Case Studies From the Brave New World of Whole Genomic Sequencing

John D. Lantos MD
Children’s Mercy Hospital
KCMO

Disclosure

John Lantos MD does not have any financial arrangements or affiliations with a commercial entity.

He will not be discussing the unlabeled use of a commercial product in his presentation.

April 10th 2013, baby CMH487, 2 months old

• Mother at 16 week antenatal visit: blood test showed ↑ α-fetoprotein
• MRI scan showed fetus to have an omphalocele
• Baby was delivered in our materno-fetal health center
• Admitted to NICU for treatment of ruptured omphalocele
• Acute liver failure developed at 2 months of age
• Underlying disease not diagnosed despite intensive testing

Decoding the family’s genomes

Discussion and permission

Decoding the family’s genomes

Obtain blood samples
Decoding the family’s genomes

- Transport samples
- Purify DNA from blood
- Prepare DNA for sequencing

Decode the genome

- Catalog the DNA letter changes
- Interpret DNA changes
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The Baby's Symptoms

254 Matching Diseases

Genome

Diagnosis

3,200,000,000
5,000,000
2,000,000
1,500

All DNA letters

DNA changes from normal

Changed in less than 1% of people

Changes that may alter body function

Changes that fit the baby's symptoms

PRF1 c.1310G>A, pAla437Val

489, mum

487, baby

488, dad

Reference genome

Decoding the family's genomes

- Diagnosis of Hemophagocytic Lymphohistiocytosis
- Treated with steroids & IV immunoglobulin
- Liver now normal
- Still in hospital, omphalocele healing
Some tough decisions

- Genomic Medicine differs from traditional genetic testing
- Unique ethical considerations

Next Generation Sequencing

- NGS = Permits rapid interrogation of DNA and better control of lab error than in sequencing of one DNA strand at a time.
- Falling cost and comparatively rapid results are creating a paradigm shift in the approach to monogenic disease.

Deep Sequencing

Deletions

Substitutions
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### Customized Recessive Genetic Screen

<table>
<thead>
<tr>
<th></th>
<th>Sequential Testing</th>
<th>Multiplex Testing</th>
</tr>
</thead>
<tbody>
<tr>
<td>Genes tested at once</td>
<td>1-20</td>
<td>500+</td>
</tr>
<tr>
<td>Time to result</td>
<td>1-3 months</td>
<td>1 month</td>
</tr>
<tr>
<td>Time to molecular diagnosis</td>
<td>Months-years</td>
<td>1 month</td>
</tr>
<tr>
<td>Cost per patient</td>
<td>$2-15 K</td>
<td>$1250</td>
</tr>
</tbody>
</table>

### Case 2: Sibs with Inflammatory Bowel Disease

<table>
<thead>
<tr>
<th></th>
<th>CMH000165</th>
<th>CMH000166</th>
</tr>
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<tbody>
<tr>
<td>Age</td>
<td>7 years</td>
<td>11 months</td>
</tr>
<tr>
<td>Gender</td>
<td>Male</td>
<td>Male</td>
</tr>
<tr>
<td>Onset of Symptoms</td>
<td>12 months</td>
<td>4 months</td>
</tr>
<tr>
<td>GI Symptoms</td>
<td>Severe</td>
<td>Severe</td>
</tr>
<tr>
<td>Bowel Resection</td>
<td>+</td>
<td>-</td>
</tr>
<tr>
<td>Rash</td>
<td>-</td>
<td>+</td>
</tr>
<tr>
<td>Anemia</td>
<td>+</td>
<td>+</td>
</tr>
<tr>
<td>Poor Growth</td>
<td>-</td>
<td>+</td>
</tr>
<tr>
<td>IV nutrition</td>
<td>-</td>
<td>+</td>
</tr>
<tr>
<td>Quality of Life</td>
<td>Poor</td>
<td>Poor</td>
</tr>
</tbody>
</table>

### Why genomics made sense for this family

- Atypical presentation of well known disease
  - Symptoms started too early
  - Symptoms are very severe
  - Not responsive to standard medications
  - Both boys affected
  - Genetics of IBD is poorly understood

### Results: Compound Heterozygous IL10RA Mutations

- Interleukin 10 receptor (IL10R) mutations have been reported to cause aggressive inflammatory bowel disease (IBD) in children
  - **Variant 1:** IL10RA, c.784C>T, p.Arg262Cys has been previously reported in Very Early Onset -IBD.
  - **Variant 2:** IL10RA, c.349C>T, p.Arg117Cys is a novel variant affecting a conserved amino acid, and is predicted to be deleterious.

### Autosomal Recessive Disease

**Homozygous**

**Compound Heterozygous**

### Possible cure, but not without risk

- IL10R mutation responsible for the brother’s illness and poor response to treatment
- Allogeneic bone marrow transplantation reported curative in children with IL10R mutations
- BMT carries risk of illness and death
- Family currently working with BMT team
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Ethical implications

• Is a novel genetic diagnosis reliable enough to use as a basis for a potentially lethal treatment?
• How reliable are these results, anyway?

Two Key Ethics Questions

1. Under which **specific conditions** should results be returned? (And to whom and by whom?)
2. What is/are the **broader guiding principle(s)** for decisions to return results?

Returning Results

- Clinical Care
- Research
- Population Screening

Aggregate

Individual

Incidental

Targeted

Common Criteria

- Validity
- Value/Utility/Significance
- Actionable
- Consent

RUNES: Variant Categorization

<table>
<thead>
<tr>
<th>Category</th>
<th>Description</th>
<th>Criteria</th>
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</thead>
<tbody>
<tr>
<td>ACMG Cat1-3</td>
<td>1. Frameshift, insertion, deletion, or nonsense mutation</td>
<td>Variant type of disease mutation</td>
</tr>
<tr>
<td></td>
<td>2. Novel, if any, expected to cause the disorder</td>
<td>Clinical significance of pathogenic</td>
</tr>
<tr>
<td></td>
<td>3. Novel, may or may not be causative</td>
<td>Evidence of de novo mutation</td>
</tr>
<tr>
<td></td>
<td>4. Novel, probably not causative of disease</td>
<td>Exome/whole transcriptome comparison with 5-10k controls</td>
</tr>
<tr>
<td></td>
<td>5. Known variant</td>
<td>Clinically actionable</td>
</tr>
<tr>
<td></td>
<td>6. New loci or variants unexpected to be a substantial contributor to condition associated with a disease</td>
<td>Clinical severity</td>
</tr>
</tbody>
</table>

Experience so far...

1. 4 babies received targeted treatment as a result of a genomic diagnosis
   - Unique surgery to cure disease
   - Specific treatments to prevent death, diminish disease severity, delay progression
   - N-of-1 clinical trials of experimental therapies
2. Palliative
   - In several babies the diagnosis avoided futile continuation of intensive care
3. Parental benefits
   - Psychosocial: Answer, guilt, less uncertainty
   - Planning: treatment intensity, duration, bonding, good-byes, last rites
   - Genetic counseling to mitigate unanticipated recurrence.
4. Societal
   - Reduced NICU and lifetime cost of care