Genomics in NBS: are we ready for it?

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ACCE framework

http://www.cdc.gov/genomics/gtesting/ACCE/
What is the goal of NBS?

- Wilson and Jungner criteria\(^1\), revisited in the genomic age\(^2,3\)

<table>
<thead>
<tr>
<th>Benefits for the child</th>
<th>Potential/future benefits for the child</th>
<th>Benefits for the family</th>
<th>Benefits for society</th>
</tr>
</thead>
<tbody>
<tr>
<td>Highly penetrant, childhood onset, treatable/medically actionable</td>
<td>Adolescent/adult onset (predictive), variable penetrance, medically actionable</td>
<td>Reproductive (carrier screening) /health</td>
<td>Research, knowledge</td>
</tr>
</tbody>
</table>

Untreatable?

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Genome sequencing of newborns?


“the ever-widening gap between what is technologically possible and the services available is creating pressure to introduce or expand screening programmes, often before adequate safeguards and regulatory frameworks are in place.”

**Box 2. Synthesis of emerging screening criteria proposed over the past 40 years**

- The screening programme should respond to a recognized need.
- The objectives of screening should be defined at the outset.
- There should be a defined target population.
- There should be scientific evidence of screening programme effectiveness.
- The programme should integrate education, testing, clinical services and programme management.
- There should be quality assurance, with mechanisms to minimize potential risks of screening.
- The programme should ensure informed choice, confidentiality and respect for autonomy.
- The programme should promote equity and access to screening for the entire target population.
- Programme evaluation should be planned from the outset.
- The overall benefits of screening should outweigh the harm.
Some issues around genomics in NBS

- Genomic sequencing
  - How much to sequence? (targeted gene panel/WES/WGS)
  - What to analyse? (targeted vs everything)
  - How much to report? (clinically significant ± VUS, vs everything)

- Consent
  - Written/informed?
  - Education/resources

- Sample and data storage
  - What to retain? (sample ± data – which data?)
  - For how long?
  - Who has access to the data?

Cost/resources, privacy, confidentiality, discrimination etc.
Research around genome sequencing of newborns

- Goldenberg et al – USA
- Surveyed 1539 parents
- Randomised to hear about one of these 2 scenarios
- Also asked about factors important in making decision
- And asked “Imagine that your state wants to store the information from your child’s whole genome sequence and use it for health-related research. Researchers would NOT be able to identify your child from the information.”
- Minimal other info given

<table>
<thead>
<tr>
<th>WGS - state newborn screening scenario</th>
<th>WGS - pediatrician’s office scenario</th>
</tr>
</thead>
<tbody>
<tr>
<td>Imagine that you have a newborn baby. Shortly after birth, your child had blood collected to test for serious diseases that affect infants. These tests are done as part of each state’s newborn screening program.</td>
<td>Imagine that you have a newborn baby. You take your child to the doctor for a routine check-up. During the visit, your child’s doctor lets you know that you can get your child’s whole genome sequenced. Testing would require a small sample of blood be taken.</td>
</tr>
<tr>
<td>Your state newborn screening program now offers you the chance to get your child’s whole genome sequenced as part of the program. You would receive the results and would not have to pay for the testing. You can decide whether or not you want the information to be a part of your child’s medical record.</td>
<td>You would receive the results and would not have to pay for the testing. You can decide whether or not you want the information to be a part of your child’s medical record.</td>
</tr>
<tr>
<td>How interested would you be in getting your newborn baby’s whole genome sequenced?</td>
<td>How interested would you be in getting your newborn baby’s whole genome sequenced?</td>
</tr>
</tbody>
</table>

Figure 1 Language from the newborn WGS scenarios presented to participants. WGS, whole-genome sequencing.

Goldenberg et al Parents’ interest in whole-genome sequencing of newborns. Genetics in Medicine, 2014, 16:78-84
## Findings

<table>
<thead>
<tr>
<th>Level of interest in:</th>
<th>WGS (%)</th>
<th>Research (%)</th>
<th>WGS (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Definitely interested</td>
<td>36</td>
<td>25.1</td>
<td>31</td>
</tr>
<tr>
<td>Somewhat interested</td>
<td>38.3</td>
<td>39.1</td>
<td>39</td>
</tr>
<tr>
<td>Not interested</td>
<td>18</td>
<td>24</td>
<td>22</td>
</tr>
<tr>
<td>Definitely not interested</td>
<td>8</td>
<td>11.8</td>
<td>8</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Factor influencing interest in WGS</th>
<th>Very important (%)</th>
<th>Very important (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Accuracy of the test results</td>
<td>74</td>
<td>68</td>
</tr>
<tr>
<td>Preventing or decreasing my child’s chances of developing disease</td>
<td>67</td>
<td>66</td>
</tr>
<tr>
<td>Privacy of the test results</td>
<td>64</td>
<td>60</td>
</tr>
<tr>
<td>Use of the test results to discriminate against my child</td>
<td>56</td>
<td>57</td>
</tr>
<tr>
<td>Choosing medical treatments that might be more effective for my child</td>
<td>57</td>
<td>54</td>
</tr>
<tr>
<td>My ability to understand the test results</td>
<td>56</td>
<td>54</td>
</tr>
<tr>
<td>Use of the test results for research without my permission</td>
<td>51</td>
<td>59</td>
</tr>
<tr>
<td>Worry that I might find out that my child is at a higher risk of developing certain diseases than other people</td>
<td>40</td>
<td>46</td>
</tr>
<tr>
<td>The need to draw blood from my child</td>
<td>N/A</td>
<td>24</td>
</tr>
</tbody>
</table>

Goldenberg et al Parents’ interest in whole-genome sequencing of newborns. Genetics in Medicine, 2014, 16:78-84
Ethical and psychosocial issues: consent in NBS

- Voluntary (Australia) vs mandatory (eg USA)

- Parents as decision-makers for their child
  - weight and limits, eg zone of parental discretion

- Concerns around:
  - Future autonomy of child
  - Child’s right to an open future (predictive/carrier testing)
  - Perceived child vulnerability
  - Parent-child bonding
  - Self and partner blame
Some options put forward in USA considering legalities of consent/data retention

King and Smith. Whole-genome screening of newborns? The constitutional boundaries of state newborn screening programs. Pediatrics, 137:s1, 2016

- Target or confirm only primary conditions
  - Discard remaining data

- Target only primary conditions
  - Give parents option to receive full genomic data in raw form

- Obtain informed consent
  - Offer parents both genomic sequence and analysis
2013: NIH funded 4 research programs in USA around use of genomic sequencing in newborn healthcare

<table>
<thead>
<tr>
<th>Organisations</th>
<th>University of North Carolina, Chapel Hill</th>
<th>Brigham &amp; Women’s Hospital/Harvard, Boston &amp; Baylor College, Houston</th>
<th>University of California, San Francisco</th>
<th>Children’s Mercy Hospital, Kansa City</th>
</tr>
</thead>
<tbody>
<tr>
<td>Study</td>
<td>Exome sequencing of newborns: healthy vs affected with usual NBS cond’ns (NC NEXUS project)</td>
<td>Genomic sequencing of newborns (BabySeq project)</td>
<td>Exome sequencing of usual NBS cond’ns plus extra cond’ns</td>
<td>Genomic sequencing in NICU (neonatal intensive care units)</td>
</tr>
<tr>
<td>Aims</td>
<td>Identify best ways to return results to doctors and parents</td>
<td>Genomic data available as a resource for parents &amp; doctors during infancy &amp; childhood to inform health care</td>
<td>Value of additional info from exome sequencing to existing NBS - improved care &amp; treatment?</td>
<td>Examine benefits &amp; risks of using rapid genomic sequencing technology in this NICU population</td>
</tr>
</tbody>
</table>
NC NEXUS
North Carolina Newborn Exome Sequencing for Universal Screening

- Semi-quantitative metric to help define medical actionability, then plotted against predicted age of onset

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<thead>
<tr>
<th></th>
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</thead>
<tbody>
<tr>
<td>(1)</td>
<td>Childhood onset, medically actionable</td>
<td>(2)</td>
<td>Childhood onset, <em>not</em> medically actionable</td>
</tr>
<tr>
<td>(3)</td>
<td>Adult onset, medically actionable (± carrier status)</td>
<td>(4)</td>
<td>Adult onset, <em>not</em> medically actionable</td>
</tr>
</tbody>
</table>

Sub-group randomised:
Choose options 2 ± 3 ± carrier status

- Discrete choice experiment – parent preferences
- Decision-aid (tablet optimised, web-based application)
- Psychosocial outcomes

Lewis et al, Supporting parental decisions about genomic sequencing for newborn screening: the NC NEXUS decision aid. Pediatrics, 137:S1, 2016
Research in Australia?

• Parental views obtained from surveys (n=359) and interviews

Themes:
- parents of healthy children quite positive about genome sequencing of newborns for conditions that meet classical criteria (ie medically actionable)
- also interested in screening for predisposition conditions and untreated, but interest variable depending on certainty of information and for adult-onset
- if information is known (to lab/clinician), want to receive it at time of testing
- parents of children with Duchenne muscular dystrophy or spinal muscular atrophy, less certain about wanting to have known about these conditions at birth, even though they experienced a ‘diagnostic odyssey’ and would have preferred an earlier diagnosis

• concerned about impact on parent-child bonding, valued a period of ‘normality’ with their child –conditions for which there is currently no cure

Students: Wong, Lawton, Atkinson, Cloney and Taylor (Genetics Education and Health Research group, MCRI)
Research in Australia?

• Need more research around genomics and NBS

• eg Melbourne Genomics Health Alliance
  – Patient preferences regarding return of genomic results (not NBS)

• New flagship
  – Babies identified through newborn screening hearing program, parents offered panel of genes associated with deafness plus others?? (Amor and Halliday)

• Research needs to include ethical and psychosocial aspects as well as analytical and clinical validity, and health economics
Genomics and NBS: are we ready for it?

50 years of newborn screening in Victoria
GOD... THE HUMAN GENOME CODE'S BEEN UNRAVELLED

DAMN HACKERS!!! NOW, I HAVE TO CHANGE THE PASSWORD