Genomics and its impact on rare diseases in acutely ill children – Next Generation Children Project

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Introduction

- Next Generation Children Project Co-ordinator
- Parent of a child with a rare condition
Rare Diseases in Numbers

- 1 in 2000 have a rare monogenic disease, (6%) of the population
- Account for 35% of deaths of children <1 yr
- 30% of children with a rare disease die by the age of 5 years
- Out of ~600,000 deliveries a year in the UK, 95,000 admitted to NICU or PICU
Genomic medicine initiatives around the world

Figure 1. Map of Currently Active Government-Funded National Genomic-Medicine Initiatives

Stark et al., AJHG 104, 13–20, January 3, 2019

https://www.genomicspolicy.org/
Newborn Sequencing in Genomic Medicine and Public Health (NSIGHT)

The Newborn Sequencing in Genomic Medicine and Public Health (NSIGHT) program explores the implications, challenges and opportunities associated with the possible use of genetic sequence information in the newborn period.
Project Rationale

Improving time to diagnosis has the potential to inform clinical management and treatment options and/or influence quality of life of infants and their family.
NICU & PICU in Addenbrooke’s Hospital

- NICU 42 cots ~896 admissions a year
- PICU 13 beds ~639 admissions a year
- 8-10% of all NICU/PICU admissions offered trio WGS

Photo: Jasper, courtesy of parents
Consenting and recruitment

- undecided
- discharged
- back to local hospital

Consented (45%)
- to find diagnosis
- to rule out genetic cause
- to help other families

Other (40%)
- not ready or too overwhelmed
- not genetic
- concern about genetic label

Declined (15%)

French et al 2019 Intensive Care Med
Classical pathway

- Critically ill child
- Paediatrics/Genetics/Neurology
- Genetic testing
  - Hypothesis 1 to n
  - No finding
  - Finding
    - uncertain significance
    - No diagnosis
    - Familial testing
      - Diagnosis & Recurrence risk

Rapid genomics

- Eligibility assessment & consent
- Trio WGS
  - finding
  - No finding
    - Re-analysis
    - GeneMatcher
  - Agnostic analysis
  - Diagnosis & recurrence risk

Research

Isabelle Delon
Trio analysis

Healthy parents

✔ Advantages
- Safe: Avoids most incidental findings
- Rapid: Limited number of variants to analyse
- Powerful: All genes are examined

✖ Limitations
- It may be difficult to get parental samples
- Variable penetrance conditions may be missed

Affected child

Isabelle Delon
Pipeline in continuous improvement

- Sample processing (5 days)
- Sequencing (9 days)
- MDT and variant interpretation (2 days)
- Variant interpretation, confirmation, and clinical reporting (10 days)

Clinical report: 1-2 weeks
Preliminary findings: 2-4 weeks

Courtney French
Family structure

- Trio (86%)
- Child only (2%)
- Child + 1 parent (10%)
- Trio + sibling (2%)

Dec 2016-June 2019

Courtney French
Age at recruitment

- 1 day – 17 years (23 y outlier)
- 320 families have been sequenced (919 samples)
- 90 children have received results to date

Dec 2016-June 2019

Courtney French
90 probands have had a result so far

- Inherited dominant: 5 (5.5%)
- De novo: 50 (56%)
- X-linked: 5 (5.5%)
- Compound heterozygous: 19 (21%)
- Homozygous: 7 (8%)
- Mitochondrial genome: 4 (4%)

Pathogenic: 49 (54%)
 Likely pathogenic: 27 (30%)
 VUS: 14 (16%)

Full: 82 (91%)
 Partial: 8 (9%)

French et al 2019 Intensive Care Med
Clinical utility: impact on clinical management

<table>
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<tr>
<th>Impact of diagnosis</th>
<th># cases</th>
<th>% cases</th>
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<tbody>
<tr>
<td>Specialist care</td>
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<tr>
<td>Informed existing specialised care</td>
<td>9</td>
<td>29%</td>
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<tr>
<td>Initiated new specialised care</td>
<td>15</td>
<td>48%</td>
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<tr>
<td>Modification of treatment</td>
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<tr>
<td>Recurrence risk</td>
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<tr>
<td>Significant recurrence risk</td>
<td>12</td>
<td>39%</td>
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<tr>
<td>Lethal condition</td>
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<td>Diagnosis explained death</td>
<td>5</td>
<td>16%</td>
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<tr>
<td>Supportive/ palliative care</td>
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<td>19%</td>
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<th>infants (1-24 months)</th>
<th>Children 2-16 years</th>
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Summary & Next Steps

- Rapid turnaround of trio whole genome sequencing can be integrated into existing healthcare infrastructure
- Rare genetic diseases are common in critically ill children
- Neonatal presentations are commonly different from classical descriptions
- Need to explore families’ experiences of genomic testing & its impact
- Expanding to other sites

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