Facilitating Choice and Maximizing Benefit in Return of Secondary Results from Exome Sequencing

Holly K. Tabor, PhD
Associate Professor, Division of Bioethics, Department of Pediatrics
Adjunct Associate Professor, Department of Bioethics and Humanities
The Integrated Ethicist in Genomics Research

- What important ethical challenges arise out of the development and implementation of new genetic technologies in research and clinical care?
- A novel approach to identify, characterize and address emerging ethical challenges
- The ethicist is a key and ongoing member of the research team, participating in study design, implementation, execution and analysis
- Provide real time ethics consultation on a range of issues (e.g., informed consent, data sharing, recruitment)
- Identify areas for parallel empirical ethics research and develop and implement projects to address them
- Work collaboratively to address normative and policy issues
The Integrated Ethicist in Genomics Research and Clinical Care

- Center for Clinical Genomics (UW)
  - First family to undergo ES/WGS, first Mendelian condition solved by ES
  - Developed and implemented 1st informed consent form/process for ES/WGS
  - Developed and implemented 1st study of informed consent, family perspectives on ES/WGS

- NHLBI Exome Sequencing Project (ESP)
  - Chair of ELSI Working Group, managed dbGaP review
  - Empirical project on number of returnable variants in ESP6500

- NHGRI Centers for Mendelian Genomics (CMG)
  - Co-Chair of Regulatory Group, managing consent and data sharing review
  - Coordinate CMG response to NIH proposed data sharing policy

- Seattle Children’s Clinical Exome Sequencing Review Committee
  - Ethics representative and participant in review of all cases sent for exome sequencing
Innovative Approaches to Returning Results in Exome and Whole Genome Sequencing Studies

- The My46 Study: NHGRI R01 study, part of NHGRI Clinical Sequencing Exploratory Research (CSER) Consortium, 2011-2014
- Recruit and reconsent ~150 participants from Mendelian and complex disease studies whose exomes have already been sequenced
- Allow participants to use My46, a web-based tool for self-guided results management, to select result preferences for a range of secondary results
- Randomize return of secondary results through either My46 or genetic counselor
- Assess outcomes over 12 months
Research Questions

• What kinds of secondary (incidental) results do people want to receive from exome and whole genome sequencing (ES/WGS) and why or why not?

• What kinds of results do they not want to receive and why?

• How do people characterize the relative benefits and harms of ES/WGS secondary results?

• What does this information suggest about policies and practices for management of ES/WGS results?

• How can we improve the process of return and translation of genetic results from research and clinical care?
Self-directed results management with My46
Choose among incidental results organized by type of trait.

Set preferences for return of individual results. Change preferences for return at any time.
Key Innovations of My46

• Allows individuals to:
  • Learn about what kinds of results are available, benefits and risks of return
  • Set preferences for results return and change preferences over time
  • Securely review results at their convenience and as frequently as desired
  • Generate reports to share with doctors/family members, improving translation
  • Query a genetic counselor via e-mail, phone, LSV at any time
Key Innovations of My46

• Is scalable for the volume and nature of results, new results
• Can be deployed easily in large or remote populations
• Standardizes and centralizes result information for participants in lay language
• Allows care providers to focus on:
  • Interpretation (what does a result mean for individual or family)
  • Translation (how does a result change surveillance, prevention strategies, or medical management)
Methods

• Semi-structured phone interviews:
  • 42 participants before preference setting
  • 51 participants after preference setting

• Topics:
  • Previous experiences with genetic results
  • Results wanted and results not wanted
  • Feelings and expectations about results
  • Potential positive and negative aspects of results
  • Potential impact of results
  • Experience of using My46

• Interviews transcribed and coded by two coders using Atlas.ti
• Codes summarized and cross-cutting themes generated through team consensus
## Methods

<table>
<thead>
<tr>
<th>Role</th>
<th>Count (Percentage)</th>
<th>Female</th>
<th>Age range (mean)</th>
<th>Self-reported “white”</th>
<th>Living w/ partner or married</th>
<th>BA/BS or higher</th>
<th>Family annual income &gt;$75,000</th>
</tr>
</thead>
<tbody>
<tr>
<td>Role</td>
<td></td>
<td>Female</td>
<td>Age range (mean)</td>
<td>Self-reported “white”</td>
<td>Living w/ partner or married</td>
<td>BA/BS or higher</td>
<td>Family annual income &gt;$75,000</td>
</tr>
<tr>
<td>Parent of minor</td>
<td>85 (59%)</td>
<td>111 (77%)</td>
<td>18-81 (45) yrs</td>
<td>138 (96%)</td>
<td>118 (83%)</td>
<td>76 (53%)</td>
<td>73 (60%)</td>
</tr>
<tr>
<td>Adult participant</td>
<td>59 (41%)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Condition</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Autism</td>
<td>16 (11%)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Brain malformation</td>
<td>44 (31%)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Craniofacial</td>
<td>7 (5%)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Cystic Fibrosis</td>
<td>9 (6%)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Dilated cardiomyopathy</td>
<td>17 (12%)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Limb malformation</td>
<td>22 (15%)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Thoracic aortic aneurysm/dissection</td>
<td>27 (19%)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Other</td>
<td>2 (1%)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
Secondary Results Preferences

- Majority (79%) selected all secondary result categories
  - 83% of parents, 75% of adults

- Average number of secondary result categories refused:
  - Parents: 1.8 (most commonly refused category: ancestry)
  - Adults: 3.5 (most commonly refused category: brain and nervous system)

- Interviews with 51 participants
  - 92% expressed optimism and excitement
  - 31% volunteered that they were not worried or anxious
  - 22% expressed ambiguity and nervousness about possible “bad” results, but said that optimism and benefits outweighed concerns
  - Two parents refused secondary results to defer until adulthood (carrier status) or avoid worry in childhood (cancer)
Results Wanted: Anything and Everything

• “Anything and everything that comes out of this study that has to do with any part of his DNA, chromosome, genome, all of it.” (1030)

• “To me I just want as much information as I, as I can get...And I know you’re probably trying to isolate which types are more valuable, but you know the reality is, is I can’t necessarily tell whether something that seems invaluable today won’t be valuable later on.” (1045)

• “We just want more information. There’s not really a negative thing about it...anything that is wrong with him or you know anything that we get back wouldn’t necessarily be bad news. It would be helpful to know anything.” (1002)
Long Term Planning for Children

• “Knowledge is power and autism is this great mystery, and our daughter is especially a great mystery.” (1052)

• “Our son is nonverbal, so we have the added trick of he can’t tell us how he’s feeling, so, yeah, if he would develop symptoms, we would have no idea. And so there’s that variable is he’s, he’s kind of a bit of a puzzle, we’re reading tea leaves now, so if there is diagnostic information we can get to tell us stuff that he can’t tell us, that’s to our benefit.” (1095)

• “Because it’s for a dependent child and I would really have to think about you know estate planning and his future needs when we’re not here, I think we would really want to know everything. We could use the help of a crystal ball I guess.” (1095)
The Tradeoff is Worth it

• “I think the primary negative is that if, if I were to have information that may indicate that I have some risks for some factor in the future, and I could certainly see it causing me anxiety, whether I want it or not....*I think the tradeoff with having the knowledge and being able to be aware for myself and for, and for my children, it’s worth it, so.*” (1034)

• “I mean at this point in our lives, we already got so many challenges in front of us and what’s a few more? You know we might as well just figure it all out from the beginning. ‘Cause we already have a, you know, a challenging road with him...*I’m willing to work through it.*” (1006)

• “I guess we’d do just like what we’ve done her whole life is *we deal with it when it comes.*” (1053)
Impact of Scholarship/Research

- Notable Grants Received
  - R01HG006618, Innovative approaches to returning results from exome and whole Genome Sequencing, NHGRI, NIH, (PI); 8/6/2011 – 8/31/2015

- Notable Papers to date in 2014
  - Pathogenic variants for Mendelian and complex traits in exomes of 6,517 European and African Americans: implications for the return of incidental results. AJHG, 2014; 95: 183-93. (1st author)
  - “We don’t know her history, her background”: Adoptive parents’ perspectives on whole genome sequencing results. J Genet Couns, Epub ahead of print. (last author)
  - Attitudes of non-African American focus group participants toward return of results from exome and whole genome sequencing. Am J Med Genet, 2014, Epub ahead of print. (last author)
Future Directions

• Completing The My46 Study
  • Analyze survey and interview data about short and medium term responses and translation
  • Assess changes to result preferences over time
  • Explore parents’ response to secondary results information about their children, how and whether they share results with their children

• Studying My46 for results management in other settings/contexts:
  • Return/management of targeted clinical genetic test results (Fragile X)
  • Return/management of primary research results in other populations/studies (Joubert Syndrome, PCORI Application Spring 2015)
  • Return/management of primary and secondary results from clinical exome sequencing (NHGRI R01 Application Fall/Winter 2014)
Acknowledgements

• University of Washington
  • Michael Bamshad
  • Wylie Burke
  • Peter Byers
  • Seema Jamal
  • Debbie Nickerson
  • Aditi Shankar
  • Joon-Ho Yu

• Seattle Children’s Research Institute
  • Julia Crouch

• University of Utah
  • Karin Dent

• Funding
  • NHGRI/NIH: R01HG006618
  • NHGRI/NIH: U54HG006493
  • NHGRI/NIH: P50HG003374
  • NHGRI/NIH: U01HG007307