Ending the Diagnostic Odyssey

• Research to evaluate the utility of rapid genome sequencing to identify the root cause of illness in newborns

• Level IV Neonatal Intensive Care Units
  – Rady Children’s Hospital, San Diego
  – Children’s Mercy Hospital, Kansas City
### Randomized, controlled, prospective trial of clinical utility

**Inclusion criteria**
- Likely genetic disease
- Genetic test order
- Congenital anomalies
- Poor response to care

**Exclusion criteria**
- >4 months old
- Chromosome anomaly
- Known molecular diagnosis

<table>
<thead>
<tr>
<th>Time</th>
<th>Event</th>
<th>Control Group</th>
<th>WGS Group</th>
<th>Refusal Assessment</th>
</tr>
</thead>
<tbody>
<tr>
<td>$t_0$</td>
<td>Consent, Blinded Randomization</td>
<td>Control group (n=125)</td>
<td>WGS group (n=125)</td>
<td>Refusal Assessment</td>
</tr>
</tbody>
</table>

**Pretest**
- Clinician/parent questionnaires on hopes / fears
- Acuity guided WGS: 3 – 5 days

**Return of Diagnostic Results**
- Verbal
- EHR report
- Care conference
- Chart note = no Dx
- Potential crossover

**After test results**
- Parent Questionnaires
- Clinician Questionnaires

**Outcomes assessment**

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NIH
April 10, 2013
Baby CMH487

Abdominal viscera herniating into base of umbilicus (omphalocele)

Jaundice
Yellowing of eyes
Yellowing of skin
Excess bilirubin in blood
• 8,000 named diseases
• 20 more discovered each month
• Affect 1 in 25 children
• Leading cause of infant death
Solution:
Test all 8,000 Genetic Diseases in 26 hours by WGS*

*Whole Genome Sequencing
Genetic Testing in Newborns: A Breakthrough

For the first time, researchers can now sequence the genomes of newborns with mysterious conditions.

In every neonatal intensive care unit (NICU), about half of the infants are there because they were born prematurely and/or have health conditions that help to breathe and get accustomed to their new environment outside the womb.

But about third of NICU patients are there because doctors do not know what's wrong with them. They may have seizures, not be eating or breathing normally, and nobody knows what is causing it.

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

New 26-hour test delivers faster diagnoses, which hold special promise for newborns.
April 10, 2013

Parents gave consent
Blood sample from mum, dad and baby
April 10, 2013

00:60

Transport to Institute
Prepare DNA for sequencing

April 10, 2013 06:00
Each of my 37 trillion cells contains 2 genomes of 3.2 billion DNA letters.

We are fearfully and wonderfully made. Psalm 139
Illumina genome sequencing
19,000 genes are translated into 250,000 proteins.

3,200,000,000 nucleotides x 2

19,000 genes are translated into 250,000 proteins.

Proteins act alone or in complexes to perform many cellular functions.
Total DNA letters detected

Infant CMH487

24:30

120,000,000,000,000
25:00

Infant CMH487

120,000,000,000
2,832,342,927
4,883,961

DNA letter changes from “normal”
DNA changes present in less 1 in 100 people
A single DNA letter change can cause a genetic disease

Hemoglobin-β DNA code

G₂ G₂ T₁ G₂ T₁ T₁ G₂ G₂ G₂
T₁ T₁ A₁ T₁ C₃ C₃ T₁ A₁ A₁
A₁ G₂ C₃ C₃ A₁ C₃ G₂ G₂ A₁

Normal red blood cell

Sickle cell
DNA changes that could cause disease
Computer-Generated List of 341 Possible Diagnoses
DNA changes in genes causing the 341 diseases
Interpret DNA changes: Diagnosis

- Two mutations (DNA letter changes) affecting one protein
- Diagnosis (Hemophagocytic lymphohistiocytosis type 2)
April 17, 2013

Precision medicine:
Stop non-specific treatments
Start specific treatments

Result:
Liver failure corrected within 7 days
Today

He is 31 months old

72 quality adjusted life years saved
57% diagnosis

<table>
<thead>
<tr>
<th>1st Author</th>
<th>Journal</th>
<th>Number of Subjects</th>
<th>Age (mean or median)</th>
<th>Diagnosis Rate</th>
</tr>
</thead>
<tbody>
<tr>
<td>Soden</td>
<td>Sci Trans Med</td>
<td>100</td>
<td>7 years</td>
<td>47%</td>
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<tr>
<td>Srivastava</td>
<td>Ann Neurol</td>
<td>78</td>
<td>9 years</td>
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<tr>
<td>Yang</td>
<td>JAMA</td>
<td>1756</td>
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<tr>
<td>Lee</td>
<td>JAMA</td>
<td>814</td>
<td>520 &lt;18 yr</td>
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<tr>
<td>Wright</td>
<td>Lancet</td>
<td>1133</td>
<td>6 years</td>
<td>27%</td>
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</table>
Acute clinical utility in 65% diagnoses
Strongly favorable impact on outcome in 20%

<table>
<thead>
<tr>
<th>Diagnosis Prior to Discharge</th>
<th>65%</th>
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</thead>
<tbody>
<tr>
<td>Genetic Counseling Change</td>
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<tr>
<td>Subspecialty Consult (non-genetic) Initiated</td>
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<tr>
<td>Medication Change</td>
<td>20%</td>
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<tr>
<td>Procedure Change</td>
<td>15%</td>
</tr>
<tr>
<td>Diet Change</td>
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<tr>
<td>Palliative Care Initiated</td>
<td>30%</td>
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<tr>
<td>Imaging Change</td>
<td>15%</td>
</tr>
<tr>
<td>Transferred to Another Facility</td>
<td>5%</td>
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