RAPID WHOLE GENOME SEQUENCING IMPROVES THE CARE OF HOSPITALIZED INFANTS
Acknowledgements

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Initial Focus For Precision Medicine-Infants

8,000 known genetic diseases
These affect 3% of US children

• Leading cause of death in infants,
• Leading cause of death in PICUs and NICU

Presentation less confounded by environment

Biggest timespan for benefit
WGS and NBS

Concerns about discrimination
  • Different when a child has already presented

Significant cost impact to get timely turn around
  • Need to target who gets sequenced (pre-screening)
  • Different use case than panel

WGS is not a screening test – it is diagnostic of 5,000 diseases
  • Need to decide what characteristics make a condition reportable rather than condition by condition approval
San Diego Synergy
Industry Collaboration for Rapid WGS

How:
1. Same work-day blood sample to HiSeq 2500
2. 2 x 101 nt WGS in RRM
3. DRAGEN alignment & variant calling
4. Deep phenotyping and differential diagnosis
5. Sophisticated bioinformatics Pipeline
6. FDA permission to report WGS results before confirmation in life-threatening situations in not life threatening confirm via sanger or array
Earlier rapid comprehensive genetic testing

Timely specific care

Better patient outcomes
Less than 1 year of age and inpatient: 42

Non-Diagnostic: 24

Diagnosis: 18 (17)
Less than 1 year of age and inpatient: 42

Diagnosis: 18 (17)

Non-Diagnostic: 24

No change in care: 6 cases
<table>
<thead>
<tr>
<th>Presentation</th>
<th>Causative Gene</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cholestasis</td>
<td>SERPINA1</td>
</tr>
<tr>
<td>Seizure-like/spasm activity. Cluster of infantile spasms</td>
<td>SCN1A*</td>
</tr>
<tr>
<td>Apnea, cyanosis, posturing, abnormal EEG</td>
<td>Tetrasomy for 15q1.2q13.1</td>
</tr>
<tr>
<td>Cardiomegaly, heart block, prolonged QT interval, respiratory failure</td>
<td>POLR1C*</td>
</tr>
<tr>
<td>Myelomeningocele, congenital hydrocephalus</td>
<td>CELSR1</td>
</tr>
<tr>
<td>Preterm pulmonary atresia with intact ventricular septum with sinusoids, poor weight gain, feeding intolerance, recurrent pneumonia</td>
<td>ACTG2*</td>
</tr>
</tbody>
</table>
Less than 1 year of age and inpatient: 42

Diagnosis: 18 (17)

Change in management: 12

Non-Diagnostic: 24

No change in care: 6 cases

Unable to identify concrete cost changes: 6
<table>
<thead>
<tr>
<th>Presentation</th>
<th>Etiology</th>
<th>Outcome</th>
</tr>
</thead>
<tbody>
<tr>
<td>Infantile Spasms</td>
<td>GABRA1</td>
<td>Appropriate seizure medication</td>
</tr>
<tr>
<td>Hydrops fetalis, cardiomyopathy</td>
<td>TPM1</td>
<td>LSD and arhythmogenic cardiomyopathy excluded – heart transplant</td>
</tr>
<tr>
<td>Complex partial epilepsy</td>
<td>PCDH19</td>
<td>Switched to targeted therapy referred for research</td>
</tr>
<tr>
<td>IUGR, Complex cardiac disease, vertebral segmentation defect, GU anomalies</td>
<td>PHEX</td>
<td>Medication started to prevent rickets</td>
</tr>
<tr>
<td>Hirschprung’s disease, congenital ileal stenosis</td>
<td>RET</td>
<td>Comprehensive surgical approach, medication</td>
</tr>
<tr>
<td>Pulmonary atresia, osteopenia, frequent unexplained fevers.</td>
<td>NF1</td>
<td>Pre-emptive management of extra cardiac disease</td>
</tr>
</tbody>
</table>
Less than 1 year of age and inpatient: 42

Diagnosis: 18

Change in management: 12

Change in management possible to model: 6

Non-Diagnostic: 24

No change in care: 6 cases

Unable to identify concrete cost changes: 6

Prospective Change in care: 4

Prospective Retrospective Change in care: 1

Retrospective care model: 1
Term Neonate with Seizures

- Cord Gas Acidotic 7.12/64/11/-10
- Noted to be “jittery” after birth
- 16 hours – tonic clonic seizures
- Brought to our facility
- EEG – revealed burst suppression in addition to seizures consistent with Ohtahara Syndrome or early myoclonic encephalopathy.
- Treated with Phenobarbital, levetiracetam, topiramate
Isolate DNA
Prepare DNA for sequencing
Rapid genome sequencing
Infant with liver disease

Total DNA letters detected

140,000,000,000
Infant with liver disease

120,000,000,000

2,818,876,737

DNA letters of genome code assigned
Infant with liver disease

DNA letter changes from “normal”

140,000,000,000
2,818,876,737
4,805,162

68:31
Infant with liver disease

- DNA changes present in less 1 in 100 people

- 1,353,514
- 4,805,162
- 2,818,876,737
- 140,000,000,000
Infant with liver disease

DNA changes that could cause disease

1,188
1,353,514
4,805,162
2,818,876,737
140,000,000,000
DNA changes in genes causing the 1100 diseases

80:43

Infant with liver disease

1,188

2

Diagnosis

1,188

1,353,514

4,805,162

2,818,876,737

140,000,000,000
Term Neonate with Seizures

- Diagnosis Communicated to Clinical Team <96 hours
  - c.875T>C (p.Leu292Pro) in KCNQ2 – de novo
  - Doesn’t respond to first line therapy (keppra and phenobarbital)
- Patient received a change to appropriate medication
  - phenytoin & carbamazepine
- Seizures Promptly Stopped
  - “Early recognition of KCNQ2 encephalopathy followed by the most appropriate and effective treatment may be important for reducing…neurodevelopmental impairment” Pisano et al. Epilepsia 2015 56:685-91.
Clinical impact

Diagnosis allowed switch of seizure medication to those specific for genetic problem
Prompt control
Home 12 days after results (18 days after admission) in time for family Christmas
Neurologically normal at 6 months
Case Comparison Study

Seizing Baby 2015 (1 Year before WGS at RCH)

• Admitted to NICU
• Seizures, burst EEG
• Sample sent for standard genetic testing (Panel)
• Diagnosis: Ohtaharasysyndrome (\textit{KCNQ2 related})

Time to diagnosis: \textasciitilde6 weeks
## Est. cost savings from care avoided

<table>
<thead>
<tr>
<th>Case</th>
<th>Cost avoided</th>
<th>Cost saving</th>
</tr>
</thead>
<tbody>
<tr>
<td>KCNQ2</td>
<td>prolonged hospitalization</td>
<td>$153,000</td>
</tr>
<tr>
<td>ARID1B</td>
<td>prolonged hospitalization</td>
<td>$269,000</td>
</tr>
<tr>
<td>JAG1</td>
<td>surgery avoided</td>
<td>$36,000</td>
</tr>
<tr>
<td>NEB</td>
<td>surgery avoided</td>
<td>$10,000</td>
</tr>
<tr>
<td>ABCC8</td>
<td>prolonged hospitalization</td>
<td>$50,000</td>
</tr>
</tbody>
</table>
Est. savings that would have accrued if WGS had been offered earlier

<table>
<thead>
<tr>
<th>Case</th>
<th>Cost avoided</th>
<th>Cost saving</th>
</tr>
</thead>
<tbody>
<tr>
<td>NPC1</td>
<td>surgeries and hospitalization</td>
<td>$54,000</td>
</tr>
<tr>
<td>ARID1B</td>
<td>multiple surgeries, ECMO etc.</td>
<td>$1,410,000</td>
</tr>
</tbody>
</table>
First 95 cases

40% WGS genetic diagnostic rate (38/95)

5 additional diagnosis

- 2 reported incidental findings explain part of presentation
- 2 Infectious disease identified (1 by WGS only)
- 1 DNA duplication (reported on CMA first)
WHAT IS GOING TO HAPPEN NOW?
Partnership

1) improve the process of WGS (case identification, phenotyping, sequencing and bioinformatics technology, implementation of clinical management changes)

2) Establish the effectiveness and utility of WGS in the clinical context of acutely ill children.
2 Sequencing Protocols

NSIGHT2
- 2 Arm RCT
- WES vs WGS
- If meet criteria, funded
- For new babies only

Expanded Access
- Open to all children
- Ultra Rapid
- Limited number of tests
- Not automatically funded
- Funded by RCIGM
NSIGHT2

A prospective, randomized, controlled, blinded trial to evaluate the comparative outcomes and effectiveness (clinical utility, perceived family utility, and cost effectiveness) of two methods of rapid genomic sequencing (WGS and WES) and two methods of analysis (singleton probands and familial trios) in acutely ill infants.
Specific Aim 1. Determine if, and by how much, rapid WGS is associated with better outcomes than rapid WES in acutely ill infants. The null hypothesis is that both tests are equivalent. This may occur, for example, if the diagnosis rate is similar or the additional diagnoses from WGS do not alter clinical management.
Specific Aim 2. Determine if and by how much rapid WGS is associated with better perceived outcomes in parents of acutely ill infants than rapid WES in acutely ill infants. The null hypothesis is that both tests are equivalent. In addition, this will be the first study to examine the family-centered outcomes of rapid genomic sequencing, and particularly in Hispanic/Latino families.
Specific Aim 3. To compare diagnostic rates, time to diagnosis, and outcomes of rapid genome-wide sequencing compared with historical matched cases who received standard care before genome-wide sequencing was available. The null hypothesis is that genome wide sequencing does not increase diagnosis rate, time to diagnosis or outcomes.
Specific Aim 4. To compare diagnostic rates of singleton analysis versus familial analysis (ideally trio) and the cost-effectiveness of each testing method (rapid singleton WGS, rapid singleton WES, rapid trio WGS and rapid trio WES). The null hypothesis is that adding familial sequencing data does not significantly increase diagnostic yield.
Inclusion Criteria

Individual in whom one of the following criteria is met:

1. Acutely ill inpatient of less than 4 months of age and within 96 hours of admission

2. Acutely ill inpatient of less than 4 months of age and within 96 hours of development of an abnormal response to standard therapy for an underlying condition

3. Acutely ill inpatient of less than 4 months of age and within 96 hours of development of clinical feature or laboratory test value suggestive of a genetic condition

4. Biological relative of an infant enrolled in this study
Exclusion Criteria

Inpatients of greater than 4 months of age, or who do not meet any of the inclusion criteria, or with:
1. Neonatal infection or sepsis with normal response to therapy
2. Isolated prematurity
3. Isolated unconjugated hyperbilirubinemia
4. Hypoxic Ischemic Encephalopathy with clear precipitating event
5. Previously confirmed genetic diagnosis that explains their clinical condition (i.e. have a positive genetic test)
6. Isolated Transient Neonatal Tachypnea
7. Permission is unable to be obtained by a legal guardian or court-appointed representative within 96 hours of becoming eligible for enrollment.
8. Nonviable neonates- newborns less than 28 days of life with a modified code status (only full code patients may be enrolled).
Assessment Tools: Quantitative (published and/or validated instruments or modified versions of such instruments) and qualitative methods (researcher chart notes on consent process and interviews with selected participants at long-term follow-up).

<table>
<thead>
<tr>
<th>Variables/Instruments</th>
<th>Research Staff</th>
<th>Parents (both when possible)</th>
<th>Clinicians (APPs &amp; Physicians)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Enrollment</td>
<td>Post-Results (Short-term follow-up)</td>
<td>1-Year (Long-term follow-up)</td>
</tr>
<tr>
<td>Informed Consent Process (descriptive note)</td>
<td>X</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Highest Level of Education</td>
<td></td>
<td>X</td>
<td></td>
</tr>
<tr>
<td>Primary Language Spoken</td>
<td></td>
<td>X</td>
<td></td>
</tr>
<tr>
<td>Trust in Health Care System (Musa)</td>
<td></td>
<td>X</td>
<td></td>
</tr>
<tr>
<td>Adequacy of Consent (Item from Holmes-Rovner)</td>
<td>X</td>
<td>X</td>
<td>X</td>
</tr>
<tr>
<td>Utility/Benefits of Sequencing (based on Holm)</td>
<td></td>
<td>X</td>
<td>X</td>
</tr>
<tr>
<td>Satisfaction with Sequencing (based on Brennan)</td>
<td>X</td>
<td></td>
<td>X</td>
</tr>
<tr>
<td>Change in Management</td>
<td></td>
<td></td>
<td>X</td>
</tr>
<tr>
<td>Decisional Regret (Brehaut)</td>
<td>X</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
Clinician Assessment  
(Post-Results)

Patient Name: ____________________________

Clinician Credentials (MD, NNP, PA, etc.): ____________________________

Years of Experience of Clinician: ____________________________

Clinical Utility of Genomic Testing:  
1- Not Useful At All  2- Not Very Useful  3- Neutral  4- Useful  5- Very Useful

Genomic findings…(select all that apply):

- allowed avoidance of complications.
- enabled targeted treatment that may improve long-term outcomes.
- enabled improved communication of outcomes/expectations/prognosis with families.
- increased stress for family.
- increased confusion for family.
- increased confusion among clinical staff.
- enabled cessation of additional testing.
- required additional testing to confirm diagnosis.
- required additional testing to screen for comorbidities.
- did not lead to require additional testing.
- resulted in a diagnosis not fully understood at this time.
- Other: ____________________________

Change in clinical management (select all that apply):

- Surgical intervention added
- Surgical intervention removed
- Surgical intervention changed
- Medication added
- Medication removed
- Medication changed
- Diet changed
- New specialty service sought
- Prior specialty service no longer required
- New imaging sought
- Prior imaging cancelled
- New test ordered
- Prior testing cancelled
- Screening for additional comorbidities added
- Screening for additional comorbidities removed
- Palliative care initiated
- Palliative care withdrawn
- Other: ____________________________

Other care changes (select all that apply):

- Genetic Counseling to understand risks for the individual or family members recommended.
- Clinical monitoring of family members recommended.
- Genetic testing of family members recommended.
- Family planning counseling recommended.
- Patient eligible for new research study
- Patient and/or family members enrolled into a new research study
- Other: ____________________________
Acknowledgements

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