Accurate and Rapid Genome Interpretation – in clinical care

Martin Reese, Ph.D.
Overview

- Who we are?

- Our unique bioinformatics technologies VAAST/Phevor - ready to scale

- Three clinical applications
  - Discovery novel disease genes and diagnoses - The Utah Genome Project
  - Diagnostic Odyssey patients – Genomics England 100,000 Genome Project
  - NICU/ICU babies – Stephen Kingsmore’s Rady’s Children Hospital
Company Overview

- **Company**
  - Founded 2009 as Omicia

- **Product**
  - Comprehensive end-to-end Precision Medicine platform for genomic data analysis (SaaS)
  - Opal™ Clinical is a single, scalable unified clinical database solution (>65,000 genomes)

- **Strategic Collaborators**
  - University of Utah: VAASTPHEVOR papers published in 2011 by Yandell, Reese *et al.*, originally funded by multiple NIH grants

- **Customer Segments**
  - Clinical Labs, Hospital Labs, Pharmaceutical Research and Country Projects
  - >1,000 research and clinical licensees, >25 clinical labs supported
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 reproducibly within a team of variant scientists?

How do we find the important variants at scale?
Fabric Genomics’ End to End Platform

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

VAAST and Phevor
• **VAAST**: probabilistic disease gene finder

• **Phevor**: belief network for integration of phenotype data via HPO and GO with genome sequences


VAAST rhymed with BLAST

<table>
<thead>
<tr>
<th>BLAST</th>
<th>VAAST</th>
</tr>
</thead>
<tbody>
<tr>
<td>query</td>
<td>case genomes</td>
</tr>
<tr>
<td>database</td>
<td>control genomes (1K Genomes Project)</td>
</tr>
<tr>
<td>hits</td>
<td>hits</td>
</tr>
<tr>
<td>Expect</td>
<td>P-value</td>
</tr>
<tr>
<td>Fast</td>
<td>Fast</td>
</tr>
</tbody>
</table>

BLAST searches for statistically significant similarity between sequences.

VAAST searches for statistically significant dissimilarity between sequences. It uses a Burden Test to do so.

VAAST work supported by NIH SBIR grants 1R4HG003667 to Fabric/Yandell, SBIR 1R44HG002991 to Fabric, an NIH ARRA GO grant 1RC2HG005619-01 to Yandell/Reese, all administered by the National Human Genome Research Institute (NHGRI). VAAST+ by R01GM104390 from the NIGMS to Yandell and NSF DEB-1149160 to M. Shapiro
Why is a Burden calculation necessary?

• Variant prioritization only gets you partway there.
• Consider an individual with a *de novo* highly damaging missense allele, e.g. His->Trp.
• Judged to be maximally damaging by Sift, PolyPhen etc.
• Allele is completely absent from gnomAD and 1KG.
• Is this a allele responsible for the proband’s genetic disease?
• But what if 20% of gnomAD and 1KG individuals carry one or more different, but *equally* ‘damaging’ alleles in the same gene?
Why is a Burden calculation necessary?

• The VAAST p-value speaks to this question, i.e. what % of the population have greater than the observed genotype burden at that locus.
• Every variant in the population, every genotype is considered in this calculation.
• Additional benefits include that it controls for LD, ethnic stratification, and unknown sources of noise in the data, etc.
• VAAST also models phenomena such as mode of inheritance, penetrance, disease prevalence, etc.
VAAST, Families and Disease

A family with a Tay-Sachs affected child
Phenotype Driven Variant Ontological Re-Ranking Tool

Patient phenotype (symptoms) are big clues

<table>
<thead>
<tr>
<th>Plain language</th>
<th>Medical term</th>
</tr>
</thead>
<tbody>
<tr>
<td>Webbed toes</td>
<td>Syndactyly</td>
</tr>
<tr>
<td>Deformity due to premature fusing of skull bones</td>
<td>Craniosynostosis</td>
</tr>
<tr>
<td>Wide-set eyes</td>
<td>Ocular hypertelorism</td>
</tr>
</tbody>
</table>
Phevor Combines Phenotype and Genotype

Phenotype description

Improved power to identify causative variants


Fabric Genomics™
What problem does Phevor solve?

Search tools are underpowered for single individuals and nuclear families.

The exome of a child with severe liver disease

What problem does Phevor solve?

Search tools are underpowered for single individuals and nuclear families.

The exome of a child with severe liver disease

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How does Phevor do this?

Bayesian belief network for integration of phenotype data via HPO and GO with genome sequences
What’s an Ontology?

Examples:
The Gene Ontology (GO)
The Human Phenotype Ontology (HPO)
The Mammalian Phenotype Ontology (MPO)
The Disease Ontology (DO)

... and many others
What’s an Ontology?

Ontologies are often directed acyclic graphs (DAGs). GO, for example, is a collection of 3 DAGs with more than 40,000 of nodes.
How Phevor Works (seeding)

A  Observed Phenotype
    Cardiomyopathy
        HP:0001638
    Ventricular septal defect
        HP:0001629
    Arrhythmia
        HP:0011675

B  Ontology Seeding

C  Known Linked Genes
    LAMA4
    PEX13
    SCO2
    AKT3
    CREBBP
    NODAL
    KCNA5
    PEX3
    TLL1
How Phevor Works (seeding)

D Observed Phenotype

Cardiomyopathy
HP:0001638

Ventricular septal defect
HP:0001629

Arrhythmia
HP:0011675

E Ontological Propagation

F Expanded Gene List with Priors

- GATA4, CPT2, PRPS1, COX7B, MRPS22, MAP2K1, H19, MRPL44, BOLA3
- LAMA4, PEX13, SCO2, AKT3, CREBBP, NODAL, KCNA5, PEX3, TLL1
How Phevor Works (combining ontologies)
Phevor Scores

\[
P^D_g = \frac{(1-V_g) \cdot N_g}{((1-V_g) \cdot N_g) + (V_g \cdot (1-N_g))}
\]

\[
P^H_g = \frac{V_g \cdot (1-N_g)}{((1-V_g) \cdot N_g) + (V_g \cdot (1-N_g))}
\]

\[
S_g = \log_{10}\left(\frac{P^D_g}{P^H_g}\right)
\]

Where, \(N_g\) is the percentile rank of the node score for gene \(g\), and \(V_g\) is the percentile rank of gene \(g\) assigned by the variant prioritization tool.
2 examples
A family with Common Variable Immune disease (CVID)

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)

A Family with Common Variable Immune disease (CVID)

Phenotype
- Recurrent infections (HPO:0002719)
- Abnormality of Humoral immunity (HPO:0005368)

Is this diagnosis correct?

- In family A, c.2564delA mutation introduces a stop at amino acid 861.
- In unrelated proband, c.2557C>T mutation introduces a stop at amino acid 853.
- Follow up functional analyses establish the non-canonical NF-kB signaling pathway as a cause of this immunodeficiency syndrome.
- Demonstrates Phevor’s ability to identify a novel gene using *latent knowledge* in biomedical ontologies.
Polygenic case-control datasets

- Increasingly clear that many (most?) common disease cohorts are highly polygenic.
- Often no one variant or gene has sufficient PAR to achieve genome-wide significance using GWAS or Burden testing approaches, e.g. PCGC.
- VAASST & Phevor well suited for this situation.
- Cohort pipeline allows use of individual phenotypes w/Phevor.
- Fast
- Easy-to-interpret results.
- VAASSTc Coming soon to Opal.
The outputs of the pipeline

1-02504

GDF1
p.M364T

Phevor Score

Chromosome
UGP projects since 2016

17,303 Whole Exomes
8,999 Whole Genomes
4,773 Families
Select Global Clinical Lab Accounts
Country Sequencing Program
Genomics England & 100,000 Genomes Project

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

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

Sequencing → Primary & Secondary Analysis Phenotype → API Upload & Annotation → VAAST Analysis → Phevor Analysis → Omicia Clinical Services → Clinical Report

Opal Annotation Engine

Opal Genome Interpretation – Silver Service

- 20 min
- 2 minutes
- 1 minute
- 2 hours
- 2 minutes
Performance highlights:

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

1200+ Cases returned as of September 2017

44.7% Disease causing candidate yield\(^1\)

(industry average: 29%)\(^2\)

43.9% Candidates identified by VAAST / Phevor as Top hit\(^1\)

Initial WGS interpretation < 2 hours

Delivering reports to multiple main program sites

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\(^1\)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\(^{TM}\) 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.
Using Phevor-ranking to Identify Causative Candidates in GeL

Genes with rank >20 were not exhaustively reviewed. Support from Tiers, ClinVar, and HGMD were mostly used in this range.
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

“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
Case Study: Fabric Genomics / Rady Children’s Hospital

STAT Pediatric Clinical Genome

October 18, 2019 08:00 AM Eastern Daylight Time

OAKLAND, Calif. -- (BUSINESS WIRE) -- Fabric Genomics, 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 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, MD, PhD, President and CEO of Rady Children’s Institute for Genomic Medicine, praised the use of rapid genome sequencing to diagnose life-threatening and life-altering issues, and has recently demonstrated a Rady Children’s record setting time of 24 hours from receipt of clinical sample to diagnosis.

The goal of Rady Children’s rapid genomic testing is to identify a 24-hour turnaround time for sequencing and analysis, on average.

Rady Children’s and Fabric Genomics deliver STAT Rapid Genome Testing for critically ill infants

“Rapid genomic testing has emerged as being of increasing importance for neonatologists and pediatric intensivists working with urgent, life-threatening issues. To support the turnaround time we have today, Fabric Genomics has introduced a new STAT Whole Genome Software package that delivers clinically interpretable information from next-generation sequencing (NGS) data within an hour. This rapid decision support service enables Rady Children’s clinical team to quickly and accurately diagnose patients and develop targeted treatment plans,” said Stephen Kingsmore, MD, PhD, President and CEO of Rady Children’s Institute for Genomic Medicine.

Historically, as many as one-third of infants admitted to a neonatal intensive care unit (NICU) in the US 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 genomic testing, can help save lives and improve long-term outcomes.

“The time is now: neonatologists often care for newborns who cannot tell us about their symptoms,” explains Kingsmore. “We are excited to have developed the streamlined approach for whole genome sequencing and the Fabric Genomics interpretation platform enables us to quickly and accurately interpret the results, which will change the way we care for infants.”

The work of 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 genomic interpretation,” said Martin Reese, MD, PhD, Diabetic and President and Chief Scientific Officer of Fabric Genomics. “We are honored to provide this service to Rady Children’s, 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 100,000 Genomes Project, adding the element of urgency and fast turnaround, which we plan to offer with Rapid Outreach.

Our goal is to further the NSF-Diabetes interpretation service to every infant care team in the country to help in the diagnosis of critically ill children.”

Fabric Genomics is a recognized leader in its field, and this latest partnership exemplifies its ongoing commitment to providing high-quality services to a wide range of healthcare providers. The company’s expertise is dedicated to accelerating the interpretation of genomic data, making it accessible to healthcare providers and enabling them to make more informed decisions about patient care.

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 CICU. 90% of parents of children who our Intensive Care Unit physicians referred for genome analysis said yes. 11 of 21 infants received a diagnosis! In 5 of the 21 diagnosis changed how the infant was managed in the NICU, PICU or CICU (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...
Rapid Whole Genome Sequencing (rWGS) in the Intensive Care Unit

Shimul Chowdhury, PhD, FACMG, CGMB
Rady Children’s Institute for Genomic Medicine, Laboratory Director
Rady Children’s Institute for Genomic Medicine

Mission

• Enabling the prevention, diagnosis and treatment of childhood diseases through genomic and systems medicine research.

Goal

• To make genetic screening fast, easy and routine care for diagnosing and delivering precision medical care to critically ill babies and children.
Initial Focus for Neonatal Precision Medicine

8,000 known genetic diseases
Affecting 3% of children in U.S.

- Leading cause of infant death
- Leading cause of death in NICU / PICU

Presentation less confounded by environment
Biggest timespan for benefit
The screening paradigm

- Earlier (genetic) testing
- Timely specific care
- Better patient outcomes
### RCIGM Diagnoses (all cases)

<table>
<thead>
<tr>
<th>Causal/Critical Genes</th>
<th>( ) number of diagnoses</th>
<th>*Copy Number Variation</th>
<th>AR HOM – 3</th>
<th>AR CMPHET – 7</th>
<th>DE NOVO – 27</th>
<th>DOMINANT/X-Linked - 12</th>
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</thead>
<tbody>
<tr>
<td>SERPINA1</td>
<td>ANTXR2</td>
<td>FGFR2, HDAC8</td>
<td></td>
<td></td>
<td></td>
<td></td>
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<tr>
<td>*Tetrasomy 15q1.2q13.1</td>
<td>ATM</td>
<td>PYGM</td>
<td></td>
<td></td>
<td></td>
<td></td>
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<tr>
<td>NPC1</td>
<td>FOXP3</td>
<td>STAT1</td>
<td></td>
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<td></td>
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<tr>
<td>ARID1B</td>
<td>KMT2D</td>
<td>NODAL (2)</td>
<td></td>
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<tr>
<td>NEB</td>
<td>CHD7 (2)</td>
<td>COL4A2</td>
<td></td>
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<td></td>
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<tr>
<td>POLR1C</td>
<td>ASL</td>
<td>*TBX1</td>
<td></td>
<td></td>
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<tr>
<td>GABRA1</td>
<td>FOXF1</td>
<td>TH</td>
<td></td>
<td></td>
<td></td>
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</tr>
<tr>
<td>TPM1</td>
<td>GBA</td>
<td>*ELN</td>
<td></td>
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<td>*PCDH19 (2)</td>
<td>ZEB2 (2)</td>
<td>SDHA</td>
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<tr>
<td>PHEX</td>
<td>PIEZO1</td>
<td>ACVRL1</td>
<td></td>
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<tr>
<td>RET</td>
<td>APOB</td>
<td>*SNRPN (2)</td>
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<tr>
<td>CELSR1</td>
<td>NIPBL</td>
<td>*TANGO2</td>
<td></td>
<td></td>
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<td></td>
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<tr>
<td>ACTG2</td>
<td>G6CP3</td>
<td>EFHC1, GABRB3</td>
<td></td>
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<td></td>
</tr>
<tr>
<td>*JAG1</td>
<td>TSC2</td>
<td>ABCC8</td>
<td></td>
<td></td>
<td></td>
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<tr>
<td>NF1</td>
<td>KCNQ2</td>
<td>RYR2</td>
<td></td>
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<tr>
<td>FBN1</td>
<td>TRNT1</td>
<td></td>
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</tr>
</tbody>
</table>

- Diagnosis rate: 33%
- Change in management: 66%
- Total Patients – 160
• Variant and Phenotypic Algorithms
Creating a Clinical Analysis in Opal

New Trio Report

You can either create a clinical report from a pre-existing VAAST Report, or set up a new VAAST analysis below. Fabric Genomic’s VAAST algorithm ranks variants and their associated genes by their likelihood to cause disease. VAAST evaluates predicted impact on protein function, allele frequency as well as evolutionary conservation, and can identify known and novel causative variants.

Enter Patient Accession ID

Choose Project

RCIGM_production

Choose Panel - Optional

None

Choose Filter - Optional

None

Choose Assay Type - Optional

None

Include COSMIC Evidence

New VAAST Analysis

Existing VAAST Analysis

Unaffected Father

Unaffected Mother

Affected Child

Panel
Solo
Trio
Quad
Flexible Family
### Analysis and Interpretation by Inheritance Mode

![Screenshot of genetic analysis software](image)

**Clinical Report ID:** 213081
**Project:** ROOM_production
**Status:** Approved
**Clinical Grade:** G
**Patient Accession:** 100110_C16082_F6041
**Patient Information:** View

**Text:** ACMG Mendelian
**VAAST Release:** 3.0.4.3
**Pipeline Version:** 6.0.6
**COMIC Included:** False

**Proband:** R1600061_F6041_daughter (Genome ID: 012852) Female (Affected)
**Mother:** R160002_F6041_mother (Genome ID: 013653) Female (Unaffected)
**Father:** R160003_F6041_father (Genome ID: 013004) Male (Unaffected)

**HPO Terms:** Generalized myoclonic seizures, EEG with burst suppression, Epileptic encephalopathy

**Note:** This report was approved by Shimul Chowdhury on Jan 12, 2017 at 12:43 PM. It can no longer be edited.

**Review Variant Selection**

| Filtering Protocols | Report Priority | Gene | Position dbSNP | Change | Effect | Zygosity | Mother Zygosity | Father Zygosity | Quality GQ | Coverage | JKAS AF | EVS AF | ExAC AF | Omics Score | Evidence | Phedor gene rank |
|---------------------|-----------------|------|----------------|--------|--------|----------|----------------|----------------|------------|-----------|---------|---------|---------|----------|------------|----------|------------------|
|                      |                 | FANCM | chr14:46505497 | A>G    | missense | splice site impact | ⬇️ | □ | 1870 | 99 | 45 | 0:45 | 0.927 | □ | 1 |
|                      |                 | KCNQ2 | chr20:52071003 | A>G    | missense | | ⬇️ | □ | 1870 | 99 | 658 | 99 | 33:15:18 | 0.752 | □ | 1 |
|                      |                 | KCNQ2 | chr20:52071003 | A>G    | missense | | ⬇️ | □ | 1870 | 99 | 658 | 99 | 33:15:18 | 0.752 | □ | 1 |
|                      |                 | KIA0047 | chr5:55457445 | A>C    | missense | | | | 293 | 66 | 22 | 0:22 | 0.418 | □ | 2 |
|                      |                 | MBDO5 | chr2:149240677 | A>T    | acceptor | | | | 35 | 64 | 14 | 10:4 | 0.700 | □ | 2 |

**Gene Filters**

- Zygosity
  - Proband Zygosity
  - Any
  - Mother Zygosity
  - Any
  - Father Zygosity
  - Any

**Variant Interpretation**

- [Variant ID: FANCM](#)
- [Variant ID: KCNQ2](#)
- [Variant ID: KIA0047](#)
- [Variant ID: MBDO5](#)
## ACMG Scoring with Opal

### Scoring Criteria

**Allele frequency**
- Code: BA1
- Section: Frequency
- Support: Benign
- Level: Stand alone
- Rubric: ACMG Mendelian, version 1.0

Criteria met?
- Yes
- No

### Scoring Criteria

**Located in a mutational hot spot and/or critical and well-established functional domain without benign variation**

**Code:** PM1  
**Section:** Location  
**Support:** Pathogenic  
**Level:** Moderate  
**Rubric:** ACMG Mendelian, version 1.0

Criteria met?
- Yes
- No

### Scoring Tools

**1000 Genomes Project**
- Allele Frequency: -

**ExAC Allele Frequency**
- Allele Frequency: -

### Scoring Tools

**Protein Domains**

<table>
<thead>
<tr>
<th>Database</th>
<th>Accession</th>
</tr>
</thead>
<tbody>
<tr>
<td>Superfamily domains</td>
<td>0048280</td>
</tr>
<tr>
<td>Pfam domain</td>
<td>PF01365</td>
</tr>
</tbody>
</table>

View Gene

Pathogenic - ClinVar GeneDx

Results: A de novo pathogenic variant has been identified in the RYR2 gene. The c.1646C>T (p.Ala549Val) variant was identified. Variants in the RYR2 gene have been implicated in Arrhythmogenic right ventricular dysplasia and Ventricular tachycardia, catecholaminergic polymorphic ventricular tachycardia (CPVT; OMM:180902).
RCIGM Diagnostic Rate and Change in Care Based on our initial 150 cases

<table>
<thead>
<tr>
<th></th>
<th>San Diego</th>
</tr>
</thead>
<tbody>
<tr>
<td>Enrollment</td>
<td>Early</td>
</tr>
<tr>
<td>Method</td>
<td>Rapid trio WGS</td>
</tr>
<tr>
<td>Diagnoses</td>
<td>~35%</td>
</tr>
<tr>
<td>Change in care</td>
<td></td>
</tr>
<tr>
<td>*Palliative Care Guidance</td>
<td>8%</td>
</tr>
<tr>
<td>**Medication Change</td>
<td>28%</td>
</tr>
<tr>
<td>Life-saving treatment</td>
<td>8%</td>
</tr>
<tr>
<td>NICU stay decreased by &gt;1 month</td>
<td>8%</td>
</tr>
<tr>
<td>*+Major morbidity avoided</td>
<td>16%</td>
</tr>
<tr>
<td>*+Major Procedure Change</td>
<td>8%</td>
</tr>
</tbody>
</table>

*ARID1B: Coffin-Siris Syndrome—palliative care

**NPC1: Niemann-Pick C1 – miglustat: diagnosis at 2 months of age; miglustat treatment was started in a child showing isolated splenomegaly, treated even before the onset of any neurological manifestation

*+JAG1: Alagille Syndrome 1 – stopped Kasai; drug treatments 9 changes; 7 drug rx; 2 surgery delta; 1 palliative care
Economic Impact: NGS Pediatric Odysseys (US)

- 14% of newborns end up in the NICU in the US (3.9M births, 546K)
- ~33% of infants admitted to the NICU have an underlying genetic disease (180K)
- Average cost of a NICU stay: $8K-$15K / night

- “Pediatric Odyssey” (PO) cases are frequently “NGS send outs” (up to $5K)
- Average turnaround time on PO send-outs: 12-15 weeks*
- Cost to patient / family: anguish, disability, lost work, unemployment, death**
- Potential cost to full-risk hospital for POs (3 week stay): up to $315K / patient

*Several Top US Health Systems
** Impact of hypothesis-driven testing on families with PO children (average 5.6 years in EU, 7.6 yrs US to resolution, respectively)
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

**Consumer**
Wellness / Population Health

**Clinical**
Interpretation and Reporting

**Research**
Drug Targets, Novel Diagnostics and Data Storage

*Fabric Genomics™ Confidential*
Genomic Medicine – Bioinformatics Solutions

- Hereditary Disease
- Somatic Mutations/Immune System
- Infectious Disease
Thank you!

Martin Reese, Ph.D.
martin@fabricgenomics.com
A global healthcare platform for genomic data analysis
## Pan-Birth Capabilities

<table>
<thead>
<tr>
<th>Carrier screening</th>
<th>Carrier screening</th>
<th>Newborn screening</th>
<th>Early Childhood</th>
<th>Late Childhood</th>
<th>Teen</th>
<th>Young Adult</th>
</tr>
</thead>
<tbody>
<tr>
<td>pre-conception</td>
<td>prenatal</td>
<td></td>
<td></td>
<td></td>
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</tr>
<tr>
<td>427+ genes</td>
<td>CFTR</td>
<td>200 genes</td>
<td>Developmental</td>
<td>Allergies</td>
<td>Inherited cancer syndromes</td>
<td>Carrier Screening Mental Health</td>
</tr>
<tr>
<td>Carrier Screening</td>
<td>Tay-Sachs</td>
<td>including</td>
<td>Delay</td>
<td>Thrombophilia</td>
<td>syndromes</td>
<td></td>
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<tr>
<td>Panel for expecting</td>
<td>Sickle-cell anemia</td>
<td>Mitochondrial</td>
<td>Autism</td>
<td>Scoliosis</td>
<td>Insulin resistance</td>
<td></td>
</tr>
<tr>
<td>parents</td>
<td>anemia</td>
<td>Metabolism</td>
<td></td>
<td>Epilepsy</td>
<td></td>
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<tr>
<td></td>
<td>Thalassemia</td>
<td>Hearing</td>
<td></td>
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</tbody>
</table>

**Precision Medicine Project recruitment strategy:**

Global sequencing at birth