Improving the Diagnostic Odyssey for Rare Disease Patients

July 29, 2021
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Panelists

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Director
Hugh Kahl Precision Medicine Institute
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President & CEO
Rady Children’s Institute of Genomic Medicine
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Moderator
Matthew Might, Ph.D.
Professor, Department of Medicine
Director
Hugh Kahl Precision Medicine Institute
Stephen Kingsmore, M.D., DSc
President & CEO
Rady Children's Institute of Genomic Medicine
@radychildrens
We now know 6,000 genetic diseases

- Genetic diseases for which molecular basis is known: 6,138
- Increase in known genetic diseases: ~1 per day
- MANY causes of common childhood disorders:
  - Seizures: 1,283 genetic diseases
  - Intellectual disability: 1,681 genetic diseases
  - Recurrent infection: 699 genetic diseases
  - Congenital heart disease: 1,889 genetic diseases
  - Metabolic abnormalities: 3,402 diseases

There is an ongoing technology revolution

- Genome sequencing now possible for ~$700
- Automated, diagnostic whole genome sequencing now possible in 13.5 hours
Genome Sequencing Saves Lives

213 infants in Intensive Care Units

Critical illness of unknown etiology at admission

Genomic sequencing within 96 hours of admission

Deep phenotype extraction from health record

Abbreviated empirical treatment

21-46% positive results in 2 days

12% of admissions

54-79% negative tests in 5 days

41% of admissions

MD: 93% clinical utility; 63% change in clinical management

Parent: 100% results were useful; 98% better able to manage symptoms

39% Δ in outcome; 69% improved communication

100% benefit to child; 100% benefit to parent

MD: 72% clinical utility; 16% change in clinical management

Parent: 96% results were useful; 92% better able to manage symptoms

8% Δ in outcome; 32% improved communication

96% benefit to child; 97% benefit to parent

# The Evidence Is Overwhelming

<table>
<thead>
<tr>
<th>Ref.</th>
<th>Date</th>
<th>Study Type</th>
<th>Seq Type</th>
<th>Neonatal &amp; Pediatric Intensive Care Unit Enrollment Criteria</th>
<th>Size</th>
<th>Dx Rate</th>
<th>Change in Management</th>
<th>Change in Outcome</th>
<th>TAT (d)</th>
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<tbody>
<tr>
<td>1</td>
<td>2012</td>
<td>Cases</td>
<td>urWGS</td>
<td>NICU infants with suspected genetic disease</td>
<td>4</td>
<td>75%</td>
<td>n.d.</td>
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<td>2,3</td>
<td>2015</td>
<td>Cohort</td>
<td>rWGS</td>
<td>&lt;4 months of age; Suspected actionable genetic disease</td>
<td>35</td>
<td>57%</td>
<td>31%</td>
<td>29%</td>
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<td>2017</td>
<td>Cohort</td>
<td>rWES</td>
<td>&lt;100 days of life; Suspected genetic disease</td>
<td>63</td>
<td>51%</td>
<td>37%</td>
<td>19%</td>
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<tr>
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<td>2018</td>
<td>RCT</td>
<td>rWGS</td>
<td>&lt;4 months of age; Suspected genetic disease</td>
<td>32</td>
<td>41%</td>
<td>31%</td>
<td>n.d.</td>
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<td>2018</td>
<td>Cohort</td>
<td>rWGS</td>
<td>infants; Suspected genetic disease</td>
<td>42</td>
<td>43%</td>
<td>31%</td>
<td>26%</td>
<td>23</td>
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<tr>
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<td>2018</td>
<td>Cohort</td>
<td>rWES</td>
<td>Acutely ill children with suspected genetic diseases</td>
<td>40</td>
<td>53%</td>
<td>30%</td>
<td>8%</td>
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<td>Cohort</td>
<td>rWGS</td>
<td>Children; PICU and Cardiovascular ICU</td>
<td>24</td>
<td>42%</td>
<td>13%</td>
<td>n.d.</td>
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<tr>
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<td>2019</td>
<td>Cohort</td>
<td>rWGS</td>
<td>4 months-18 years; PICU; Suspected genetic diseases</td>
<td>38</td>
<td>48%</td>
<td>39%</td>
<td>8%</td>
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<td>2019</td>
<td>Cohort</td>
<td>rWGS</td>
<td>Suspected genetic disease</td>
<td>195</td>
<td>21%</td>
<td>13%</td>
<td>n.d.</td>
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<td>2019</td>
<td>Cohort</td>
<td>urWGS</td>
<td>Infants; Suspected genetic disease</td>
<td>7</td>
<td>43%</td>
<td>43%</td>
<td>n.d.</td>
<td>0.8</td>
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<td>2020</td>
<td>Cohort</td>
<td>rWES</td>
<td>&lt;4 mo of age; ICU; hypotonia, seizures, metabolic, multiple congenital anomalies</td>
<td>50</td>
<td>54%</td>
<td>48%</td>
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<td>2020</td>
<td>Cohort</td>
<td>rWES</td>
<td>NICU &amp; PICU; complex</td>
<td>130</td>
<td>48%</td>
<td>23%</td>
<td>n.d.</td>
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<td>2020</td>
<td>Cohort</td>
<td>rWES</td>
<td>Critical illness; medical genetics selected</td>
<td>46</td>
<td>43%</td>
<td>52%</td>
<td>n.d.</td>
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<td>2020</td>
<td>Cohort</td>
<td>rWES</td>
<td>PICU; &lt; 6 years; new metabolic/neurologic disease</td>
<td>10</td>
<td>50%</td>
<td>30%</td>
<td>n.d.</td>
<td>9.8</td>
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<td>16</td>
<td>2020</td>
<td>Cohort</td>
<td>rWES</td>
<td>ICU</td>
<td>368</td>
<td>27%</td>
<td>n.d.</td>
<td>n.d.</td>
<td>n.d.</td>
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<td>2020</td>
<td>Cohort</td>
<td>rWES</td>
<td>&gt;1 year; ICU and inpatient</td>
<td>102</td>
<td>31%</td>
<td>27%</td>
<td>n.d.</td>
<td>11</td>
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<td>18</td>
<td>2020</td>
<td>Cohort</td>
<td>rWES</td>
<td>Various</td>
<td>41</td>
<td>32%</td>
<td>n.d.</td>
<td>n.d.</td>
<td>7</td>
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<tr>
<td>19</td>
<td>2020</td>
<td>Cohort</td>
<td>rWES</td>
<td>&lt;18 yr; NICU and PICU</td>
<td>108</td>
<td>51%</td>
<td>44%</td>
<td>n.d.</td>
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<td>20</td>
<td>2020</td>
<td>Implement</td>
<td>rWES</td>
<td>Infant; disease of unknown etiology; within 96 hours of admission</td>
<td>94</td>
<td>19%</td>
<td>24%</td>
<td>10%</td>
<td>3</td>
</tr>
<tr>
<td>12, 21</td>
<td>2019</td>
<td>RCT</td>
<td>rWES</td>
<td>Infant; disease of unknown etiology; within 96 hours of admission</td>
<td>95</td>
<td>20%</td>
<td>20%</td>
<td>18%</td>
<td>11</td>
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<tr>
<td>22</td>
<td>2021</td>
<td>Cohort</td>
<td>rWGS,panel</td>
<td>Infant; disease of unknown etiology</td>
<td>113</td>
<td>33%</td>
<td>26%</td>
<td>n.d.</td>
<td>n.d.</td>
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<td>23</td>
<td>2021</td>
<td>Implement</td>
<td>rWGS</td>
<td>Medicaid infants; unknown etiology; within 1 week of admission</td>
<td>178</td>
<td>43%</td>
<td>31%</td>
<td>n.d.</td>
<td>3</td>
</tr>
</tbody>
</table>

**Weighted Average**: 1839 36% 29% 25%

References at the end of this presentation.

Implement, Implementation science study
RCT, randomized, controlled trial. rWES, rapid whole exome sequencing.
Legislative Action Is Needed

Speaker's own illustration.
California Medicaid Example

Dots represent zip codes of enrolled infants

UC Davis Children's Hospital

UC San Francisco Benioff Children's Hospital Oakland

Valley Children's Hospital (Madera)

CHOC Children's (Orange County)

Rady Children's Hospital- San Diego


CHOC, Children's Hospital of Orange County; UC, University of California; ZIP, zone improvement plan.
Results: Genome Sequencing Decreases Medicaid Cost of Care

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Principal
Avalere
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The Diagnostic Journey for Rare Disease Patients: Scaling Sustainable Solutions
What Does Good Look Like?

Key Steps in the Ideal Patient Journey

Ideal rare disease patient diagnosis begins with genotypical/phenotypical symptom identification facilitated through robust technology platforms which lead to a rapid and appropriate diagnosis.
Challenges and Barriers to Scale and Spread

1. High Demand, Complex Needs
2. Clinician Education
3. Data Maturity and Regulatory Barriers
4. Payment, Coverage and Reimbursement
5. Adoption and Workforce
6. Equity
7. Sustainability
A Technology Solution

Key Elements of an Ideal Technology Environment

Clinical Support  Transparency  Treatment  Scaling Solutions
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