Enabling neonatal precision medicine by rapid whole genome sequencing

Stephen Kingsmore MD DSc
skingsmore@rchsd.org
Rady Children’s Hospital Baby 6026

- 2 month old admitted to PICU with severe jaundice & poor weight gain for 1 month
- Weight 0.05%ile
- Acidotic, tachypneic
- Echo: Congenital heart disease, underdeveloped pulmonary arteries
The conventional paradigm in medicine does not work well in rare diseases

- Clinical diagnosis $\rightarrow$ Empiric Treatment
- Molecular diagnosis $\rightarrow$ Targeted Treatment
Clinical diagnosis: biliary atresia
  - Incidence 1 in 10,000
Empiric treatment: Kasai procedure
  - Prognosis worsens with time to surgery
Liver biopsy not diagnostic: giant cell hepatitis, sample too small to count bile ducts
Unique Requirements for Diagnosis of Genetic Diseases in Neonatal, Pediatric and Cardiovascular ICU

Leading cause of NICU and PICU death

Conventional testing too slow to guide NICU and PICU care

Simplest genetics = interpretable, actionable, scalable in 2017

Timely Diagnosis of 5,000 Genetic Diseases in NICUs and PICUs
San Diego Synergy: Illumina + Edico + Rady Children’s

Rapid Whole-Genome Sequencing for Genetic Disease Diagnosis in Neonatal Intensive Care Units
Carol Jean Saunders et al.
Sci Transl Med 4, 154ra135 (2012);
DOI: 10.1126/scitranslmed.3004041

Miller et al. Genome Medicine (2015) 7:100
DOI 10.1186/s13073-015-0221-8

A 26-hour system of highly sensitive whole genome sequencing for emergency management of genetic diseases

GUINNESS WORLD RECORDS

RATIONALE FOR RECORD

In May 2016, Rady Children’s Hospital San Diego in collaboration with Illumina, Edico and the Center for Medical Genomics at the Sanford Burnham Prebys Medical Discovery Institute in La Jolla, Calif. established a Rapid Whole-Genome Sequencing program that is able to provide comprehensive whole genome sequencing results within 26 hours of sample submission. This new system has the ability to provide clinicians with an understanding of the full genome of a patient giving them new insights into the genetic basis of disease. As the only rapid whole-genome sequencing program in the world, Rady Children’s in San Diego, has the potential to become the global leader in the field.
Whole-genome sequencing for identification of Mendelian disorders in critically ill infants: a retrospective analysis of diagnostic and clinical findings


Overview of Rapid WGS-based Precision Medicine

Children’s Hospital Regional NICU/ICU

- Improved outcomes
- Empowered families
- Cost effectiveness

Rady Children's Hospital San Diego

Children's Hospitals and Clinics of Minnesota

Children's Hospital Colorado

Children's Hospital

Rady Children's Institute

Genomic Medicine
<table>
<thead>
<tr>
<th>HPO</th>
<th>Feature</th>
<th>Modifier</th>
<th>Num diseases</th>
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<td>Conjugated hyperbilirubinemia</td>
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<tr>
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<td>HP:0001508</td>
<td>Failure to thrive</td>
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### Phenomizer or Phenolyzer

**Algorithm:** resnik (Unsymmetric)  |  **Features:** 6

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<tr>
<th>p-val</th>
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<td>#613404 ARTHROGRYPOSIS, RENAL DYSFUNCTION, AGED, DYSMORPHIC FEATURES</td>
<td>VPS33B, VIP10, WDR49, PRKD1, DPH2, CGD5</td>
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<td>0.0240</td>
<td>#229600 FRUCTOSE INTOLERANCE, HEREDITARY;FRU...</td>
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<td>GILBERT SYNDROME</td>
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</table>
43 Hours Later: Provisional Diagnosis

**JAG1: Alagille Syndrome Gene**
Jaundice, bile duct paucity on liver biopsy; congenital heart disease, primarily involving the pulmonary arteries

Genome sequence coverage

- Position 10,471,400
- Position 13,459,331
The Need for Speed in NICU/PICU Diagnosis

Kasai hepatopportoenterostomy for biliary atresia
Outcome: 50% Reduction in Likelihood of Death

“5% of infants with Alagille syndrome are diagnosed clinically as biliary atresia and undergo Kasai operation. Among 15 children with Alagille syndrome, mortality was 60% among the Kasai group, and 10% in the non-Kasai group. Liver transplantation was performed in 100% of the Kasai group, and 20% of the non-Kasai group.”
Rady Children’s 6 Month Experience: Over $\frac{1}{3}$ of Infants Receive Precision Medicine

<table>
<thead>
<tr>
<th>Infants tested</th>
<th>Willig et al. Lancet Resp Medicine, 2015</th>
<th>Rady Children’s San Diego</th>
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<tbody>
<tr>
<td>Number</td>
<td>35</td>
<td>48</td>
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<tr>
<td>Diagnoses</td>
<td>57%</td>
<td>52%</td>
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<tr>
<td>Change in care</td>
<td>37%</td>
<td>36%</td>
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<tr>
<td>Palliative Care Guidance</td>
<td>17%</td>
<td>8%</td>
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<tr>
<td>Medication Change</td>
<td>11%</td>
<td>28%</td>
</tr>
<tr>
<td>Life-saving treatment</td>
<td>3%</td>
<td>8%</td>
</tr>
<tr>
<td>NICU stay decreased by &gt;1 month</td>
<td>3%</td>
<td>8%</td>
</tr>
<tr>
<td>Major morbidity avoided</td>
<td>9%</td>
<td>16%</td>
</tr>
<tr>
<td>Major Procedure Change</td>
<td>9%</td>
<td>8%</td>
</tr>
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</table>
History:
Dizygotic twin, prematurity, small for gestational age, congenital diaphragmatic hernia, pulmonary hypertension, failure to thrive, chronic lung disease, stage 1 retinopathy of prematurity, status post ECMO, repair of VSD and coarctation of aorta, small bowel obstruction

Exam:
Low nasal bridge, developmental delay, with some tracking, no smiling, very low tone, dysmorphic, eyebrows penciled in their external half with a striking medial flare. Long eyelashes
Background to the Economic Argument for NICU/PICU Rapid WGS

- **Children with Severe Chronic Illness**: 70% cost, 10% children
- **High Risk Children**: 20% cost, 14% children
- **Healthy Children**: 10% cost, 76% children

NICU, PICU, CVICU
Diagnosis DOL 242

• Autosomal Dominant Coffin-Siris Syndrome
• ARID1B c.3096_3100delCAAAAG; p.Lys1033ArgfsTer32)
• Sanger confirmed/reported DOL 250
• Family requested palliative care that day and patient expired
Medical Geneticist Comment:

Hospital charge (excluding physician fees): $1.4M
Cost of WGS: ~$5000

“What is incredible about this case is how much of what I think of the tax payers money was spent in totally futile care (that assumes the family would have stopped if they had a diagnosis in the first months). This child lacked the nail hypoplasia that would have allowed one of us clinical folks to make this diagnosis clinically at the outset.”
• 3 day old, full term female with tonic and myoclonic seizures since birth
• EEG: tonic & myoclonic seizures and background burst suppression
• Head circumference 5\textsuperscript{th} \%\textsuperscript{ile}
• Brain MRI: normal
• First line treatments ineffective:
  • Levetiracetam then phenobarbital then lorazepam
Provisional diagnosis in 68 hours

- **KCNQ2** c.875T>C; p.Leu292Pro
- Indicated specific treatment regimen: carbamazepine, phenytoin
- Seizures controlled – child discharged
- Hospital charge (excluding physician fees): $14,000
- Cost of WGS: ~$5000
Previous Otohara diagnosis in same NICU 1 year earlier (pre-WGS)

• 2 month hospital stay: $165,000; diagnosis after discharge

• “Early recognition of KCNQ2 encephalopathy followed by the most appropriate and effective treatment may be important for reducing the neurodevelopmental impairment associated with this disorder” Pisano et al. Epilepsia. 2015 56:685-91.

• Ezogabine – KCN opening AED not yet approved in children
NSIGHT Study: RCT of trios with NICU/PICU infants aged <4 months & illnesses of possible genetic etiology

Level IV NICU & PICU infants of age < 4 months with clinical features suggestive for a genetic disease

$t_0$
- Informed consent, deep clinical phenotype extracted, blood draw

Blinded Randomization

Standard Diagnostic Tests
- Standard Tests and Trio Rapid WGS

$t_{10}$
- Unblinding; Provisional WGS diagnosis communicated to neonatologist if acutely actionable; Cross-over if requested

$\sim t_{17}$
- Confirmatory testing of WGS results and diagnostic report in EHR

DOL$_{28}$
- Day of life (DOL) 28 rate of molecular diagnosis

$t_{28}$
- 28-day rate, method and type of molecular diagnosis and actionability, time to diagnosis
Enrollment (October 2014 – June 2016) at Children’s Mercy Hospital, Kansas City

129 infants were assessed for eligibility

64 were excluded
- 11 already had a molecular diagnosis
- 7 age > 4 months
- 1 team declined
- 9 discharged or died prior to enrollment
- 11 incomplete nomination
- 8 exceeded maximum parental consent attempts
- 17 family declined

65 underwent randomization

32 were assigned to receive rapid WGS + standard tests
- 32 received rapid WGS

33 were assigned to receive standard tests as indicated
- 32 received standard tests as indicated

5 cross-over to rapid WGS after day 10 unblinding

32 were included in intention to treat analysis of primary end-points rate of diagnosis within 28 days of test order and by day of life 28

33 were included in intention to treat analysis of primary end-points rate of etiologic diagnosis within 28 days of test order and by day of life 28
Results: Rate of neonatal diagnosis and diagnosis within 28 days of test order was greater with rapid whole genome sequencing sequencing.

<table>
<thead>
<tr>
<th></th>
<th>Rapid WGS + Std Testing</th>
<th>Std Testing (Inc. crossovers)</th>
<th>P-Value</th>
<th>Statistical Test</th>
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<tr>
<td>Subjects</td>
<td>32</td>
<td>33</td>
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<td><strong>Primary End-Points</strong></td>
<td></td>
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<tr>
<td>Diagnosis by DOL 28 (n,%)</td>
<td>7 (22%)</td>
<td>0 (0%)</td>
<td>0.0048</td>
<td>Fisher's exact test</td>
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<tr>
<td>Diagnosis within 28 days of test order (n, %)</td>
<td>10 (31%)</td>
<td>0 (0%)</td>
<td>0.0004</td>
<td>Fisher's exact test</td>
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<tr>
<td><strong>Secondary End-Points</strong></td>
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<td>Total Diagnosis (n, %)</td>
<td>13 (41%)</td>
<td>7 (21%)</td>
<td>0.11</td>
<td>Fisher's exact test</td>
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<tr>
<td>Clinical Utility of Dx (n,%)</td>
<td>13 (41%)</td>
<td>6 (18%)</td>
<td>0.06</td>
<td>Fisher's exact test</td>
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<tr>
<td>DOL Hospital Discharge (average, range)</td>
<td>66.3 (3-456)</td>
<td>68.5 (4-341)</td>
<td>0.91</td>
<td>Two sample t-test</td>
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<td>Deaths (n, %)</td>
<td>5 (15.62%)</td>
<td>5 (15.15%)</td>
<td>0.91</td>
<td>Fisher's exact test</td>
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<td>DOL Death (median, range)</td>
<td>62 (14-228)</td>
<td>173 (4-341)</td>
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<td>Log Rank Test</td>
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Kaplan Meier Curves of time period where WGS had a higher diagnostic rate
<table>
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<th>County</th>
<th>Population 2015</th>
<th>Level III/IV NICU Infants</th>
<th>Min. NICU Families Sequenced</th>
<th>Timely Diagnoses</th>
<th>QALYs Saved Per Year</th>
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<td>San Diego</td>
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<td>2,537</td>
<td>381</td>
<td>198</td>
<td>1,104</td>
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<td>California</td>
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<td>1,232</td>
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<td>USA</td>
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<td>125,000</td>
<td>18,750</td>
<td>9,750</td>
<td>54,375</td>
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</table>

GOING BIG FOR THE LITTLE ONES
Rapid WGS will invigorate Rare Disease Drug Development

- Early diagnosis
- Complete ascertainment
- Economically tractable rare disease targets
The children are waiting....