medicine Clinic.

Recent case – solved by Fabric Genomics

Patient diagnosed with:

- Intellectual Disability
- Multiple Epiphyseal Dysplasia

Findings:

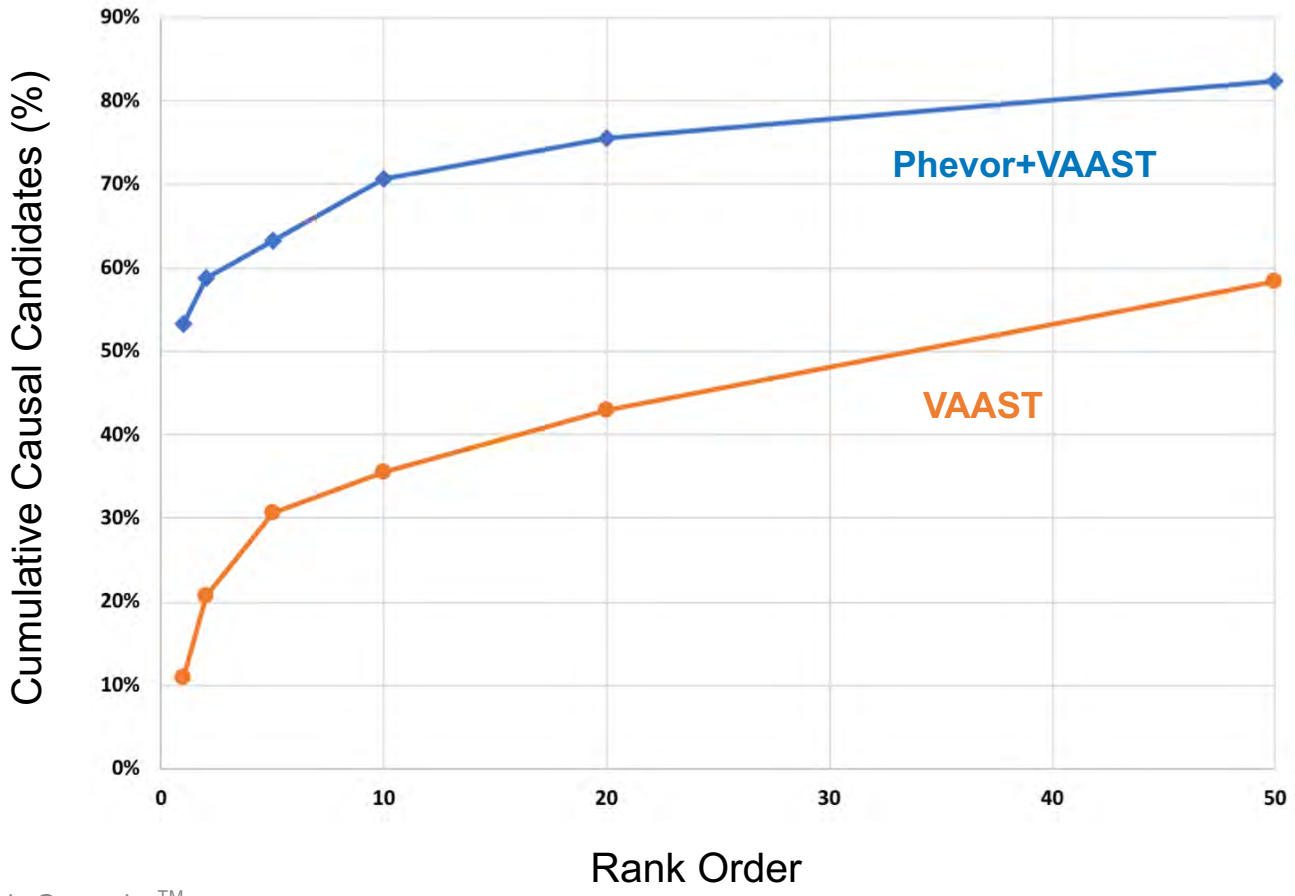
- Misdiagnosis
- Fabric Genomics discovered a change in OBSL1 gene, associated with Three M syndrome*

Result:

- Patient was accurately diagnosed with Three M syndrome

*Three M syndrome is an extremely rare genetic disorder characterized by low birth weight, short stature (dwarfism), characteristic abnormalities of the head and facial (craniofacial) area, distinctive skeletal malformations, and/or other physical abnormalities.

Phevor significantly improves ranking of variants



Genome England cases

- Causative candidate variants n=644
- 450 Probands with positive findings

Rady Children's Hospital Launches Rapid Genome Service

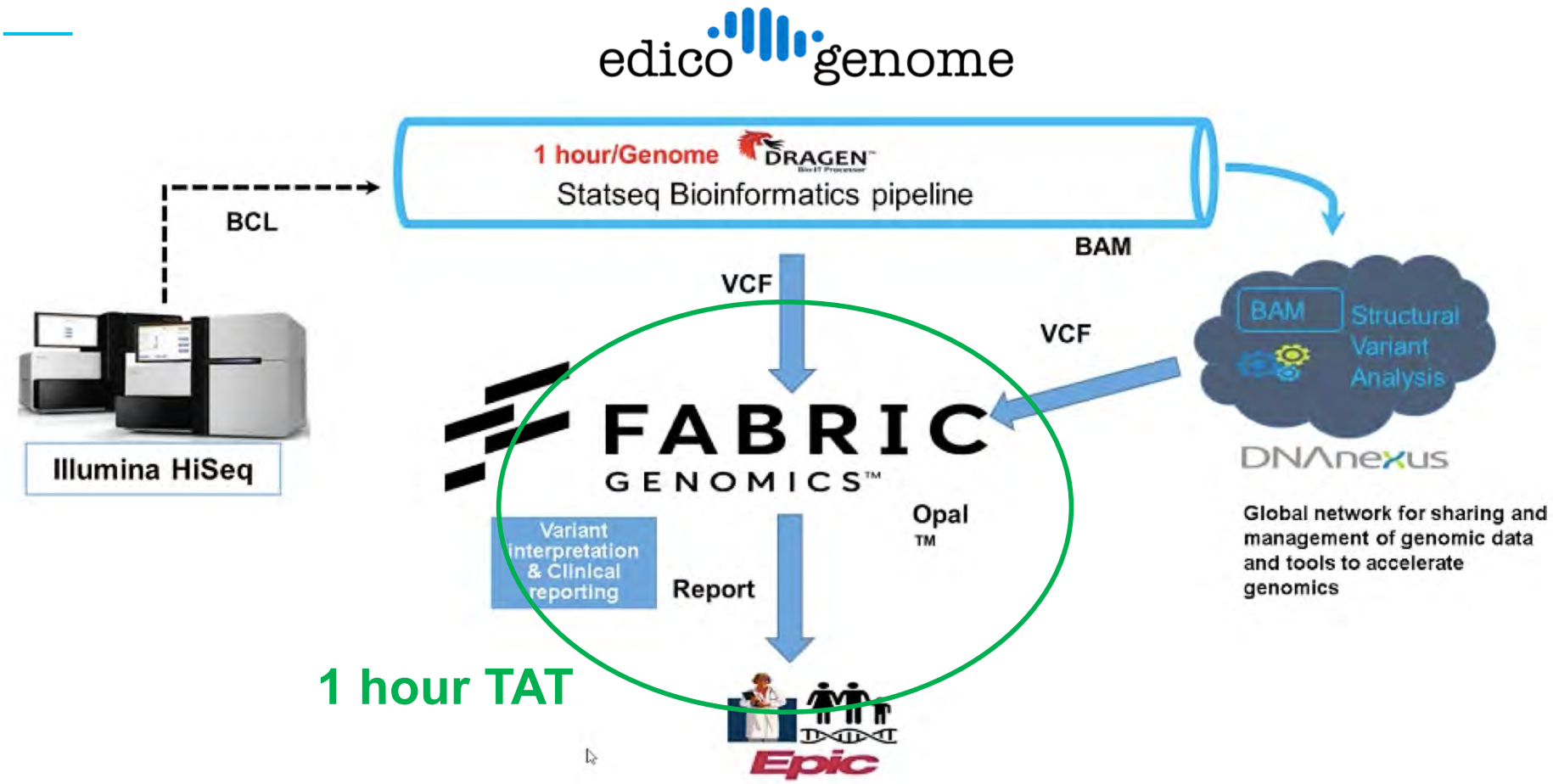
- **Goal:** Set up rapid genome testing for newborns and infants in Intensive Care Unit
- **Need:** 1 hour turnaround time for interpretation
- **With Fabric Genomics' solution:** Delivering 1 hour interpretation made it possible to now routinely turnaround a sample from collection, sequencing to clinical report in < 36 hours

Rady Children's Institute Genomic Medicine

"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 of Rady Children's Institute for Genomic Medicine

Rady's Rapid Whole Genome Interpretation Pipeline



Case Study: Fabric Genomics / Rady Children's Hospital

STAT Pediatric Clinical Genome – 19.5 hours from sample to report


FABRIC GENOMICS

OUR SOLUTIONS · ABOUT US · NEWS & EVENTS · RESOURCES · CASE STUDIES · LOG IN · CONTACT US

PRESS

New GUINNESS WORLD RECORDS™ Title Set for Fastest genetic diagnosis

Date: February 12, 2018

Share:

Scientists at the Rady Children's Institute for Genomic Medicine (RCIGM) have compressed the time needed to decode rare genetic disorders in newborns through DNA sequencing to less than a day. RCIGM set a new GUINNESS WORLD RECORDS™ title for Fastest genetic diagnosis in 19.5 hours. Dr. Kingsmore has pioneered the rapid turnaround and delivery of genetic test results to neonatal and pediatric intensive care (NICU/PICU) physicians.

Fabric Genomics' platform was a critical technology enabler. Fabric's clinical decision support software enables rapid diagnosis by helping to pinpoint the source of genetic disease out of hundreds of possibilities. Fabric's platform includes the Fabric STAT pipeline that provides guaranteed rapid turnaround time for urgent pediatric genomic tests.

Genetic diseases are the leading cause of death in infants in North America affecting an estimated four percent of newborns. Rare genetic diseases also account for approximately 15 percent of admissions to children's hospitals.

"Our evolving ability to find the answers to medical mysteries through rapid Whole Genome Sequencing is providing hope for babies and children with rare, genetic diseases," said Dr. Kingsmore. "By speeding delivery of genomic insights, we are equipping physicians with the information they need to provide precision care for the youngest and most fragile patients."


THE JOURNAL OF PRECISION MEDICINE

HOME · NEWS · ARCHIVE

NEWS

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

Dr. Stephen Kingsmore, MD, DSc, is the President and CEO of the Rady Pediatric Genomics and Systems Medicine Institute. Dr. Kingsmore spoke at the...

Read More

January 26, 2017

Francis Collins: Tenure as NIH Director Extended Under New Administration

Bethesda, MD – The Trump administration has asked current National Institutes of Health (NIH) Director Francis Collins to remain in his position for the...

Read More

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

Dr. Stephen Kingsmore, MD, DSc, is the President and CEO of the Rady Pediatric Genomics and Systems Medicine Institute. Dr. Kingsmore is the inaugural Precision Medicine Leaders Summit Get-together. We spoke with him about his program for rapidly sequencing the genomes of sick children and what he's looking for in the field of next generation sequencing and genomics.

Allbeq: Please tell us a little bit about what prompted your move to the Rady Pediatric Genomics and Systems Medicine Institute.

Dr. Kingsmore: Obviously multi-factorial, but from a career perspective this is very logical. So you know I'm fifty-five going on fifty-six and for most of my career I have been pushing the idea that biotechnology is going to revolutionize medicine. Over the last decade or so that has focused on genome sequence information. Two jobs ago I was at a research institute and we were one of the first to start to sequence human genomics. And at some point during that process, we realized, "wow there's information in here that's going to transform medicine." And so their very purposefully I moved to a children's hospital where they had lots of kids with genetic diseases and we could start to get experience. Over the five years or so that I was at the Children's Mercy in Kansas City, the results completely stunned me. We published a lot of papers but two that really stand out. One was thirty-two babies in a neonatal intensive care unit. We decoded their genomes and fifty-seven percent of those babies got a diagnosis and two-thirds of those diagnoses changed how the baby was managed. So that made me realize that this is ready for prime time. You know this is stunningly successful. And so at that point you know it was sort of "first base to go to," "You know doing thirty-five babies is nice. It's pioneering, but we know I need to think about ways to assess how generalizable is that. And then if it is generalizable, how do we implement that for all babies. I couldn't do that at Children's Mercy Hospital, that wasn't my job description. And so I started the search to figure out where might that be possible and I believe that where we are at

2ND ANNUAL PRECISION MEDICINE LEADERS SUMMIT AUGUST 21-24 2017 BOSTON AND NEW SAFFRON

PRECISION MEDICINE LEADERS SUMMIT

SAVE the DATE

>52%

Diagnostic Candidate

Find the right answer faster using VAAST/Phevor

	Candidate Yield	Avg Rank Causative Variant	% Cases Where Causative Variant Ranked in	
			Top 1	Top 20
Rady Institute for Genomic Medicine	52%	4.5	**60%**	93%
Genomics England	45%	12.5	**45%**	74%
Labcorp	54%	12	**52%**	89%

Immediately identify causative variant in ~50% of cases

Financing Modeling

★ Matched control

Rady Children's Institute Genomic Medicine

Subject ID	Site	Presentation	Gene	Admission to Diagnosis, days/(Test Method)	Type of cost	Hospital stay (days)	Decrease in Hospital Stay, days (%)	WRVU	WRVU Avoided	Medicaid Payment, $1000	Medicaid Payment Avoided, $1000 (%)	Commercial Payment, $1000	Commercial Payment Avoided, $1000 (%)
6041	NICU	Seizures	*KCNQ2*	4 (rWGS)	Case: Rapid diagnosis and precision treatment	18		120		85		157	
				42 (std)	Model: Case + 6 week time to diagnosis	59	41 (69%)	280	156 (57%)	234	149 (64%)	429	272 (63%)
Ctrl 1					Control: With standard time to diagnosis			326	205 (63%)	210	125 (60%)	383	226 (59%)
6014	NICU	Hypotonia	*NEB1*	7 (rWGS)	Case: no muscle biopsy	n.a.		n.a.					
Ctrl 2			n.a.	n.a.	Control: whole hospitalization	35	2 (6%)	246	24 (8%)	165	32 (20%)	302	59 (20%)
					Control: muscle biopsy, pathology, postop. care x 1 day	2		24		33		59	
6026	PICU	Cholestasis & CHD	*JAG1*	3 (rWGS)	Case: Kasai cancelled	11		n.d.		40		72	
Ctrl 3	GI	Cholestasis	n.a.	n.a.	Control: Kasai surgery whole hospitalization	14	3 (21%)	104	90 (87%)	80	54 (68%)	147	100 (68%)
					Control: Kasai surgery & postop. care only			90		54		100	
6053	NICU	Hypoglycemia	*ABCC8*	7 (rWGS)	Case: rapid diagnosis and transport for surgery	10	21 (68%)	105	175 (62%)	60	108 (64%)	109	197 (64%)
				28 (std)	Model: average published time to diagnosis	31		280		168		306	
6012	NICU	Complex	*ARID1B*	26 (rWGS)	Case: Palliative care started 250 days after admission	250		1,714	1,624 (81%)	1,941		3,538	
					Model: Case + 6 weeks antibiotics	292	262 (90%)	2,001		2,587	2,362 (91%)	4,707	4,299 (91%)
					Model: Palliative care started 30 days after admitted	30		377		224		408	
6011	GI	Cholestasis	*NPC1*	7 (rWGS)	Case: First hospitalization (rWGS unavailable)	8	15 (35%)	26	33 (56%)	26	27 (51%)	47	50 (51%)
					Case: Second hospitalization (rWGS available)	15		33		27		50	
Average						76	57 (76%)	499	354 (71%)	546	477 (87%)	994	826 (83%)

omicia is now FABRIC GENOMICS™




NEXT-GEN SEQUENCING | SECONDARY ANALYSIS | INTERPRETATION AND REPORTING | CLINICAL MANAGEMENT

a2 sigma Inc.

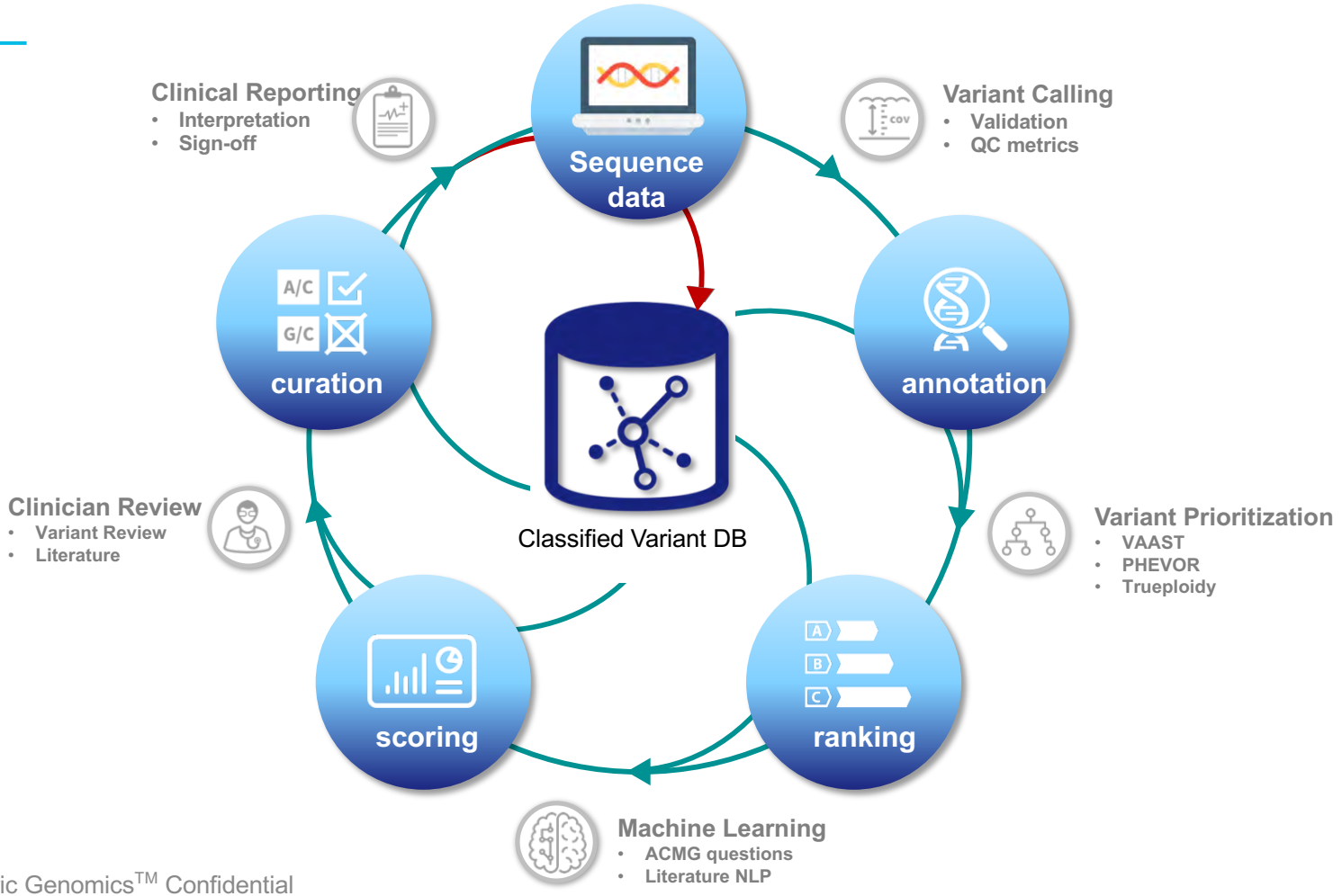
Fabric Genomics' End to End Platform

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

VAAST and Phevor

edico genome

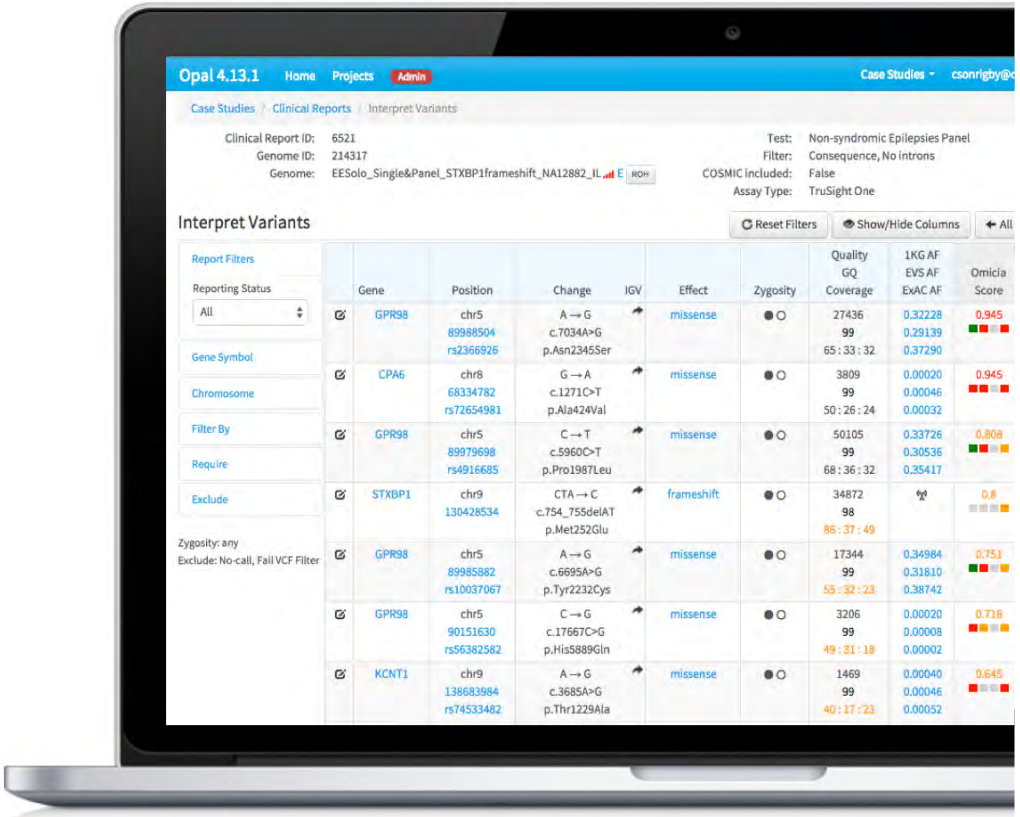
Classified Variant Database to Provide Largest, Highest Quality Database of Human Genetic Variation via Network Effect



- Variants classification are shared within organization
- Option to share with other labs
- Share at different levels to protect patient privacy
- Leverage massive data and sharing to enable more accurate diagnoses

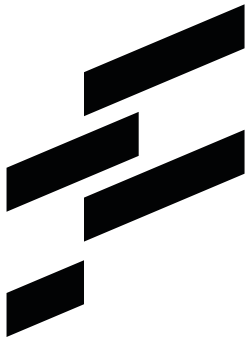
Opal™ Clinical – Tertiary Analysis
Decision Support System for Hereditary Disease

- 90+ public and proprietary databases and analysis algorithms per variant
- All testing types supported: solo, trio, and flexible family
- Proven health systems integrations with electronic medical records (Epic and Cerner) and LIS



Thank you!

Martin Reese, Ph.D.
martin@fabricgenomics.com

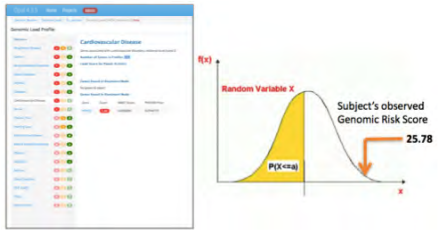


FABRIC GENOMICS™

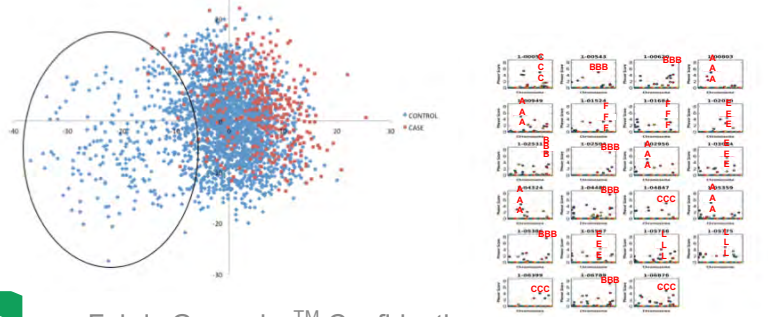
A global healthcare platform for genomic data analysis

Comprehensive Computational Genomics Platform

Grouper
Genetic disease burden scores for wellness applications and population health management



VAAST3 for Target Discovery
Case / Control studies



Opal™ Clinical (VAAST + Phevor)
End-to-end clinical software that turns raw genome sequence data and phenotype into high-quality clinically meaningful insights

BioGraph™
Advanced graph technology for structural variant detection, population-specific, reference-free diagnostics, genome data storage