ABSTRACT

Return of Genetic Research Results: An Analysis of Participant Preferences

A thesis presented to the Graduate Program in Genetic Counseling

Graduate School of Arts and Sciences
Brandeis University
Waltham, Massachusetts

By Chelsea Kois, MPH

Growing discussion on advancing genetic technologies, including whole exome sequencing (WES) and whole genome sequencing (WGS), has raised concerns regarding the types of genetic information that they can yield. A major area of concern regards incidental findings (IFs), or results that do not directly relate to the primary indication for genetic testing but could be revealed. IFs became a topic of discussion upon the release of the American College of Medical Genetics (ACMG) guidelines that recommended that significant and actionable IFs be reported to patients. Literature to determine whether patients consenting to WES or WGS wish to receive all of the results or only a subset of them has been sparse. We performed a review of research charts including consent forms that allowed participants to choose the types of results they wished to receive from the study in which they were participating. To supplement the review of these records, we sent an online survey to the same group of research participants. We found that 88% of participants requested all of their genetic information including IFs, while 12% did not. This 12% included both participants who chose only to receive information that could explain
the cause of the condition for which they enrolled in the study as well as participants who declined all results. Some would argue that an individual’s autonomy might be infringed upon if they are not provided with the choice to opt out of certain types of findings when taking advantage of evolving genetic testing options. Thus, our findings suggest that practices and policies related to WES or WGS should consider individuals who may not wish to know all of their possible results.

Keywords: whole exome sequencing, whole genome sequencing, incidental findings, patient autonomy
# TABLE OF CONTENTS

Introduction ...................................................................................................................... 1

Methods ............................................................................................................................ 6

- Chart Review ................................................................................................................. 6
- Online Survey ............................................................................................................... 7

Results ............................................................................................................................. 9

- Chart Review ................................................................................................................. 9
- Online Survey ............................................................................................................... 11

Discussion ....................................................................................................................... 16

Limitations ....................................................................................................................... 20

Conclusion ....................................................................................................................... 21

References ....................................................................................................................... 23

Appendices .................................................................................................................... 24
LIST OF TABLES

Table 1……………………………………………………………………………………….10

Distribution of the choices made by adult participants

Table 2……………………………………………………………………………………….11

List of eight families in which one individual’s choice differs from the others

Table 3……………………………………………………………………………………….12

Demographics of survey respondents

Table 4……………………………………………………………………………………….13

Distribution of choices made by survey respondents regarding the return of genetic research results about their child and themselves

Table 5……………………………………………………………………………………….14

Survey responses regarding the experience of deciding how much genetic information to receive

Table 6……………………………………………………………………………………….15

List of verbatim free text responses from survey participants
INTRODUCTION

Genetic technologies have evolved such that it is now possible for an individual to provide a single blood sample and receive back an immense amount of genetic information. Clinical genetic tests have progressed from a basic karyotype and single gene analysis to detailed microarray chromosome analysis and sequencing of approximately 20,000 genes simultaneously. However, not every individual offered genetic testing feels prepared or even wants to know all of the possible information. This issue is compounded when considering how much more information can be generated with current testing options, and the uncertainty of what the information might reveal (Bernhardt, 2013).

Whole exome sequencing (WES) is defined as sequencing of the coding regions, or exons, of all the genes in each human cell. Like many genetic technologies, it was first used as a tool in genetic research for screening a large number of genes at once before becoming available in the clinical setting. Now, rather than obtaining information from the hundreds to thousands of base-pairs or nucleotides that make up a typical single gene, WES provides sequencing information on some 30 million base pairs at once.

Despite the large amount of information provided with this technique, the coding region of human DNA represents only 1-2% of the genome, the entirety of our genetic information. Whole genome sequencing (WGS) differs from WES in that WGS includes noncoding regions
and untranslated regions and thus sequences a significantly larger amount of genetic material. WES and WGS are currently clinically available, however their utilization is often restricted to patients who have either exhausted all other genetic testing options or for whom ordering multiple smaller-scale genetic tests would be less economical.

An issue that arises from large-scale sequencing is that gene variants unrelated to the indication for testing can be revealed, including genetic predispositions to cancer or cardiovascular disease (Green et al., 2013). These types of results are called incidental findings (IFs).

Recognizing the emerging issue and possibilities of such IFs, the American College of Medical Genetics and Genomics (ACMG) released the 2013 policy statement “ACMG Recommendations for Reporting of Incidental Findings in Clinical Exome and Genome Sequencing” (Green et al., 2013). Although these are guidelines and are therefore not mandatory, they recommend that certain actionable conditions like hereditary cancer syndromes and genetic cardiovascular problems be reported to the patient regardless of his or her age or desire to be made aware of that information. For example, people who carry a mutation in either the \( BRCA1 \) or \( BRCA2 \) gene have an increased risk for developing cancer, particularly breast and ovarian cancers. This information is considered actionable because there are both surgical options that would significantly reduce the risk of developing cancer as well as screening options to identify tumors in early stages.

The ACMG guidelines promote the idea that laboratories have a duty to report certain IFs. Furthermore, the ACMG has suggested that patients should not necessarily be extensively counseled about their preferences regarding receiving IFs because it would impose a large
burden on the provider and would overwhelm the patient (Green et al., 2013). This idea has been contested because it denies patients their right to provide informed consent to sequence certain genes. Additionally, it preempts the right of minors to provide informed consent to receive information about adult-onset conditions (Allyse and Michie, 2013; Bookman et al., 2006; Wolf, Annas and Elias, 2013). The general population has demonstrated reservations regarding obtaining this information about their children (Bombard et al., 2014).

Patients who are determined in their search for a cause, treatment, or cure for their or their child’s symptoms, may be lead to the option of WES by their provider. The perspectives and preferences of these patients to whom large-scale sequencing has been offered clinically, have not been studied. Thus, we currently do not know whether they would want to be told about IFs. There have, however, been studies that have utilized focus groups to describe the types of genetic results that healthy individuals might choose to receive (Lakes et al., 2013; Wright et al., 2013). Furthermore, there have not been studies published on what research participants are choosing when given the option to receive or decline incidental results in the context of WES or WGS in the research setting.

To provide further insight into the issue of returning various types of genetic results, we focused on a population of individuals who enrolled into a neurogenetics research study when they or a close family member had been diagnosed with a developmental brain condition. This study is ongoing in the laboratory of Dr. Christopher A. Walsh at Boston Children’s Hospital where the genetics of human brain development are studied by enrolling individuals affected with brain malformations, microcephaly, familial epilepsy, autism, and intellectual disability, as well as their affected and unaffected family members. Participants or their legal guardians are
given an informed consent document that provides information about the study, including the benefits and limitations of enrollment. They are subsequently consented into the study after discussion with research study staff, typically a genetic counselor.

With the introduction of whole exome and whole genome sequencing technology to their research strategy, the Walsh Laboratory study investigators adapted the research consent form to reflect the possibility that variants unrelated to the reason the individual or family was recruited into the study might be identified. As part of the consent process, individuals are informed that the research lab might use large-scale sequencing technologies that examine all of their genes, to try to identify causative or pathogenic gene variants that underlie the condition in their family. Enrollees are educated about the general types of findings and that some results may be determined to be related to their family’s diagnosis and others may be unrelated to the diagnosis that lead to their enrollment. However, only findings determined by the researchers to be medically significant are eligible to be returned. The currently approved consent document allows for individual autonomy by permitting participants some control over the type of genetic information they receive as a result of their participation in the study. Participants are provided with these three options to choose from:

1. **I do not** want to learn about any results found about me/ my child. Please **do not** contact me.

2. I want to learn only about results found about me/ my child that could explain the condition that was the reason for my/ my child’s research participation (e.g. a brain malformation, epilepsy, mental retardation or autism).
3. I want to learn about results found about me/my child, including results that could (1) explain my/my child’s condition (e.g. a brain malformation, epilepsy, mental retardation or autism) and/or (2) be the cause of another disorder or disease that could significantly affect my/my child’s health or medical care but is unrelated to the reason for my/my child’s research participation (Walsh, 2013).

The aim of the present study is to explore research participants’ choices and experiences regarding return of results including IFs in the context of large-scale gene sequencing in an attempt to gain better understanding of what genetic information people are interested in learning about themselves and their children. Results of this and future studies may help guide revisions to the ACMG and possibly other guidelines addressing return of genetic results and IFs.
METHODS

We conducted a systematic review of research participant charts from the Walsh Laboratory study, Genetics of Epilepsy and Cognitive Disorders, at Boston Children’s Hospital [Research Chart Review] as well as a survey of the same group of research participants [Online Survey]. Both the Boston Children’s Hospital Committee on Clinical Investigation and the Brandeis University Institutional Review board approved this study.

Research Chart Review

Our cohort included only those who provided informed consent after the study consent document was amended to reflect the introduction of large-scale sequencing and referenced the three options for results return as previously detailed. Thus research charts were reviewed for individuals enrolled from January 2010, when the amended consent form was implemented, through October 2013. In addition to the consent forms, we reviewed the medical information and correspondences collected in the research record. We included non-English speaking participants, as they signed consent forms translated in their native languages and/or had been enrolled with the assistance of an interpreter.

The information pulled from the research charts included the choice for return of results documented on the consent form, demographic data including the participants’ sex, age at consent, race, ethnicity, the year of consent, participant occupation, and diagnosis. We also recorded whether the participant was personally affected or unaffected by the condition for
which the family was recruited, as well as the number of affected members of each family. Lastly, we noted whether each participant had been seen by a clinical genetics professional (geneticist or genetic counselor) and whether there was evidence that clinical genetic testing had been performed prior to enrollment. Data were analyzed using SPSS® version 22.0.0 to conduct quantitative statistical analyses.

**Online Survey**

We developed an anonymous online Qualtrics® survey tool to gain adult participants’ perspectives regarding the return of their research results. Questions addressed the participants’ demographics and others were posed to help gain insight into the experience surrounding participant choice of the return of results. They were asked to rate their perceived level of difficulty, stress, and confidence in making the choice about their results by reading several statements and responding on a Likert scale with one of the following choices: strongly disagree, disagree, neutral, agree, or strongly agree. The Likert statements used were based on the Decisional Conflict Scale (O’Connor, 1995). Other questions asked respondents to report whether they felt they had enough information and support to make this choice (Appendix A). All other questions were multiple-choice, some with the option of including free text.

The cohort of research participants for the survey included participants of the same Walsh Laboratory study who enrolled in the timeframe described above and for whom an email address was available. These individuals were invited to participate in the online survey through an email explaining that the survey was anonymous and could not be linked to their original participation in the Walsh Laboratory study. It also indicated that by clicking the link to begin the survey, they were providing their informed consent. Recipients were encouraged to share the
email and survey with other adult family members who had also enrolled in the original Walsh Laboratory study, since usually only one email per family was on file. The introduction also informed participants that if they chose to complete the survey, they would have the option to be entered into a raffle for one of three $50 Amazon gift cards (Appendix B). We sent a single reminder email 13 days later to all eligible participants except those who had already been entered into the raffle (Appendix C). The survey was open to participants for a total of 18 days.
RESULTS

Research Chart Review

We conducted a chart review on 140 families with a total of 420 study participants who were enrolled between January 2010 and October 2013. Ten families (35 individuals) were excluded due to incomplete records, resulting in a complete data set of 130 families with a total of 385 participants.

Of the 385 participants whose consents and information were reviewed, 148 (38%) were affected by the neurogenetic condition that prompted enrollment in the study and 237 (62%) were unaffected. Males represented 51% of the affected group and 44% of the unaffected group. The mean age of affected individuals was 7.2 years and the mean age of unaffected individuals was 32.9 years with 44% of these between the ages of 30 and 39. White non-Hispanic individuals comprised 88% of the study sample. We identified occupation information for 77 of the 203 unaffected adult participants.

Regarding the choice of genetic research results return, 340 participants (88%) checked the box for option 3, indicating they wanted to receive “all” types of medically significant genetic findings, 43 participants (11%) requested to learn only about medically significant results that were related to the reason the family was initially offered study enrollment, and the remaining 2 individuals (1%) did not wish to have any results returned. We found that this distribution of choices was similar between adults choosing for themselves, or on their affected
or unaffected child’s behalf (Table 1). When the choice each participant made was compared with the year of enrollment, age, sex, race, and diagnosis, there were no statistically significant correlations.

Table 1. Distribution of the choices made by adult participants

<table>
<thead>
<tr>
<th>Choices made for affected children</th>
<th>Frequency</th>
<th>Percent</th>
</tr>
</thead>
<tbody>
<tr>
<td>No results</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Some results</td>
<td>17</td>
<td>11.5</td>
</tr>
<tr>
<td>All results</td>
<td>131</td>
<td>88.5</td>
</tr>
<tr>
<td>Total</td>
<td>148</td>
<td>100</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Choices made for unaffected children</th>
<th>Frequency</th>
<th>Percent</th>
</tr>
</thead>
<tbody>
<tr>
<td>No results</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Some results</td>
<td>2</td>
<td>6.1</td>
</tr>
<tr>
<td>All results</td>
<td>31</td>
<td>93.9</td>
</tr>
<tr>
<td>Total</td>
<td>33</td>
<td>100</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Adults choosing for themselves</th>
<th>Frequency</th>
<th>Percent</th>
</tr>
</thead>
<tbody>
<tr>
<td>No results</td>
<td>2</td>
<td>1.0</td>
</tr>
<tr>
<td>Some results</td>
<td>24</td>
<td>11.8</td>
</tr>
<tr>
<td>All results</td>
<td>178</td>
<td>87.3</td>
</tr>
<tr>
<td>Total</td>
<td>204</td>
<td>100</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>All choices made</th>
<th>Frequency</th>
<th>Percent</th>
</tr>
</thead>
<tbody>
<tr>
<td>No results</td>
<td>2</td>
<td>0.5</td>
</tr>
<tr>
<td>Some results</td>
<td>43</td>
<td>11.2</td>
</tr>
<tr>
<td>All results</td>
<td>340</td>
<td>88.3</td>
</tr>
<tr>
<td>Total</td>
<td>385</td>
<td>100</td>
</tr>
</tbody>
</table>

*“Choice” refers to the option the adult participant chose regarding the types of results he wanted for himself or for his child. “No results” represents choice 1 on the Walsh Laboratory consent form that indicates that the participant did not want to know any of his genetic results. “Some results” represents choice 2 on the consent form that indicates that the participant only wanted to receive information that was relevant to the condition for which he enrolled in the Walsh Laboratory study. “All results” represents choice 3 on the consent form and indicates that the participant wanted to receive all types of results including medically significant IFs.

In two families (1 and 2), parents chose to receive all of their own results but only the relevant results for their children. Within four families (3-6), the parents were discordant for the types of genetic results they requested. The fathers of three families (3, 4 and 5) requested only the relevant results about themselves whereas all results including IFs will be returned to the affected children and their mothers. The father of Family 6 requested more information about
himself than the mother or their child. Extended relatives in two more families (7 and 8) chose to receive less information than the rest of their family (Table 2).

**Table 2.** List of eight families in which one individual’s choice differs from the others

<table>
<thead>
<tr>
<th>Family</th>
<th>Participant</th>
<th>Choice</th>
<th>Family</th>
<th>Participant</th>
<th>Choice</th>
</tr>
</thead>
<tbody>
<tr>
<td>Family 1</td>
<td>Affected</td>
<td>Some</td>
<td>Family 5</td>
<td>Affected and Mother</td>
<td>All</td>
</tr>
<tr>
<td></td>
<td>Mother</td>
<td>All</td>
<td></td>
<td>Father</td>
<td>Some</td>
</tr>
<tr>
<td>Family 2</td>
<td>Affected</td>
<td>Some</td>
<td>Family 6</td>
<td>Affected and Mother</td>
<td>Some</td>
</tr>
<tr>
<td></td>
<td>Mother and Father</td>
<td>All</td>
<td></td>
<td>Father</td>
<td>All</td>
</tr>
<tr>
<td>Family 3</td>
<td>Affected and Mother</td>
<td>All</td>
<td>Family 7</td>
<td>Affected and 4 family members</td>
<td>All</td>
</tr>
<tr>
<td></td>
<td>Father</td>
<td>Some</td>
<td></td>
<td>Maternal aunt</td>
<td>Some</td>
</tr>
<tr>
<td>Family 4</td>
<td>Affected and Mother</td>
<td>All</td>
<td>Family 8</td>
<td>Affected and 11 family members</td>
<td>All</td>
</tr>
<tr>
<td></td>
<td>Father</td>
<td>None</td>
<td></td>
<td>Paternal grandfather</td>
<td>None</td>
</tr>
</tbody>
</table>

**Online Survey**

Of the 130 families included in the chart review, 10 were not native English-speakers and thus were excluded since the survey and invitation email were in English. The invitation emails including the link to the survey were sent to 97 families who have previously provided an email address to the research study. Thirteen of these emails were returned as “not deliverable” possibly due to inactive account status or an incorrect email address so emails were successfully sent to 84 participants.

Of the 84 successfully sent emails, 31 responses were received, for about a 37% response rate. Approximately 84% of respondents were female; 90% were married; 90% were
white/Caucasian; 71% reported an annual household income of at least $75,000; and 52% had a graduate education (Table 3).

We found that the survey represented a higher proportion of females than the review of research data. Both cohorts included predominately Caucasian individuals. The age group of 30-39 years represented the highest proportion of unaffected individuals in both the review of research records (44%) and the survey (45%).

**Table 3. Demographics of survey respondents**

<table>
<thead>
<tr>
<th></th>
<th>Frequency</th>
<th>Percent</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Sex</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Male</td>
<td>5</td>
<td>16.1</td>
</tr>
<tr>
<td>Female</td>
<td>26</td>
<td>83.9</td>
</tr>
<tr>
<td><strong>Age</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>18-29</td>
<td>4</td>
<td>12.9</td>
</tr>
<tr>
<td>30-39</td>
<td>14</td>
<td>45.2</td>
</tr>
<tr>
<td>40-49</td>
<td>8</td>
<td>25.8</td>
</tr>
<tr>
<td>50-59</td>
<td>5</td>
<td>16.1</td>
</tr>
<tr>
<td><strong>Marital Status</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Single</td>
<td>2</td>
<td>6.5</td>
</tr>
<tr>
<td>Married</td>
<td>28</td>
<td>90.3</td>
</tr>
<tr>
<td>Divorced</td>
<td>1</td>
<td>3.2</td>
</tr>
<tr>
<td><strong>Race</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>White/Caucasian</td>
<td>30</td>
<td>96.7</td>
</tr>
<tr>
<td>Asian</td>
<td>1</td>
<td>3.2</td>
</tr>
<tr>
<td><strong>Annual Income</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>&lt;$25,000</td>
<td>3</td>
<td>9.7</td>
</tr>
<tr>
<td>$25,000-39,999</td>
<td>2</td>
<td>6.5</td>
</tr>
<tr>
<td>$40,000-49,999</td>
<td>1</td>
<td>3.2</td>
</tr>
<tr>
<td>$50,000-74,999</td>
<td>3</td>
<td>9.7</td>
</tr>
<tr>
<td>$75,000-99,999</td>
<td>6</td>
<td>19.4</td>
</tr>
<tr>
<td>&gt;$100,000</td>
<td>16</td>
<td>51.6</td>
</tr>
<tr>
<td><strong>Geographical Setting</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Urban</td>
<td>9</td>
<td>29.0</td>
</tr>
<tr>
<td>Suburban</td>
<td>14</td>
<td>45.2</td>
</tr>
<tr>
<td>Rural</td>
<td>8</td>
<td>25.8</td>
</tr>
<tr>
<td><strong>Highest Education</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>High school</td>
<td>4</td>
<td>12.9</td>
</tr>
<tr>
<td>College/University</td>
<td>11</td>
<td>35.5</td>
</tr>
<tr>
<td>Graduate School</td>
<td>16</td>
<td>51.6</td>
</tr>
</tbody>
</table>

Participants were asked to recall their choice regarding possible return of research findings when they enrolled in the Walsh Laboratory study. Approximately 83% of respondents
reported that they chose to receive all types of their child’s genetic information and 10% could not recall which choice they made. When indicating the choice they made regarding the types of genetic results they requested about themselves, 93% requested all of their results (Table 4). Of those who indicated that they made this choice on behalf of their child, 69% made the decision with the child’s other parent while the remaining 31% reported that the child’s mother alone chose how much information to receive about the child. We compared the choice that respondents made for receipt of their own genetic information as well as their child’s to the year of enrollment, age group, sex, race, level of education, income, geographical setting, and marital status; there were no statistically significant correlations.

Table 4. Distribution of choices made by survey respondents regarding the return of genetic research results about their child and themselves

<table>
<thead>
<tr>
<th></th>
<th>Frequency</th>
<th>Percent</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>For their child</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>No results</td>
<td>1</td>
<td>3.4</td>
</tr>
<tr>
<td>Some results</td>
<td>1</td>
<td>3.4</td>
</tr>
<tr>
<td>All results</td>
<td>24</td>
<td>82.8</td>
</tr>
<tr>
<td>I don’t remember</td>
<td>3</td>
<td>10.3</td>
</tr>
<tr>
<td>Total</td>
<td>29</td>
<td>100</td>
</tr>
<tr>
<td><strong>For themselves</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>No results</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Some results</td>
<td>2</td>
<td>6.7</td>
</tr>
<tr>
<td>All results</td>
<td>28</td>
<td>93.3</td>
</tr>
<tr>
<td>I don’t remember</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Total</td>
<td>31</td>
<td>100</td>
</tr>
</tbody>
</table>

There were a total of 6 participants (19%) who were discordant for the choice they made for themselves and for their child. Two of these parents requested more information about
themselves than they did for their children, and one participant chose to receive less information about herself than for her child. These three participants represented 10% of the survey sample. The remaining three participants indicated that they could not recall the choice they made for their child’s results, but that they wanted all of the information about themselves.

The survey asked participants to respond to a series of Likert statements. The objective of the Likert statements was to understand the participants’ experience with choosing the types of results they wanted for themselves and their child. At least 80% of participants responded positively for each statement. The framing of each question was considered in this calculation such that “agree” and “strongly agree” responses to a positively framed statement are positive responses. Similarly, “strongly disagree” and “disagree” responses to a negatively framed statement are also positive responses. Respondents also generally felt as positively about making the decision for their child’s results as they did for their own (Table 5).

Table 5. Survey responses regarding the experience of deciding what genetic research results to receive

<table>
<thead>
<tr>
<th>Statement</th>
<th>Strongly Disagree (%)</th>
<th>Disagree (%)</th>
<th>Neither Agree nor Disagree (%)</th>
<th>Agree (%)</th>
<th>Strongly Agree (%)</th>
<th>Positive Response (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>For child</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>I had enough information to choose</td>
<td>0 (0)</td>
<td>1 (3.4)</td>
<td>2 (6.9)</td>
<td>10 (34.5)</td>
<td>16 (55.2)</td>
<td>89.7</td>
</tr>
<tr>
<td>I felt confident with my choice</td>
<td>0 (0)</td>
<td>1 (3.3)</td>
<td>1 (3.3)</td>
<td>8 (26.7)</td>
<td>18 (60)</td>
<td>86.7</td>
</tr>
<tr>
<td>The decision was easy for me</td>
<td>0 (0)</td>
<td>1 (3.7)</td>
<td>4 (14.8)</td>
<td>6 (22.2)</td>
<td>16 (59.3)</td>
<td>81.5</td>
</tr>
<tr>
<td>I had enough support from others to make this choice</td>
<td>0 (0)</td>
<td>1 (3.4)</td>
<td>4 (13.8)</td>
<td>10 (34.5)</td>
<td>14 (48.3)</td>
<td>82.8</td>
</tr>
<tr>
<td>I felt stressed making this decision</td>
<td>16 (55.2)</td>
<td>11 (37.9)</td>
<td>1 (3.4)</td>
<td>1 (3.4)</td>
<td>0 (0)</td>
<td>93.1b</td>
</tr>
<tr>
<td><strong>For self</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>I had enough information to choose</td>
<td>0 (0)</td>
<td>1 (3.4)</td>
<td>1 (3.4)</td>
<td>11 (37.9)</td>
<td>16 (55.2)</td>
<td>93.1</td>
</tr>
<tr>
<td>I felt confident with my choice</td>
<td>0 (0)</td>
<td>1 (3.4)</td>
<td>1 (3.4)</td>
<td>8 (27.6)</td>
<td>19 (65.5)</td>
<td>93.1</td>
</tr>
<tr>
<td>The decision was easy for me</td>
<td>0 (0)</td>
<td>2 (8.0)</td>
<td>3 (12.0)</td>
<td>7 (28.0)</td>
<td>13 (52.0)</td>
<td>80.0</td>
</tr>
<tr>
<td>I had enough support from</td>
<td>0 (0)</td>
<td>1 (3.4)</td>
<td>3 (10.3)</td>
<td>13 (44.8)</td>
<td>12 (41.4)</td>
<td>86.2</td>
</tr>
</tbody>
</table>
We received a total of nine free-text responses. Three were excluded because they were comments regarding the original Walsh Laboratory study and were not relevant to the current study. Overall, the remaining six respondents indicated that they prefer to have as much information as possible. One respondent noted that she wanted to have all of her information but that her husband only wanted to know about genetic information relevant to their daughter’s condition (Table 6).

Table 6. List of verbatim free text responses from survey participants

<table>
<thead>
<tr>
<th>Free text responses, verbatim</th>
</tr>
</thead>
<tbody>
<tr>
<td>1   Of course we wanted to know. Im [sic] not quite sure why anyone would choose not to know</td>
</tr>
<tr>
<td>2   We are a family who is continually searching. We want to learn all that we can about our children's disorder and possible future risk.</td>
</tr>
<tr>
<td>3   I always said my daughter held the answer to the puzzle. She proved us right and indeed, she showed us how to piece the puzzle pieces to save others' lives. That was her mission and mine to carry through on her behalf.</td>
</tr>
<tr>
<td>4   I feel like the more information I have the better. I want to know and understand the cause of my daughter's disability.</td>
</tr>
<tr>
<td>5   After waiting so incredibly [sic] long for a diagnosis for my daughter, PVNH, I wanted as much info as possible.</td>
</tr>
<tr>
<td>6   While I chose C, my husband chose B. He does not want to know about any condition he may have, unless it affects our daughter's condition.</td>
</tr>
</tbody>
</table>
DISCUSSION

Historically, research protocols, due to their non-clinical nature, did not offer return of individual results. The ethical issue of the “duty to disclose” clinically significant results has been raised and thus researchers began offering a binary yes/no option to participants (Heaney, Tindall, Lucas and Haga, 2010). Evolving philosophies about providing research participants with their results and the introduction of WES and WGS have changed the landscape of results return dramatically and lessons learned from the research experience may help guide clinical applications of results disclosure in the setting of WES and WGS.

The current study, comprised of a chart review and online survey, attempted to better understand the experiences of research participants who had previously been counseled about the possibility of receiving unexpected genetic results. They were given three options regarding the types of information they wanted to receive from the potential use of large-scale sequencing technologies in the research setting. The study design did not permit linking of the anonymous survey responses to the relevant research chart on file to compare responses, as such linkage would have made the survey respondents identifiable. Therefore, we collected demographics as part of the chart review and compared them with the self-reported information from the survey to determine if the survey respondents accurately represented the larger study sample from the review of research data.
The survey cohort was not representative of the general population when considering income and education level. We found that 71% of our participants reported an annual household income greater than $75,000 and more than half of our participants had a graduate degree. These measures differ from the median household income in the United States, which is approximately $51,000, as well as from the percentage of the US population with a graduate degree, which is 10% (US Census Bureau, 2012). Income and education level information were not available for the research record review, thus we do not know if our survey group represented the larger cohort for income and education. The survey population has a clear selection bias toward wealthy, well-educated individuals. A larger study would be necessary in order to determine whether this bias has an impact on our results.

We calculated the percentage of families that had one person who chose, or whose parent chose on his behalf, to receive different types of results than the rest of the family. These families were discordant for the choices they made and accounted for 6% of families of the larger chart review cohort and 9% in the survey group. While the majority of families were concordant in their choices, this subset of families cannot be ignored. It is possible that families are typically concordant for the choices they make due to shared values or family pressure to make a particular choice. The adult research participants each signed an individual consent document, however many families were consented as a group. It is not possible with the current study to determine what individuals would choose in the absence of familial influences.

We did not identify significant correlations between the types of genetic results that participants chose to receive and their age, race, income, level of education, marital status, geographical setting, year of enrollment, number of affected individuals in their family, or
diagnosis of the affected child. This is likely due to the small sample size of the study, particularly of the survey group.

Research chart review revealed that the vast majority of participants (88%) marked option 3 on their consent form, indicating that most participants were interested in receiving as much genetic information as possible. When the sample was stratified into groups for affected children, unaffected children, and adults, the results of each group remained similar to the overall distribution of choices. Overall, approximately 88% of people wanted all of their results and 12% did not.

Our results clearly demonstrate that the majority of participants opted to receive all of the information they could, however the 11% that chose to know only about the relevant results and the 1% that declined all results should not be disregarded. This combined 12% constitutes a significant proportion of people whose personal choices regarding return of IFs would not be respected by the ACMG guidelines. Given our results, one might expect that almost 1 in 8 clinical patients undergoing WES would receive information about themselves or their children that they do not want according to the ACMG guidelines.

Following the annual ACMG meeting in March of 2014, the ACMG board revised the 2013 recommendations on the return of IF results to individuals subjected to WES or WGS in the clinical setting. The updated guidelines came in part because of a member survey in which clinicians raised opinions favoring more flexibility in result reporting. The ACMG continues to promote that IFs are important and should be included in WES or WGS results, however it recommends that patients are given the opportunity to opt out of such results at the time of consent (ACMG, 2014). This recent update to the clinical guidelines strengthens our position
that both research participants and clinical patients benefit from having autonomy over their genetic information. The results of our survey provide evidence that not everyone who has been consented for WES or WGS wants to receive IF results.
LIMITATIONS

We recognize that our study has several limitations. Although we reviewed 385 consent forms, the study sample lacked diversity. The sample of the Walsh Laboratory study participants that met our criteria for review of their research record consisted primarily of Caucasian individuals. Additionally, the survey cohort included wealthier and more highly educated individuals than we would expect from the general population. The number of participants who chose not to receive all of their results was small, thus statistically significant correlations could not be made (i.e. the effect of age on the choice that was made).

We also acknowledge that our investigation was based on research records. It is not clear whether the distribution of the choices research participants make regarding the return of genetic results in a research study would definitively mirror choices made in a clinical setting. Another limitation of the current study is that we were not able to explore participants’ experiences or expectations with more depth. Future studies might include interviews to gain additional perspective.
CONCLUSIONS

The current study has shown that the majority of individuals participating in a genetic research study request to receive results that are clinically significant and actionable when given the choice. However, 12% of individuals undergoing appropriate genetic counseling choose to not be informed about results unrelated to the reason their family enrolled into the study, even though some of those incidental findings may be considered medically significant. The desires and wishes of this minority should be recognized and honored. Our findings underscore the relevance of respecting an individual’s decision-making related to the type of information revealed by genetic testing.

By providing individuals with some informed control over the return of their genetic results, researchers, clinicians, and policy statements promote individual autonomy, a fundamental bioethical principle. This autonomy is infringed upon by guidelines recommending that all large-scale sequencing tests, including WES and WGS, report on actionable incidental findings without regard to individual choice or preference. The relevance of our study is highlighted by the fact that the ACMG’s update on returning results from WES or WGS now provides the option for patients to opt out of IFs (ACMG, 2014). Basic science findings and techniques are often initially uncovered in the research setting. Thus, we hope that lessons learned by better understanding the choices and experiences of research participants regarding the return of their genetic results will inform the implementation of practices in the clinical setting. Our study proves that a blanket policy on returning IFs may not be ideal. It is reassuring
that the ACMG membership apparently agrees and supports that an individualized approach is preferred and that the ACMG board recognizes that their recommendations may require refinement and reconsideration over time.
ACMG 2014. ACMG Updates Recommendation on "Opt Out" for Genome Sequencing Return of Results.


APPENDICES

APPENDIX A: Online Survey Questions

Thank you for your interest in this online survey.

Your responses are very important to us. Please answer the questions to the best of your understanding and memory.

As noted in the recruitment notice, the survey should take 10-15 minutes to complete. All responses are anonymous and cannot be linked back to your original consent form or responses. You may skip questions or exit the survey at any time.

To show our appreciation for your participation, three (3) participants will be chosen at random to receive an Amazon Gift Card worth $50. Directions to enter into the raffle will be provided at the end of the survey.

Thank you!

Part A – for ALL participants

For the questions below, please choose ONE (1) answer.

1. What is your gender?
   Male
   Female

2. What is your age group?
   18-29
   30-39
   40-49
   50-59
   60-69
   70-79
   80+

3. What is your marital status?
   Single
   Married
   Separated
   Divorced
   Widowed

4. What is your race?
   White/Caucasian
Black
Asian
Latino/Latina
Native American/Alaska Native
Native Hawaiian/Pacific Islander
Other: (text)
I choose not to answer

5. What is your average annual household income range?
   Less than $25,000
   $25,000-$39,999
   $40,000-$49,999
   $50,000-$74,999
   $75,000-$99,999
   $100,000+

6. In what geographical setting do you live?
   Urban
   Suburban
   Rural

7. What is your highest level of education completed?
   Less than High School
   High School
   College/University (i.e. Associates or Bachelor’s degree)
   Graduate school (i.e. Master’s, Ph.D, MD, etc.)

8. Prior to enrolling in the studies of the Walsh Lab, had you/your child undergone genetic testing?
   Yes
   No
   I’m not sure

Part B – for all participants

The rest of this survey relates to your participation in the research study on the genetics of brain development, titled The Genetics of Epilepsy and Cognitive Disorders, at Boston Children's Hospital.

1. For which of the following reasons did you enroll in the study about the genetics of brain development? (Check all that apply)
   For the benefit of research
   To find a genetic cause or contribution for a condition that I have
   To find a genetic cause or contribution for a condition that my child has
   To find a better treatment for my family’s condition
   To find a cure for my family’s condition
   My/my child's doctor suggested it to me
   To find out potential health risks to future children
Part C - If “Self” is NOT selected, THEN:

This section is to be completed by adult individuals who were involved in providing consent for participation on behalf of their child.

1. When you enrolled in the genetic research study, you were given the following information:

“During the course of this research, we might find the gene(s) causing the disorder of brain development in your child. Although we do not intend to, we might also find a gene that causes a different disorder or uncovers a risk of developing a disorder or disease in the future that is unrelated to the reason for your child’s participation in this study.”

You were then given three choices related to amount of genetic information you were willing to receive back, should results become available. These choices were:

A. I do not want to learn about any results found about my child. Please do not contact me.
B. I want to learn only about results found about my child that could explain the condition that was the reason for my child’s research participation (e.g. a brain malformation, epilepsy, mental retardation or autism).
C. I want to learn about results found about my child, including results that could (1) explain my child’s condition (e.g. a brain malformation, epilepsy, mental retardation or autism) and/or be the cause of another disorder or disease that could significantly affect my child’s health or medical care but is unrelated to the reason for my child’s research participation.

Please keep in mind it is possible that individuals may make different choices for their children compared to the choices they make for their own information.

1. What was the choice made for your CHILD? (Choose one as detailed above)
   A
   B
   C
   I don't remember
2. Study participants under the age of 18 (or who have impaired functioning below that age) are required to have a parent complete the consent form for study enrollment. With this in mind, who made the choice for return of results, at outlined above, on behalf of your child?
   The child’s mother primarily made the decision
   The child’s father primarily made the decision
   Both parents made the decision together
   I don’t remember
   Other: (free text)

3. Please rate how strongly you agree or disagree with the following 5 statements relating to how much genetic information you agreed to possibly learn about research results for your CHILD:

<table>
<thead>
<tr>
<th>Strongly Disagree</th>
<th>Disagree</th>
<th>Neutral</th>
<th>Agree</th>
<th>Strongly Agree</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>2</td>
<td>3</td>
<td>4</td>
<td>5</td>
</tr>
</tbody>
</table>

a. I had enough information to choose how much genetic information I wanted to learn about my CHILD.

b. I felt confident with my choice.

c. This decision was easy for me.

d. I felt stressed in making this choice.

e. I had enough support from others to make this choice.

**ALL respondents:**

*This section should be completed by adult participants who completed a consent form for their own participation, either as a parent or based on their own diagnosis.*

“During the course of this research, we might find the gene(s) causing the disorder of brain development in you/your child. Although we do not intend to, we might also find a gene that causes a different disorder or uncovers a risk of developing a disorder or disease in the future that is unrelated to the reason for your/your child’s participation in this study.”

You were then given three choices related to amount of genetic information you were willing to receive back, should results become available. These choices were:

A. I do not want to learn about any results found about me. Please do not contact me.
B. I want to learn only about results found about me that could explain the condition that was the reason for my/my child’s research participation (e.g. a brain malformation, epilepsy, mental retardation or autism).
C. I want to learn about results found about me, including results that could (1) explain my/my child’s condition (e.g. a brain malformation, epilepsy, mental retardation or autism) and/or be the cause of another disorder or disease that could significantly affect my health or medical care but is unrelated to the reason for my/my child’s research participation.

1. What was the choice made for YOU? (Choose one)
   A
   B
   C
   I don't remember

2. Please rate how strongly you agree or disagree with the following 5 statements relating to how much genetic information you agreed to possibly learn about research results for YOURSELF:
a. I had enough information to choose how much genetic information I wanted to learn about MYSELF.

b. I felt confident with my choice.

c. This decision was easy for me.

d. I felt stressed in making this choice.

e. I had enough support from others to make this choice.

3. Did you utilize any outside resources (such as friends, the internet, medical providers) to better understand which choice was best for your family?
   No, I made the decision on my own.
   Yes

4. Which outside resources did you utilize to understand which choice was best for your family? (Check all that apply)

   Online search
   Asked questions of the study staff at the time of providing informed consent
   Asked my/my child’s doctor
   Consulted with my child’s other parent
   Consulted with my spouse/partner who is not related to my child
   Asked a different family member
   Asked a friend
   Other (free text)

Free text: Is there anything else you would like to share about your experience with making a choice regarding return of genetic research results? (Comment box)

You have reached the end of the survey.
Thank you for your participation!

See below for raffle information.

If you would like to be entered into the raffle for a $50 Amazon gift card, please send an email to walshresearch@childrens.harvard.edu with “raffle” in the subject line. You do not need to include anything in the body of the email. The three (3) winners will be selected at random and will receive the e-gift card by email no later than April 1, 2014.

Your email address is not linked to your survey responses. All information will remain secure and will only be used to send you the gift card if you win the raffle. Thank you!

Lastly, if you have any questions about your participation in the original study, please feel free to contact one of the Walsh Lab research coordinators. You may contact a coordinator by email at walshresearch@childrens.harvard.edu or by phone at 617-919-4371 or 617-919-2865.
Sincerely,

Chelsea Kois, MPH
Masters Degree Candidate
Genetic Counseling Program
Brandeis University

Brenda Barry, MS & Jennifer Partlow MS
Research Coordinators
Walsh Laboratory
Boston Children’s Hospital
APPENDIX B: Recruitment Email

Hello,

My name is Dr. Christopher Walsh, a neurologist and research physician at Boston Children’s Hospital [BCH] who directs a lab dedicated to understanding the genetics of brain development. I and my coordinators, Brenda Barry and Jennifer Partlow, are working with Chelsea Kois, a graduate student at Brandeis University, on a supplemental research project related to the experiences of individuals enrolled in our genetic studies. We would like to request your participation in this short survey that will also form the basis of Ms. Kois’ thesis for her Master’s degree in Genetic Counseling.

The goal of the current study is to understand what information people participating in genetic research agree to learn about when they are offered options for results that may be returned. We hope that understanding the choices and experiences of participants will improve the way that genetic research and tests are managed in the future.

You are being contacted because your family previously enrolled in my laboratory’s genetic research study, The Genetics of Epilepsy and Cognitive Disorders. At the time that you enrolled you were informed that there was no timeline or guarantee for results becoming available from this particular study. However, you were also provided with the opportunity to make a choice between three options for receiving results, should they become available. We are interested in understanding the factors involved in how you made your decision regarding return of results.

This study will consist of a one-time online survey questionnaire, which should take approximately 10-15 minutes to complete. It has been approved by the Institutional Review Boards at Boston Children’s Hospital and Brandeis University. You will first be asked multiple-choice questions about demographics and then you will be asked about your experiences regarding information related to return of research results. You will receive one follow up email from us to remind you about this survey.

Your participation will not be linked back to nor will it influence your involvement in the original research study on the genetics of brain development. Participation in this study will not affect your/your child’s medical care. Your participation is completely voluntary and anonymous, and you may exit the survey at any time. To show our appreciation for your time, you will be given the option to enter a raffle to win an Amazon gift card worth $50 once you complete the survey. This will require that you share your email address, but your email will NOT be able to be linked to your survey responses and will be kept completely confidential.

Because we may not have on file separate email addresses for all adult members of families that participated in the study, you may forward this email to, or otherwise invite participation of, other adult relatives who enrolled in the original study on the genetics of brain development.

By clicking the link below, you have acknowledged that you have read the above information and you consent to participate in the survey.

Click here to take the survey!

Best regards,

Christopher Walsh, MD, PhD
Chief, Division of Genetics
Principal Investigator, Walsh Laboratory
Boston Children’s Hospital
Chelsea Kois, MPH  
Masters Degree Candidate  
Genetic Counseling Program  
Brandeis University

Brenda Barry, MS & Jennifer Partlow MS  
Licensed & Certified Genetic Counselors & Research Coordinators  
Walsh Laboratory  
Boston Children’s Hospital
APPENDIX C: Reminder Email

Hello,

My name is Dr. Christopher Walsh, a neurologist and research physician who directs a lab dedicated to understanding the genetics of brain development. Two weeks ago, I sent you an email requesting your voluntary participation in an online survey. This email serves only as a reminder that the survey will be closing in 2 weeks. If you have already completed the survey, thank you for your participation and please disregard this email.

If you have not completed the survey, the link is provided below. Please remember that your participation is completely voluntary and confidential and you may exit the survey at any time. To show our appreciation for your time in participating, at the end of the survey you will be given the option to enter a raffle to win an Amazon gift card worth $50. This will require that you share your email address, but your email will NOT be able to be linked to your survey responses and will be kept completely confidential.

Click here to take the survey!

Best regards,

Dr. Christopher Walsh
Chief, Division of Genetics
Boston Children’s Hospital

Chelsea Kois, MPH
Masters Degree Candidate
Genetic Counseling Program
Brandeis University

Associated Personnel
Walsh Laboratory
Boston Children’s Hospital