WHOLE EXOME SEQUENCING: ASSESSING
WHAT PATIENTS WANT TO KNOW

A Project Presented to the Faculty
of
California State University, Stanislaus

In Partial Fulfillment
of the Requirements for the Degree
of Master of Science in Genetic Counseling

By
Kelly Hitch
May 2013
CERTIFICATION OF APPROVAL

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ABSTRACT

Whole exome sequencing is a powerful new genetic test that uses next generation sequencing technology to provide information on nearly all functional, protein-coding regions in an individual’s genome. Due to the vast amount of information and incidental findings that can be generated from this technology, patient preferences regarding consent and return of results must be investigated. The perspectives of 19 adult patients who consented to undergo whole exome sequencing were explored through semi-structured interviews. All participants were previously clinically diagnosed with Lynch syndrome, but received uninformative negative Lynch syndrome genetic results through traditional molecular testing methods. Nearly all participants believed that the benefits of receiving all possible results generated from whole exome sequencing outweighed the undesirable effects. The majority of participants conveyed the sentiment that relative to coping with a cancer diagnosis, information generated from whole exome sequencing would be manageable. Participants’ experience with Lynch syndrome also seemed to impact their notions of genetic determinism, tolerance for uncertain results, and family communication plans. Participants would prefer to receive whole exome sequencing results in person from a genetic counselor or medical geneticist so that an expert could help explain the meaning and implications of the potentially large quantity and range of complicated results. These results underscore the need to study various populations with regard to the clinical use of whole exome sequencing in order to effectively and empathetically communicate the possible implications of this new technology and return results.
INTRODUCTION

Whole exome sequencing is a powerful new genetic test that uses next generation sequencing to provide information on nearly all functional, protein-coding regions, referred to as “exons,” in an individual’s genome. Since most Mendelian disorders originate from mutations in exons, whole exome sequencing has the potential to uncover many more underlying genetic mutations than conventional genetic testing can encompass (Bamshad et al., 2011; Haimovich, 2011). With recent declines in price and increasing numbers of Clinical Laboratory Improvement Amendments (CLIA)-approved laboratories offering the testing clinically, whole exome sequencing has already begun to revolutionize genetic testing (Jamal et al., 2013). Thus far, whole exome sequencing has successfully identified underlying mutations for rare, monogenic syndromes (Choi et al., 2009; Ng et al., 2010), unveiled complex features of more common monogenic disorders (Grillo et al., 2013), and accelerated diagnostic discoveries (Worthey et al., 2011).

In the near future, whole exome sequencing is likely to become a routine clinical procedure and perhaps even a first-tier test for patients who have suspected genetic diseases but have not yet been diagnosed with a particular condition. An illustrative example is Lynch syndrome, the most common cause of hereditary colorectal cancer caused by loss-of-function mutations or deletions in any of seven known mismatch repair genes (MLH1, MSH2, MSH6, MSH3, PMS1, PMS2, and EPCAM) (Ku, Cooper, Iacopetta, & Roukos, 2012; Schneider, 2012). Colorectal and other Lynch-associated cancers that arise due to defects in one of these mismatch
repair genes often exhibit specific tumor findings, particularly microsatellite instability high (MSI-H) and absence of one or more mismatch repair proteins based on immunohistochemistry (IHC) results (Robinson et al., 2007; Schneider, 2012). Individuals can be diagnosed with Lynch syndrome based on family history criteria in addition to such clinical findings, or through genetic testing. However, the sensitivity for conventional genetic testing for the genes causative of Lynch syndrome is only around 70%, leaving many families without accurate ways to establish who is at risk now or in the future (Robinson et al., 2007). Effective screening and prevention techniques (e.g. colonoscopy, prophylactic hysterectomy and bilateral salpingo-oophorectomy, and esophagogastrroduodenoscopy (EGD)) have been established for individuals with Lynch syndrome that decrease morbidity and mortality rates while cutting down on cost (Burt et al., 2010).

In families without known genetic mutations but where Lynch syndrome cannot be ruled out, the surveillance recommendation is for all family members to follow stringent screening guidelines (Lindor et al., 2006; Mvundura, Grosse, Hampel, & Palomaki, 2010). Because Lynch syndrome screening guidelines are intensive, it is both time and cost-effective to correctly diagnose individuals so that appropriate screening is enacted. Additionally important is avoiding the risks and burdens of unnecessary cancer screening for those individuals found to not have deleterious Lynch syndrome genetic mutations.

Whole exome sequencing has the capability to uncover the unknown, underlying genetic causes for Lynch syndrome and other genetic diseases, allowing
for powerful public health applications and implications. If utilized earlier in the diagnostic odyssey, whole exome sequencing has the capability to diagnose many conditions more rapidly than previous genetic testing technologies, thus ensuring better and more cost-effective patient care and treatment. Even when identifying conditions without available treatment, whole exome sequencing can provide reassurance and answers for patients and their families.

Yet, with such transformative implications, whole exome sequencing can also generate so-called “incidental” or “secondary” genetic findings that may be unrelated to the condition or phenotype under investigation. In an individual exome, it is estimated that whole exome sequencing will find several thousands of variants, which must be filtered to deduce only those variants of clinical significance (Bamshad et al., 2011; Singelton, 2011). Variants of clinical significance can include carrier status for recessive disorders, later-onset genetic conditions, and predispositions to cancer or common diseases such as diabetes, obesity, and coronary artery disease. In addition, a challenging number of variants of unknown significance or mutations in genes of unknown significance are expected to result from any sequenced exome. Due to the likelihood of variants of unknown significance, incidental findings and the vast amount of results generated, exome sequencing findings, can also pose many more genetic implications for a patient’s closely related family members than traditional genetic testing.

These predicted outcomes not only create a perplexing and uncharted scope of issues to deal with, but also present more immediate questions as to how and what
results clinicians should report back to patients, who should be responsible for pre-
and post-test counseling sessions and patient follow-up, and who should have access
to a patient’s whole exome or genome sequencing results. Although
recommendations for consenting to genetic testing and disclosing genetic test results
to patients and research participants are readily available, most were not crafted with
exome sequencing and the scope of its possibilities in mind (Cassa et al., 2012;
McGuire, Caufield, & Cho, 2008). Currently, there are few published guidelines that
address proper consent and the use of clinical whole exome sequencing, the return of
whole exome sequencing results including incidental findings, and the ethical
concerns that this new technology brings up. The American College of Medical
Genetics and Genomics (ACMG) issued a policy statement in 2012 (ACMG Board of
Directors, 2012) regarding the clinical application of genomic sequencing that
focuses on when to use whole exome or genome sequencing, and more recently in
March 2013 issued recommendations as to when and what types of incidental
findings to report (Green et al., 2013).

Although broad recommendations are well intentioned, providers must still
evaluate the utility of these guidelines with regard to special circumstances of each
patient and use their clinical judgment in adhering to or deviating from these
recommendations. Providers are still unsure about how and when to implement
clinical genomic sequencing. Discordance among genetic specialists about whether
specific incidental findings in clinical whole exome and genome sequencing should
be reported to patients or not suggests that even professionals may not be fully prepared to deal with the implications of this new technology (Green et al., 2012).

At present, each laboratory performing whole exome sequencing sets its own policy for reporting incidental findings, and different labs have significantly different whole exome sequencing consent forms (Ambry Genetics, 2012; Baylor College of Medicine Medical Genetics Laboratories, 2013; Emory Genetics Laboratory, 2012). As clinical whole exome sequencing becomes more routine, laboratory consent forms and policies regarding the return of results may need to become more standardized to help clinicians and patients navigate through the massive amounts of data generated from the sequencing results. Furthermore, providing structure and guidance can facilitate smoother and more consistent pre- and post-test counseling sessions by genetic professionals. In order to address the vast amount of potential results generated from whole exome sequencing with patients prior to testing, scalable categorical frameworks have been proposed to organize types of genomic sequencing results on consent forms. For instance, Berg, Khoury, & Evans (2011) recommended categorizing genomic sequencing results and incidental findings into “bins,” separating known deleterious variants that have immediate clinical utility from clinically valid variants that are not directly actionable from variants of unknown or no clinical significance.

To assist in developing guidelines and protocol standards for consenting and counseling patients for whole exome sequencing, research to assess patient perspectives on this new technology is needed. Information regarding patient
preferences on what types of results should be returned, how to best communicate results, and what to do with incidental findings will provide valuable insight into patient perspectives that are vital for developing effective best practices. Previous research studies evaluating opinions with regard to whole exome and genome sequencing have focused on specific populations such as parents and families of pediatric patients, particular ethnic groups, and healthy members of the public (Tabor et al., 2012; Townsend et al., 2012; Yu, Crouch, Jarnal, Tabor, & Bamshad, 2013).

One meta-analysis study reported that out of all participants, consisting of cancer patients, pregnant women, parents of children with suspected genetic disease, participants in various genetic research studies, and randomly selected residents of Sweden and the United States, a median of 90% wanted to receive all personal genetic results that could be made available to them from the particular genetic testing research studies they were enrolled in (Shalowitz & Miller, 2008). Another study appraising the opinions of clinical genetics professionals toward genome sequencing found that 96% of subjects were interested in learning about “clinically actionable” incidental findings in themselves and an equivalent percentage felt such information should be disclosed to adult patients (Lemke, Bick, Dimmock, Simpson, & Veith, 2012).

Evidence suggests that patient attitudes toward learning personal genetic information through whole exome or genome sequencing vary depending on their previous health history, genetic testing history, age, culture, spiritual beliefs, emotionality, background, and relevant life events (Foster, Mulvihill, & Sharp, 2009;
Yu et al., 2013). Such factors are known to be relevant and important when consenting and returning more traditional genetic results to patients; however, the magnitude of results and incidental findings that can be generated from genomic sequencing further exemplify the significance of patient autonomy and empowerment during pre- and post-test counseling. Due to the unique aspects of genomic sequencing, some researchers have suggested making the whole exome and genome sequencing consent a dynamic process malleable to change by an individual over time due to such variables (Tabor et al., 2012). As such, individualized pre- and post-test counseling and patient education in conjunction with detailed and frequent follow-up will become even more significant.

Despite the trend in genome sequencing studies, little research has been conducted with adult cancer patients who have previously received uninformative or negative genetic test results. The application of whole exome sequencing in cancer genomics is becoming more popular and feasible. Consequently, gaining insight into patient preferences related to whole exome sequencing is pertinent and pressing (Berg et al., 2011; Haimovich, 2011; Majewski, Schwartzentruber, Lalonde, Montpetit, & Jabado, 2011). Additionally, questions remain as to how patients frame genomic sequencing results after experiencing a difficult disease such as cancer.

To address such gaps and extend previous research on patient preferences regarding whole exome sequencing, this study explores the preferences of cancer patients who were clinically diagnosed with Lynch syndrome, but for whom traditional molecular tests were unable to detect a deleterious mutation. The specific
questions addressed in this study include (1) What types of results generated from whole exome sequencing does this patient population want to receive and why? (2) How and by whom do patients wish to receive their whole exome sequencing results and follow-up? (3) What concerns do these patients have about whole exome sequencing? (4) Do patients want direct access to their whole exome sequencing results? (5) Who, if anyone, would this patient population choose to share their results with and why? (6) How does having previous uninformative negative Lynch syndrome genetic test results impact patient preferences in consenting to and receiving whole exome sequencing results?
METHODS AND MATERIALS

Selection of Participants

Participants were recruited from a larger research study involving whole exome sequencing on 32 cancer patients who were clinically diagnosed with Lynch syndrome, but for whom traditional molecular tests were unable to detect a deleterious mutation. Recruitment and criteria for this study mirror that of the larger whole exome sequencing study. Participants were recruited from the UCSF Cancer Risk Program and Gastrointestinal Cancer Prevention Program Registries (UCSF Institutional Review Board Protocol #s: 10-02541; 10-04932). Criteria for participation were individuals with (1) high microsatellite instability (MSI) found in Lynch-associated tumors in the absence of one or more mismatch repair (MMR) proteins based on immunochemistry (IHC) results; (2) a family history suggestive of Lynch syndrome; (3) comprehensive germline molecular testing designated as “uninformative negative” of the known mismatch repair genes associated with Lynch syndrome; (4) previous cancer risk genetic counseling for Lynch syndrome; and (5) consent obtained for whole exome sequencing for research purposes. This study was approved by the California State University, Stanislaus Institutional Review Board (Protocol #: 1213-020) and the University of California, San Francisco Committee on Human Research (IRB #: 10-02541; Reference #: 030784).

Thirty-two individuals who met inclusion criteria were contacted by phone by either their previous genetic counselor or one of the primary investigators to discuss
the study in detail and request their participation. When consenting to whole exome sequencing, individuals were also invited to participate in a semi-structured telephone interview to provide insight into what patients undergoing whole exome sequencing want to learn from this new technology. Interviews were conducted after participants consented to whole exome sequencing, but prior to the receipt of results.

**Interview Guide Development**

The first author, in consultation with an experienced genetic counselor and a medical anthropologist, developed a semi-structured interview guide. Current literature on the practices and policies of clinical exome sequencing, as well as various laboratory exome sequencing consent forms were consulted when developing the structure and content of the guide. The interview guide consisted of both structured questions with either binary or multiple answer choices, and open-ended questions to elicit more descriptive data to elucidate participants’ attitudes toward and perspectives on whole exome sequencing. Since no previous research has explored uninformative Lynch syndrome patients’ views on whole exome sequencing results, the semi-structured nature of the interview process allowed for both the quantification of data and the flexibility to pursue new and unanticipated lines of questioning. The interview guide was pretested on a sample population of four adult individuals in the general population who were unfamiliar with whole exome sequencing and was modified as needed.

The guide included standard demographic questions as well as questions to assess participants’ baseline knowledge of whole exome sequencing. Participants
were then provided with a brief description of whole exome sequencing (see Appendix A). The rest of the questions aimed to elicit participant opinions about receiving the various types of results that may be generated from whole exome sequencing. The types of results included carrier status of recessive disorders, later-onset disease, predisposition to increased risk for cancer, risk of common disease, and variants of unknown significance. These particular categories were chosen from those included on current clinical whole exome sequencing consent forms (Ambry Genetics, 2012; Baylor College of Medicine Medical Genetic Laboratories, 2013; Emory Genetics Laboratory, 2012). Examples of conditions that fit each of the result categories were also provided. A similar categorical approach has been proposed as an efficient, scalable model for consenting and returning whole genome sequencing results to individuals (Berg et al., 2011).

Subsequent questions elicited information regarding participant preferences for the return of whole exome sequencing results. Participants were asked structured questions about their overall preference, preferred mode of communication, and follow-up for receiving whole exome sequencing results. Ensuing open-ended questions focused on access, communication, and sharing of whole exome sequencing results. Finally, participants were encouraged to voice any concerns or questions about whole exome sequencing not previously addressed. A copy of the interview guide is provided in Appendix A.

**Data Collection**
Individual semi-structured interviews lasting from 25 to 50 minutes were audio taped with each of the 19 participants. The first author conducted all interviews by telephone. Telephone interviews rather than in person interviews were chosen for increased participation uptake and consistency, since some of the participants lived in another city or state.

Each topic in the interview guide was discussed with each participant; however, some flexibility was allowed to enable participants to discuss topics of particular interest and to elicit specific individual perspectives, as is standard practice in qualitative health research (Berg, 2001). Throughout the interviews, the interviewer clarified and rephrased questions as needed.

**Quantitative Data Analysis**

For those questions asked of all participants with either binary or multiple answer choices, participant answers were quantified. Chi-squared tests were used for cross-tabulations of independent samples. Exact p values were calculated and a value of \( \leq 0.05 \) was considered statistically significant for all tests. Because the interview guide was amendable to change as interviews were conducted, the sample size varied for some questions.

**Qualitative Data Analysis**

For open-ended questions that elicited participants’ perspectives and allowed them to articulate their views in their own words, qualitative analysis was conducted. An independent professional transcribed the audio-recorded interviews verbatim to allow for qualitative data analysis. The first author initially read each transcript
independently several times and developed a coding outline using a content analysis directed approach. Directed content analysis is a common approach for qualitative health research that allows the researcher to use existing theories or research to guide the identification of findings and concepts (Hsieh & Shannon, 2005). As new themes emerged, the coding outline was modified and transcripts were reanalyzed accordingly. Segments of text were also grouped by themes and analyzed separately.

A second researcher read and coded each transcript independently. Both researchers’ analyses and coding outlines were compared and were found to be consistent with one another. The researchers independently analyzed the emergent categories before coming together to agree on an overall list of themes. The findings are reported in overarching thematic headings, which reflect participant thoughts, feelings, and perspectives.
RESULTS

Sample Demographics

Of the 32 participants enrolled in the larger research study performing whole exome sequencing, 19 individuals consented to the interview portion of the research project and the remaining 13 individuals dissented from the interview. Of those who dissented from the interview, the mean age was 56 years, approximately half were male (n = 7) and approximately half were female (n = 6). The main reasons for dissent included lack of time, and for older individuals, difficulty hearing.

All 19 participants had previously been diagnosed with cancer at some time in their lives and had comprehensive germline molecular testing designated as “uninformative negative” of the known mismatch repair genes associated with Lynch syndrome. As shown in Table 1, the majority of participants were White, middle-aged, and female. The mean age of the sample was 52.6 years. A great majority (n = 17) had at least a college degree or some college education. Almost one half (n = 9) were retired or on disability leave. Most others (n = 8) were working as administrators, professionals, or tradespersons.
Table 1

**Demographic Details of the Cohort (n = 19)**

<table>
<thead>
<tr>
<th>Variable</th>
<th>n</th>
<th>Percent</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age, years</td>
<td></td>
<td></td>
</tr>
<tr>
<td>18-30</td>
<td>1</td>
<td>5.3</td>
</tr>
<tr>
<td>31-50</td>
<td>9</td>
<td>47.3</td>
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<tr>
<td>51-70</td>
<td>8</td>
<td>42.1</td>
</tr>
<tr>
<td>71-90</td>
<td>1</td>
<td>5.3</td>
</tr>
<tr>
<td>Gender</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Female</td>
<td>13</td>
<td>68.4</td>
</tr>
<tr>
<td>Male</td>
<td>6</td>
<td>31.6</td>
</tr>
<tr>
<td>Ethnicity</td>
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<td></td>
</tr>
<tr>
<td>White</td>
<td>15</td>
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</tr>
<tr>
<td>Asian</td>
<td>2</td>
<td>10.5</td>
</tr>
<tr>
<td>African American</td>
<td>1</td>
<td>5.3</td>
</tr>
<tr>
<td>Hispanic</td>
<td>1</td>
<td>5.3</td>
</tr>
<tr>
<td>Highest level of education</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Primary school</td>
<td>1</td>
<td>5.3</td>
</tr>
<tr>
<td>High school</td>
<td>1</td>
<td>5.3</td>
</tr>
<tr>
<td>Some college</td>
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<td>College/University</td>
<td>10</td>
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<td>Postgraduate</td>
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<td>15.8</td>
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<tr>
<td>Occupation</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Administrator/Professional</td>
<td>4</td>
<td>21.0</td>
</tr>
<tr>
<td>Tradesperson</td>
<td>4</td>
<td>21.0</td>
</tr>
<tr>
<td>Retired</td>
<td>5</td>
<td>26.3</td>
</tr>
<tr>
<td>Disabled</td>
<td>4</td>
<td>21.0</td>
</tr>
<tr>
<td>Homemaker</td>
<td>1</td>
<td>5.3</td>
</tr>
<tr>
<td>Student</td>
<td>1</td>
<td>5.3</td>
</tr>
</tbody>
</table>
Prior Knowledge of Whole Exome Sequencing

Following a description of, but prior to discussing various aspects of whole exome sequencing, participants were asked whether they had heard of whole exome sequencing preceding consent to this study to in order to assess participants’ baseline knowledge of this new technology. Almost all \((n = 18)\) participants had not previously heard of whole exome sequencing. Therefore, this sample had minimal outside influence regarding this type of genetic testing technology prior to the interview. One participant \((n = 1)\) had been made aware of genome sequencing “through a segment in the news” which presented a story on various cancer centers that were implementing the technology in order to discover new genes associated with cancer.

Preferences for Return of Results

In addition to defined categories of results (i.e. carrier status for recessive disorders, late-onset genetic conditions, and cancer predispositions; see Appendix A), participants were asked to indicate their general preference related to receiving whole exome sequencing results. Participants were asked to choose between the following results to receive: all possible results, only the results predicted to be causative or related to your particular medical condition, only the results your doctor deems ‘clinically relevant’ to your medical care, no results, or other. The results of participant responses to this question are illustrated in Figure 1. The majority of participants \((n = 12)\) wished to receive all possible results generated from whole
exome sequencing, while fewer participants ($n = 6$) chose only those results deemed “clinically relevant” to their medical care by their doctor. One participant ($n = 1$) preferred to receive only those results predicted to be causative or related to cancer.

![Pie chart showing preferences for receiving whole exome sequencing results](image)

**Figure 1.** Overall preference related to receiving whole exome sequencing results ($n = 19$).

Chi-squared analyses were conducted to test whether demographic variables, such as the participant’s age group, gender, ethnicity, level of education, or occupation (see Table 1), were associated with patient preferences in receiving the chosen categories of whole exome sequencing results. The categories of results included all possible results, only the results predicted to be causative or related to your particular medical condition, only the results your doctor deems ‘clinically
relevant’ to your medical care, no results, or other. The results were not statistically significant for this sample.

Participant preferences regarding communication of whole exome sequencing results are depicted in Table 2. Participants were asked whom they would prefer to inform them of their whole exome sequencing results, and were given the following choices to choose from: primary care physician, medical geneticist, genetic counselor, exome sequencing laboratory, or other. Most preferred to receive whole exome sequencing results from a genetic counselor ($n = 12$) or medical geneticist ($n = 4$), acknowledging they would have a lot of questions regarding the results and might need help understanding any medical terminology. Participants were asked to indicate their preferred mode of communication of results, including in person, over-the-telephone, through e-mail, or other. The majority of participants chose to receive whole exome sequencing results in person ($n = 11$).
Table 2

*Preferred Communication of Whole Exome Sequencing Results (n = 19)*

<table>
<thead>
<tr>
<th>Variable</th>
<th>n</th>
<th>Percent</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Informant</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Genetic counselor</td>
<td>12</td>
<td>63.1</td>
</tr>
<tr>
<td>Medical geneticist</td>
<td>4</td>
<td>21.0</td>
</tr>
<tr>
<td>Other</td>
<td>3</td>
<td>15.8</td>
</tr>
<tr>
<td><strong>Mode of initial results</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>In person</td>
<td>11</td>
<td>57.9</td>
</tr>
<tr>
<td>Letter with follow-up in person consultation</td>
<td>3</td>
<td>15.8</td>
</tr>
<tr>
<td>Letter with contact phone number</td>
<td>3</td>
<td>15.8</td>
</tr>
<tr>
<td>Over-the-telephone</td>
<td>2</td>
<td>10.5</td>
</tr>
<tr>
<td><strong>Mode of follow-up or reclassification of results</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>In person</td>
<td>4</td>
<td>21.0</td>
</tr>
<tr>
<td>Letter with contact phone number</td>
<td>7</td>
<td>36.8</td>
</tr>
<tr>
<td>Email with contact phone number</td>
<td>3</td>
<td>15.8</td>
</tr>
<tr>
<td>Over the telephone</td>
<td>2</td>
<td>10.5</td>
</tr>
<tr>
<td>Any way possible</td>
<td>3</td>
<td>15.8</td>
</tr>
</tbody>
</table>

Participants were given a brief description of variants of unknown significance (VUS) and were asked to explain their reasoning for wanting or not wanting to receive VUS results. Only a few participants (n = 3) did not wish to receive VUS results generated from whole exome sequencing. All three participants who desired not to receive VUS results also chose only to receive whole exome sequencing results that were “clinically actionable.”

All participants wanted to receive follow-up results and updates, such as VUS classification or updated clinical implications, from a genetic counselor or medical geneticist. There was, however, variation in participant preference for the mode of follow-up communication (Table 2). Several participants (n = 10) requested the
updated information in an email or letter including a phone number to call should questions arise. Some \((n = 4)\) preferred learning about reclassifications in an in-person appointment with a genetic counselor. Others preferred a phone call \((n = 2)\) with updates or did not have a strong preference as to the mode of follow-up communication \((n = 3)\).

Participant feelings regarding access to whole exome sequencing results were explored (see Table 3). The majority of participants \((n = 13)\) expressed wanting direct access to their whole exome sequencing results. Other participants \((n = 6)\) accepted that only their health care provider would have direct access to their results. The majority of participants \((n = 14)\) expressed privacy or security concerns with personal genomic results on the World Wide Web, but ultimately desired access to results online in the future with a security guarantee.

Table 3

*Access to Whole Exome Sequencing Testing and Results*

<table>
<thead>
<tr>
<th>Variable</th>
<th>(n)</th>
<th>Percent</th>
</tr>
</thead>
<tbody>
<tr>
<td>Access to results ((n = 19))</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Direct, self access</td>
<td>13</td>
<td>68.4</td>
</tr>
<tr>
<td>Health care provider access only</td>
<td>6</td>
<td>31.6</td>
</tr>
<tr>
<td>Online access to results ((n = 19))</td>
<td></td>
<td></td>
</tr>
<tr>
<td>In favor, but expressed privacy concerns</td>
<td>14</td>
<td>73.7</td>
</tr>
<tr>
<td>Not in favor</td>
<td>5</td>
<td>26.3</td>
</tr>
<tr>
<td>Direct-to-consumer whole exome sequencing ((n = 15))</td>
<td></td>
<td></td>
</tr>
<tr>
<td>In favor</td>
<td>2</td>
<td>13.3</td>
</tr>
<tr>
<td>Would consider based on cost</td>
<td>3</td>
<td>20.0</td>
</tr>
<tr>
<td>Not in favor</td>
<td>10</td>
<td>66.7</td>
</tr>
</tbody>
</table>
Nearly all participants \((n = 15)\) were asked if they would consider whole exome sequencing through an outside company, referred to as “direct-to-consumer” genomic testing (see Table 3). Most \((n = 10/15)\) felt strongly that they would not choose to undergo whole exome sequencing without their doctor’s approval. Concerns arose due to the amount of results participants could glean from whole exome sequencing without help with interpretation of results. Worries about cost, insurance coverage, and the security of testing outside the clinical setting were also contributing factors against direct-to-consumer whole exome sequencing. A few participants \((n = 3/15)\) mentioned that cost would be their only reason against direct-to-consumer whole exome sequencing, further indicating that should a company offer such testing at a reasonable price, they might consider pursuing genome sequencing in such a fashion.

**Sharing Test Results**

Participants were asked whether they would share their personal whole exome sequencing results with family members or other health providers (see Table 4). If affirmative, patient preferences regarding modes of communication and reasoning were explored. The vast majority of participants \((n = 14)\) wanted their whole exome sequencing results accessible to their other health providers. A few participants \((n = 3)\) wanted control over which providers could or could not have access to their results. Other participants \((n = 2)\) preferred not to share any whole exome sequencing results with their health care providers.
All participants \((n = 19)\) stated that they would inform all family members about those results that could impact their family members in some way. Participants were asked whether they would withhold any types of results or information generated from whole exome sequencing from family members. The vast majority \((n = 16)\) stated they would disclose all information to their family members. A few participants \((n = 3)\) only wanted to share results that were medically actionable for their family members.

Most participants \((n = 11)\) preferred telling their family members about whole exome sequencing results verbally in person. A few participants \((n = 3)\), all of whom were geographically separated from their relatives, favored providing family members with results over-the-telephone. A few participants \((n = 3)\) preferred initially giving their family members a letter explaining the results, before discussing the results verbally with them. Two participants \((n = 2)\) wanted their family members to accompany them to their results appointment, at which time they could all learn of the results that may impact them together. These participants all had previous, positive experiences bringing family members to their Lynch syndrome genetic test result genetic counseling sessions. Therefore, due to their frame of reference, these participants desired to approach sharing further genetic test results in a similar manner. No participants mentioned telling their family members via email.
Table 4

*Preferences in Sharing Whole Exome Sequencing Results (n = 19)*

<table>
<thead>
<tr>
<th>Variable</th>
<th>n</th>
<th>Percent</th>
</tr>
</thead>
<tbody>
<tr>
<td>Health providers</td>
<td></td>
<td></td>
</tr>
<tr>
<td>All providers</td>
<td>14</td>
<td>73.7</td>
</tr>
<tr>
<td>Selected providers</td>
<td>3</td>
<td>15.8</td>
</tr>
<tr>
<td>No providers</td>
<td>2</td>
<td>10.5</td>
</tr>
<tr>
<td>Family members</td>
<td></td>
<td></td>
</tr>
<tr>
<td>All family members impacted by results</td>
<td>19</td>
<td>100.0</td>
</tr>
<tr>
<td>Selected family members</td>
<td>0</td>
<td>0.0</td>
</tr>
<tr>
<td>No family members</td>
<td>0</td>
<td>0.0</td>
</tr>
<tr>
<td>Types of results communicated to family members</td>
<td></td>
<td></td>
</tr>
<tr>
<td>All possible results</td>
<td>16</td>
<td>84.2</td>
</tr>
<tr>
<td>Medically actionable results</td>
<td>3</td>
<td>15.8</td>
</tr>
<tr>
<td>Mode of family communication</td>
<td></td>
<td></td>
</tr>
<tr>
<td>In person</td>
<td>11</td>
<td>57.9</td>
</tr>
<tr>
<td>Over the telephone</td>
<td>3</td>
<td>15.8</td>
</tr>
<tr>
<td>Letter</td>
<td>3</td>
<td>15.8</td>
</tr>
<tr>
<td>Accompany proband to results appointment</td>
<td>2</td>
<td>10.5</td>
</tr>
</tbody>
</table>

**Qualitative Themes**

The key themes that emerged from our directed approach to content analysis were: value of testing, influence of prior cancer experiences, ownership of results, and family communication.

**Value of Testing**

Most participants identified both pros and cons to learning genetic information generated from whole exome sequencing.

**Motivations for receiving whole exome sequencing results.** Although not surprising given that all interviews took place after participants consented to whole
exome sequencing, participants tended to focus on the benefits of knowing information generated from whole exome sequencing.

*Prevention.* All participants felt that whole exome sequencing results would be beneficial because the information would motivate them to prevent various genetic conditions through adaptation of lifestyle, altering medical management, or seeking additional resources. Participants particularly mentioned the ability to alter their diet, exercise, and lifestyle when discussing results related to cancer or late-onset disease.

Yeah, I would want to know because I would take up dancing or whatever you can do for Alzheimer's. I would study Alzheimer's and I would find out what the heck I could do, eat or exercise, you know, I’d take up bridge if I had to! I would like to know if I’m gonna have breast cancer, for instance, because then I would try to do whatever I could do to avoid it. (Female, 63 years of age)

Participants drew from their experience with Lynch syndrome cancer screening practices in framing management and prevention of other diseases.

I’d try to be proactive about it and get more checkups than probably most people would…. I think one thing I’ve learned from my experience in cancer is that I have to keep checking in and be very proactive about it and not to freak out (Male, 46 years of age).

Another participant desired whole exome sequencing results in order to learn how to take preventative action against further disease because, after recently diagnosed with uterine cancer, she retrospectively felt she could have prevented or delayed cancer onset.

I would want to know because I would want to be preventative in, you know, I guess taking preventative action against it. I think that getting, having disease is part of life, so of course I want to be as healthy as possible. But you know, if someone had told me that I had the predisposition that I supposedly have with the cancer, I would’ve actually done a lot of things differently for the last 10 to 15 years. (Female, 29 years of age)
Some participants did not view whole exome sequencing as much different from other predictive medical tests that can lead to more effective medical management.

Right now a doctor will test blood sugar levels to see if you’re at risk for diabetes or if you’re diabetic and you can take care of yourself. I think this is just an extension of medical care and preventive medicine, to know that you have an increased risk and to get medical advice about what you can do to minimize your risk and take care of yourself. Again, I don’t see what the argument would be against people getting information that’s gonna permit them to try to improve their health. (Female, 68 years of age)

**Preparing for the future.** Participants believed that results generated from whole exome sequencing, particularly those that predispose or diagnose an individual with a condition with no current available treatment, might be valuable in preparing for the future. As advantages to receiving such results, participants mentioned the abilities to both financially and psychologically prepare, to make sure they had their “ducks in a row,” and to prepare their family or future caretakers.

I was, you know, the primary caretaker for my father and decision maker for him. I’m familiar with health deterioration. I’m sure that if I found out, you know, that I was gonna go through a similar sequence, that it would be very disturbing to me, but I guess I feel like I would rather figure out how to cope with that and go through and decide what I wanted to do with my healthy years and, you know, looking into the future, be able to make arrangements so that I didn't bankrupt my family and I had some choice about what kind of care I was gonna get. You know, I guess I would take that tradeoff. (Female, 68 years of age)

Most participants were middle aged and, therefore, also mentioned planning other aspects of their future such as retirement. Participants considered the utility of receiving whole exome sequencing results in relation to planning other areas of their life. One participant mentioned that, “as a senior citizen I think it’s good to know for my later years in life…. so you can plan your life a little bit” (Male, 79 years of age).
**Personal empowerment.** Participants recognized their curiosity of and love for information. The expression “knowledge is power” was used often when participants explained their reasoning for desiring all types of whole exome sequencing results. One participant, diagnosed with colon cancer at age 44, wanted to be aware of all genetic information possible in order to take action, stating, “The more I know, I mean, the better I can help make informed decisions along with my doctor” (Male, 46 years of age). Another participant who had been cancer-free for 10 years felt he would gain gratitude through self-reflection about results revealing information about conditions without available treatment.

You know, everyone is living within their own reality situation, but I think I’d rather know the results. And they wouldn’t really be used in any particular way except maybe spiritually or within my own self, things to think about and things to appreciate. I think I could appreciate things better, knowing about those things. (Male, 61 years of age)

Although not explicitly asked, some participants stated they were motivated to learn about their whole exome sequencing results because they were looking to receive a genetic answer for their clinical Lynch syndrome diagnoses. For instance, one participant who had survived two Lynch-related cancers mentioned:

I feel that the way I have lived, the way I’ve eaten does not warrant all of the things that have happened to me. It wasn’t all my doing. So maybe if there was some explanation of why it’s happening... I thought that, you know, that one time genetic testing would be the end of it, so if they did not find anything, it’s really sort of reassuring that you are, somebody is continuing. (Female, 70 years of age)

Another participant currently battling colon cancer was optimistic that results from whole exome sequencing would provide clarity, stating, “This is very exciting.... I’m
hoping it will provide a lot of answers to a lot of unanswered questions about my cancer, about sickness, about the future” (Female, 55 years of age).

**Empowering family members.** Nearly all participants were motivated to learn personal genomic information for their family members’ benefit. As most participants had children of their own, providing genetic information for future generations was a motivating factor for learning their own genetic make-up. One participant who was diagnosed with colon cancer nearly 50 years ago stated, “I’d want to know it for my kids, for my children more than anything else; have them know what’s going on in their lives. Their health, their life, their future” (Male, 79 years of age).

The few participants who did not have children desired to provide their siblings, parents, and other closely related family members with more genetic information through whole exome sequencing. Although not specifically asked, no participants mentioned any barriers associated with further family testing or changing family members’ medical management based on results.

**Hesitations about receiving whole exome sequencing results.** Although participants tended to desire all possible results generated from whole exome sequencing, some acknowledged the possible risks associated with receiving certain results, particularly those results associated with late-onset or untreatable conditions. No participants hesitated in choosing to receive cancer predisposition-related results, perhaps due to their experience with Lynch syndrome.

**Psychological toll.** Participants, particularly those who were of younger ages, acknowledged that late-onset diseases and conditions without available treatment
might be “emotional,” “difficult,” “depressing,” or “scary” results to receive. In regard to learning of a predisposition to a late-onset condition, one woman who had been diagnosed with colon, then endometrial cancer stated, “That’s a long time to know, to wait. It’s something that could lead to misery…. There’s no point in living in anticipation, but I wouldn’t want to miss an opportunity if something came up that would help with it down the road” (Female, 45 years of age). One male participant, 45 years of age, recognized that learning of results would “affect your day-to-day life,” and another male, 50 years of age acknowledged, “I can’t un-know that information.”

To help alleviate psychological burden and undue worry, most participants (see Table 2) preferred to have a genetic counselor help explain the meaning and implications of their results.

I mean, it depends how [the results] are presented, I guess; but taken out of context I think they could potentially be a little bit alarming. So if it’s just sort of presented as, ‘Hey, you’ve got this huge mutation in this gene,’ whoa, that seems to be bad, I don't know what that means. I’m not sure that that would necessarily be something I would like, versus somebody to sort of walk me through it and understand. (Male, 45 years of age)

Because all participants previously had genetic counseling when receiving uninformative Lynch syndrome negative genetic test results in the past, they seemed to draw from prior personal experiences. For example, one participant who had been diagnosed with uterine cancer within the last year and had recently received her Lynch syndrome genetic test results explained:

When I had that original Lynch test, my oncologist gave me the results and like, they were negative, but even, I feel like if it had been positive, she didn't really know… it wasn’t the most tender way. Whereas I felt like the genetic
counselor was a little more gentle and a little more counseling aspect or something, and I think that’s important with this subject because it’s sensitive. (Female, 29 years of age)

Other participants of all ages felt similarly, mentioning that genetic counselors would be helpful in providing both psychosocial and educational support when receiving whole exome sequencing results.

**Coping mechanisms.** Participants varied in how they would handle potential difficulties associated with receiving whole exome sequencing results. Some participants predicted that their first instinct to learning whole exome sequencing results would be to seek more information, particularly regarding those results that were uncertain or less clinically significant. Some science-savvy participants mentioned coping with results by doing “research on PubMed” or researching “any clinical trials to participate in.” One participant said, “I would want to have access to [results] so I could kind of do my own research and, you know, get a second opinion or something” (Female, 46 years of age). Another participant reflected on his experience coping with colon cancer, which was diagnosed two years ago.

I’d probably treat it like I do the colon cancer in the sense that, you know, do lots of research, find out if there’s a relation to the colon cancer, or Lynch or anything like that, and just continue to follow research on that… or push for research. (Male, 46 years of age)

Other participants felt they would cope with psychologically difficult results through positive thinking, prayer, or reflection. One participant who had been diagnosed with a chondrosarcoma at age 50 revealed:

I don’t think [the results] would really affect me ‘cause I have a positive attitude and, you know, I believe in miracles. So there’s never a no-cure or a
positive that life’s over. So I wouldn’t, I don’t think, take it to heart really. (Female, 57 years of age)

Another participant, diagnosed with colon cancer three years prior to the interview, felt he would cope well with the information he received from whole exome sequencing, but was worried about the effects on his subconscious.

No, I wouldn’t actually worry about [the results] very much, so knowing that I have a higher risk for something wouldn’t make me worry more. Well, I guess I’m concerned that in some ways I might change the way that I’m living my life now – unintentionally, you know, not even consciously but having that knowledge may potentially change what I’m doing now that I don’t actually want to change… especially if it was something that caused a later disease that I couldn’t help. (Male, 45 years of age)

Such reflection illustrates that this participant recognized that whole exome sequencing information might affect him deeply. Many participants expressed similar contemplation regarding the psychosocial implications of whole exome sequencing results, yet most felt they would ultimately deal with the information in positive ways.

Additional health burden. Participants, regardless of their stage of cancer treatment, acknowledged that they already had a lot of health issues to face, presumably with intensive Lynch syndrome cancer screening practices. Adding additional information about other health conditions; therefore, might be overwhelming and compound their current medical management. One woman diagnosed with rectal cancer four years ago revealed:

I think it may be difficult at first to hear…. It’s kind of scary that I might get a disease, especially after the whole ordeal of cancer that happened to me. It is scary, but I want to know. I want to know everything because at least I could do preventative measures to try not to get that disease. I guess I have to make sure I take care of myself and change my lifestyle. (Female, 41 years of age)
Some had concerns about disease penetrance and wrestled with wanting to know certain results based on the likelihood they would exhibit symptoms of the particular condition. Another participant diagnosed with colon cancer two years ago said:

It would depend, you know, on the risk factor. If it was probable, yes, I’d want to know, even though there is no cure. But if it was a percentage, like a low percent, less than 5% or something like that, no, I don't think I would. Not that it’d be stressful, but I think I’m so focused on maintaining a healthy lifestyle and, with colon cancer, and/or if I do have the Lynch syndrome, adding another thing to it might be a little much, especially if it was a rare disease that had no cure. (Male, 46 years of age)

This suggests a high level of health and genetic literacy, which reflects participants’ prior experience with genetic counseling and educational level.

**Influence of Prior Cancer Experiences**

All participants had previously been diagnosed with cancer; however, individuals ranged in stage of medical management decision-making, cancer treatment, and remission. Additionally, all participants were clinically diagnosed with Lynch syndrome and had received uninformative negative Lynch syndrome genetic results from a genetic counselor. This somewhat unique combination of experiences seemed to affect participants’ sense of self and how they framed their opinions regarding whole exome sequencing.

**Mental resiliency.** Participants reported psychological stableness as a result of their personal and family histories of cancer. One participant stated that after surviving two cancer diagnoses, he doesn’t “dwell on bad news” (Male, 45 years of age). While explaining her reasoning for desiring all information that could possibly
be precipitated from whole exome sequencing, another participant recently diagnosed with colon cancer said:

Well, this diagnosis that I was given in January has been a real eye-opener. Not that I didn't always take care of my health prior to that, but once you've been given a diagnosis that you have cancer, it changes your life completely and you have a tremendous appreciation for just every day living, so yes, I would definitely want to know…. In my opinion, you can never have too much information when it comes to your health (Female, 55 years of age)

Participants seemed to have a general awareness that relative to dealing with cancer, information generated from whole exome sequencing would be manageable. For instance, one participant diagnosed with uterine cancer at age 28 said, “I've already had a pretty, like, I’d say one of the heaviest diseases you can get, so I’m not really scared at this point of anything else” (Female, 29 years of age). Such comments demonstrate how living with, managing, and surviving a serious illness such as cancer, particularly when recently diagnosed, can affect one’s outlook on future health concerns and medical decision-making.

**Self-efficacy.** Self-efficacy is a concept that reflects a person’s belief in his or her ability to use existing skills in order to overcome a particular task or situation (Bandura, 1982). Participants demonstrated high degrees of self-efficacy, especially regarding the skills learned through psychologically managing cancer diagnoses. One participant diagnosed with colon cancer within the last year was ready to tackle more health information:

I’ve already changed my medical management and lifestyle with this new diagnosis and I’ve already, you know, dealt emotionally with cancer. Having all of this information gives me more, would give me more knowledge, more power in my own health care regime. (Female, 55 years of age)
Similarly, participants’ experience with Lynch syndrome seemed to impact their notions of genetic determinism. Participants expressed nondeterministic attitudes about the power of genetics. The majority felt that they could act upon whole exome sequencing results, whether it be changing their medical management or adjusting their lifestyle through diet and exercise.

I like information and anything that could potentially help me be more conscious of this potential reality, you know, because it’s nothing, it’s all malleable, I know that. Like if you told me, oh yeah, you have a predisposition to BRCA, I really believe that like a predisposition does not make it as definite. (Female, 29 years of age)

Another participant who had been in remission from colon cancer for two years, in regard to learning about conditions without available treatment, said he would want to know the information “even though quote-unquote, there’s nothing you can do” (Male, 50 years of age). This demonstrates that these participants had internal health loci of control; that is, they felt in control their own health, rather than an external locus of control in which outside factors control one’s well-being (Lau, 1982).

Managing uncertainty. Because participants had previous experience with ambiguity through their cancer diagnoses and “uninformative negative” Lynch syndrome genetic test results, they seemed tolerant of and open to receiving VUS results. Participants relied on established coping strategies for dealing with Lynch syndrome. Regarding VUS results, one participant stated:

I’d do lots of research on the bigger studies done and review those and see if I can hedge my bets, you know? And just continue to follow all the research…. I’d probably treat it like I do the colon cancer in the sense that, you know, do lots of research, find out if there’s a relation to the colon cancer, or Lynch or anything like that, and just, you know, I would just continue following research on that, or push for research. (Male, 46 years of age)
This, again, demonstrates the high confidence and degree of self-efficacy participants exhibited in their ability to manage their health.

In combination with previous experience with uncertainty, participants’ high level of genetic literacy seemed to help participants give meaning to VUS results. One participant who had been diagnosed with rectal cancer 10 years prior to the interview realized that VUS results could be difficult to receive for other individuals, but was self-aware that such knowledge might become more meaningful in the future.

I’m sure a lot of people would obsess about the fact that they have a genetic defect of some kind when they don’t know what the meaning of it is, but, you know, it could be that 10 years from now there will be a finding that would mean something and then they’ll have the chance to know that. Other people may, you know, have the feeling that they don’t want to live their lives with this information, that it’s too scary, too debilitating, whatever. And you know, I respect that and I think people should be given a choice. I really clearly lean in the direction of wanting to know and thinking I deserve to know what the other people know about my body. (Female, 68 years old)

Some participants, however, did not wish to receive VUS results generated from whole exome sequencing, like this woman diagnosed with endometrial cancer at age 46:

I think if it’s not medically necessary, you know, unless you might have something that will impact your health in the future, I don’t really know if it’s really good or useful for just anybody to get to see their whole genetic makeup. (Female, 49 years of age)

The participants who opted not to receive VUS results concomitantly chose only to receive whole exome sequencing results that were “clinically actionable,” suggesting that these participants shared the viewpoint that knowledge is only useful when it can be applied to take specific clinical action.
Ownership of Results

Access to results. Participants were informed of current clinical practices of returning whole exome sequencing results, in which a patient’s ordering clinician receives all test results and relays to the patient only the information that he or she decides is medically necessary. For instance, if a clinician adhered to the current ACMG recommendations, he or she would at least return the results listed on the ACMG’s minimum list of incidental findings that must be reported despite patient preferences (Green et al., 2013). Most participants were not particularly keen on this mode of returning results; but rather, participants expressed wanting proprietorship of their whole exome sequencing results (see Table 3). Participant reasoning included having results for future reference, ease in sharing results with other or future health providers, providing family members access to relevant results, and limiting paternalistic practices such as providers withholding certain results.

I don’t really see the argument of keeping it secret and keeping the information from the people, and it’s like someone playing God with your life. I really don’t see why some folks that are scientists or researchers or medical people should have information about me that I don’t have. I deserve to know what the other people know about my body. (Female, 68 years of age)

This concern that personal genetic information would be known but not disclosed to participants was particularly common. Most participants implied that they believed in patient empowerment and that they would appropriately cope with any and all results provided, indicating that they were competent enough to psychologically handle the information generated from whole exome sequencing.
Privacy and genetic discrimination concerns. Participants were invited to share their feelings regarding access to whole exome sequencing results via a protected online website. The majority expressed privacy or security concerns with personal genomic results on the World Wide Web. After thoughtful deliberation, however, these participants stated that they would like to access their results online in the future, as long as they were protected and secure. The participants who absolutely did not want their results online also cited security concerns as a main rationale for their proclivity. Regarding online results, one participant stated, “That kind of makes me nervous because… I think that everything gets hacked, everything. So I don't know if that’s really so useful or not. So yeah, the privacy issue makes me a little uneasy” (Male, 50 years of age). One participant did not feel her current experience with online results was as perspicuous as desired, but did not refer to any particular security concerns.

[My hospital] now has a system where you can look up test results and a lot of times it’s very unclear what the test is and what the results are. I don't think that’s a good way to get the information. I think it’s really important initially to have a consultation with someone about it, especially if there are some significant findings and it’s not all that clear. (Female, 68 years of age)

Again, participants’ prior experience, this time with online results, influenced their preferences for access to personal genomic data over the Internet.

Family Communication

Most participants were open to sharing all types of whole exome sequencing results with family members (see Table 4).
**Influence of communicating prior genetic results.** All participants stated that they would inform family members about those results that could be beneficial for family members’ medical management and treatment. Because knowledge about Lynch syndrome status offers individuals cancer screening and prevention opportunities, participants recalled their experiences communicating information about Lynch syndrome with their family members. One woman describes how her diagnosis of both colon cancer and Lynch syndrome in the past year have been beneficial for her family members:

In fact, with this diagnosis that I was recently presented with, I have shared everything that’s been shared with me from the genetics department with my immediate family and also my extended family, and they are being very proactive in their own health care…. It has really stirred up a lot of good things, I feel, in my family. They’re all wanting information. (Female 55 years of age)

Other participants felt an obligation or responsibility to communicate all types of genetic test results to their kin. For instance, one participant stated, “They deserve to know just as much as I deserve to know, about Lynch, about whatever. It all affects us all” (Female, 63 years of age). Another participant recently diagnosed with endometrial cancer described the difficult nature of explaining uninformative genetic results with family members:

Yes, I’d want to tell my family. They are really understanding of and involved with my Lynch syndrome and they ask a lot. I have so many relatives that have been dying from cancer and I wish I could tell them more. Like my father always told us, it’s best just to tell family the truth. Like with Lynch syndrome, and these ambiguous results, it was really difficult to tell them, but I know I would just have to find a way to tell them, to talk to them. They know everything and sometimes it’s hard, but we have to do it. We have to find the words to tell them. I know they will understand, especially when it affects one
of them. But it’s easier to tell them everything from the beginning. (Female, 54 years of age)

This illustrates how the personal responsibility that participants may feel to gather more information about Lynch syndrome may affect their motivation to consent to whole exome sequencing.

In response to mode of family communication, most participants preferred sharing whole exome sequencing results in person: “I’d tell them verbally, just talk to them. I’d sit them down and go over the results in the same way that I’ve done with this Lynch syndrome” (Male, 79 years of age).

Disclosing results to children. Many participants were grateful to have the opportunity to share whole exome sequencing results with their offspring: “To be able to share that with my children and their family, you know, I can't think of a better gift to give them for their own health” (Male, 59 years of age). Participants felt that sharing information generated from whole exome sequencing, particularly carrier status results, would be valuable for future generation’s reproductive knowledge, plans and decision-making. Participants with school-aged children wished to wait to tell their children about the pertinent whole exome sequencing results that could impact their reproductive decisions. One woman who had managed two Lynch-associated cancers said:

It’s not information I would share with my children until they became much older and could make their own decisions about having children. It would be something I’d want to know now so I could share that information with them when it was right. You know when they were of childbearing years they could have that information. (Female, 45 years of age)
One participant realized the psychological implications that could stem from sharing whole exome sequencing results with children, but focused on the support he could provide in doing so.

I think it would be important to discuss it with my sons and daughter, to let them know what they might, what they may be running into in the future. It wouldn’t be easy, but I could just let them know that they’re not alone in it, that somebody cares about it. (Male, 61 years of age)

Weighing risks and benefits of sharing information with family.

Participants were asked whether they would withhold any types of results or information generated from whole exome sequencing from family members. The vast majority stated they would disclose all information to their family members. Some participants were cautious about openly sharing all of their personal whole exome sequencing results with family, recognizing that “if it was going to do more harm than good by telling them certain results, there is a slight chance I would not tell them” (Male, 61 years of age). Some individuals expressed hesitation to “dumping all of this information on family that either requires lots of interpretation to understand or is less medically certain” (Male, 45 years of age). Another participant reflected on individual differences that contribute to how someone may react to the information.

I'm someone who can really handle information and not get too freaked out by it, but it’s a fine delicate balance of like telling someone if they have something that’s completely unrelated to, you know, what I’ve been going through. I think I’d ask them if they want to know and I would really think about it and probably get the opinion of a genetic counselor. (Female, 29 years of age)
This not only demonstrates the psychological confidence and high degree of self-efficacy participants exhibited personally, but also highlights the importance of individualized consent.
DISCUSSION

This study reinforces several concepts established in the literature: most adult individuals want to receive all possible results, including incidental findings, generated from whole exome sequencing and feel the benefits outweigh the risks of knowing such information (Bloss et al., 2010; Lemke et al., 2012; Murphy et al., 2008; Shalowitz & Miller, 2008); patients want direct access to their results but prefer posttest guidance and education from genetic specialists (Foster et al., 2009); and patients’ reasons to undergo whole exome sequencing parallel their reasons for consenting to genetic susceptibility testing (i.e. for the benefit of their biological relatives, to inform prevention or management strategies for future illnesses, to reduce uncertainty about the cause of current condition, etc.) (Townsend et al., 2012; Uhlmann, Schuette, & Yashar, 2009; Yu et al., 2013). Analysis of interview data also revealed several novel findings particular to this population of participants, including a perception of a high degree of self-efficacy, the impact of prior experience dealing with uncertainty, and family communication strategies. Based on these novel findings, implications for whole exome sequencing consent practices, pretest counseling strategies, and posttest return of results practices are suggested.

Perception of a high degree of self-efficacy

Interestingly, participants felt they had a great degree of control over their lives, abilities, health, and even their genes. This self-efficacious sample held a high degree of internal locus of control, and therefore, had a sense of empowerment about
using the information they expected to receive from whole exome sequencing in a positive way. The confidence participants demonstrated in their ability to use whole exome sequencing results for prevention and to cope positively with the information is consistent with previous studies on those who accept genetic testing for hereditary cancer syndromes (Vernon et al., 1999; Aktan-Collan et al., 2000; Hadley et al., 2003). Similarly, an internal locus of control has been found to facilitate positive health intentions and behaviors in cancer survivors (Park & Gaffey, 2007), which is consistent with the participants’ focus on prevention strategies.

Yet, participants may have overrated their abilities to control and manipulate their genomic destiny. This supposition is consistent with social psychology studies of Kruger and Dunning, in which people tend to overestimate their own skills particularly when they possess less knowledge about the subject in question or when competence in a particular area would be self-serving (Dunning, Johnson, Ehrlinger, & Kruger, 2003; Kruger & Dunning, 1994). Particularly when discussing the hypothetical situation of receiving whole exome sequencing results related to genetic conditions without available treatment, participants tended to focus on changing their lifestyle and nontraditional methods of healing in order to prevent the onset of such conditions. Participants may have been more prone to believe they could manipulate the onset of such genetic conditions because of their lack of knowledge about genetics or because the ability to manipulate their health would be self-serving.

According to the theory of reasoned action, “a person’s existing skills are closely tied to self-efficacy and behavioral intention” (Shumaker, Ockene, & Riekert,
2009; Uhlmann et al., 2009). Unlike other genetic counseling specialties in which “nondirectiveness” is held as an ethos, approaches to counseling individuals and families with Lynch syndrome tend to stress that knowledge of one’s Lynch syndrome genetic status can be empowering through the implementation of effective cancer screening (Lindor et al., 2006; Uhlmann et al., 2009; Weil, 2000). The concept of reasoned action highlights how participants’ experience with Lynch syndrome, cancer, and genetic counseling affect their approach to whole exome sequencing. For instance, participants’ prior understanding of the effectiveness of Lynch syndrome cancer screening and prevention may lead these individuals to overestimate their ability to control other aspects of their health. Participants in the study may also feel a sense of empowerment stemming from their existing Lynch syndrome screening practices, inflating their sense of self-efficacy and affecting their perceptions of receiving whole exome sequencing results.

Most participants mentioned that, after learning of their cancer and clinical Lynch syndrome diagnoses, they altered their lifestyle in addition to increasing cancer-screening practices in order to live a healthier life. Some felt that even if whole exome sequencing were to diagnose an untreatable or late-onset condition, there were other methods of preventing or stopping the course of the disease through holistic, lifestyle, and non-Western medicine treatments. Participant beliefs aligned with traditional Western thinking, which believes that problems are solvable via manipulation and control (Russell, 1972). Mastery of and control over one’s genes was a prominent, yet concerning idea that arose during interviews with participants.
These notions were illustrated by participants’ desire to use whole exome sequencing information for treatment, prevention, and life planning purposes. Of course, individuals cannot control their genetic makeup or how it affects their health, but rather can only affect the external factors that may or may not modify the expression of genes. Therefore, clinicians consenting patients to whole exome sequencing must be careful in clearly communicating the natural history and implications certain genetic disorders are known to carry.

Contrary to current research suggesting individuals often associate genetic concepts with fate, participants in this study had less deterministic views about genetics (Gould & Heine, 2012; Parrott & Smith, 2013). When discussing their opinions, many participants referred to their genetic susceptibility rather than addressing genes as the determinant of their health. Participants focused on their ability to prevent or delay symptom onset through environment or lifestyle changes, aligning with positive regard for efficacy in handling whole exome sequencing results. These findings suggest that having an experience of managing and coping with a difficult disease such as cancer, along with the knowledge gained in the process of Lynch syndrome genetic counseling, may increase one’s positive self-efficacy. In turn, more self-efficacious individuals may perceive genetic information as manageable and beneficial, therefore skewing their desire to receive all types of whole exome sequencing results. Also, the phenomenon that people often make decisions based on how the expected outcome is framed is known as the framing effect (Tversky & Kahneman, 1981). Participants in the present study seemed to have
the notion that the worst was behind them; therefore, this sample’s frame of reference
and mental resiliency due to their cancer experience affected their decisions to want
all types of whole exome sequencing results.

Impact of Prior Experience with Uncertainty

Because all individuals underwent genetic counseling and testing for Lynch
syndrome, participants were somewhat familiar with traditional approaches to, and
the uncertainty that may come from, genetic testing. Although this concept has been
studied in parents of pediatric patients who undergo whole exome sequencing with
previous uncertain or negative genetic results (Tabor et al., 2012), this study analyzed
adults with such previous experience. Overall, response analysis revealed that
participants seemed to understand and cope well with their previous uninformative
negative genetic results. Therefore, this sample population may be more tolerant of
ambiguity in the form of variants of unknown significance results and conditions with
incomplete penetrance, such as Lynch syndrome, than the general population.
Furthermore, participants had prior experience making decisions regarding their own
health management, communicating information to family members, and pursuing
further testing based on ambiguous results. The high comfort level with ambiguity
expressed by participants may relate to their positive, self-efficacious attitude, or may
be a learned coping response due to their previous experience with uninformative
negative Lynch syndrome results. Very often, participant rationale included drawing
upon their previous Lynch syndrome genetic counseling and cancer experiences. As
whole exome sequencing is applied clinically as a first tier test, patients may have no
experience to draw from when consenting to receiving particular results. In such a scenario, exploring a patient’s coping styles and previous experience with ambiguity outside of genetic testing may be beneficial to encourage full exploration of their thoughts and feelings prior to initiating whole exome sequencing. Encouraging patients to draw upon coping strategies that have worked for them in prior similar situations is a widely accepted counseling strategy proven effective in other situations, and is especially applicable when discussing the range of possible uncertain results that could be generated from large-scale sequencing (Gaff & Bylund, 2010). Clinicians returning genomic sequencing results should do so in the context of the individual patient’s prior experience and knowledge.

**Family Communication Strategies**

Most participants expressed that a motivating factor to desiring all possible whole exome sequencing results was the ability to provide and communicate genetic information to relatives, offspring, and future generations. Although such motivations for seeking genetic testing are not uncommon, participants drew on previous experiences of communicating their Lynch syndrome diagnoses to family members. Participants expressed that sharing their clinical Lynch syndrome diagnoses with family took courage, but that overall, their family members reacted positively by proactively changing their healthcare management. Yet, many realized the challenges that could stem from communicating the scope of whole exome sequencing results with their family.
When it came to sharing susceptibility information about the more emotionally laden condition types, such as late-onset or untreatable diseases, participants were particularly protective of their children, younger siblings, and family members currently battling health problems. Participants felt strongly about telling family members that they have potentially impactful genetic information, but each individual should ultimately decide what was to be shared. Such intrafamilial discussions may be difficult for patients to broach in a nondirective, unbiased manner after receiving results. Therefore, whole exome sequencing pretest counseling sessions need to include discussions about family communication plans should such results arise.

Interestingly, no participants discussed or mentioned telling family members of their decision to undergo whole exome sequencing prior to testing. Sobel and Cowan (2000) investigated the impact of presymptomatic Huntington disease testing within a family systems theory frame, concluding that family involvement in the decision-making process should be strongly encouraged. Because whole exome sequencing can detect similarly impactful conditions, family involvement prior to consent may need to be explored in pretest counseling discussions. Discussing and considering family communication, the impact information could have on others related to the patient, and the range of possible reactions family members could have to results of such significance in advance could minimize family conflict after results are returned.
Genetic specialists often make assumptions about what patients should or should not know about their genetic makeup. Townsend et al. (2012) found discordance between patients and clinicians regarding preferences for returning incidental findings from whole genome sequencing. Particularly, lay groups and patients believed strongly in autonomous decision-making, while clinicians emphasized the clinical relevance of results as the main criterion for disclosure. The majority of participants in this study were keen on individual choice and empowerment, as reinforced by their desire for direct access to whole exome sequencing results and transparency between clinicians and patients. Participants also acknowledged that others, including their family members, may not desire as much or the same types of genomic information as themselves. Such reflections suggest that participants value individual choice because individuals may desire, interpret, and cope with genetic information differently. However, some participants notably preferred that experts filter and interpret results prior to patient disclosure in order to reduce undue worry. This discordance may stem from the quality of the relationship or level of trust patients have in their providers, or from patient recognition of the efficacy of their individual coping styles.

Recently, the ACMG issued a report stating they “do not favor offering the patient a preference as to whether or not to receive the minimum list of incidental findings described in these recommendations” (Green et al., 2013). The minimum list of incidental findings includes high-penetrance, medically-actionable results and known and expected pathogenic mutations (i.e. not VUS results). Green et al. (2013)
recognized that such recommendations might undermine a patient’s autonomy, but also asserted the “fiduciary duty to prevent harm by warning patients and their families about certain incidental findings and that this principle superseded concerns about autonomy.” Not surprisingly, participants in this study opposed paternalistic beliefs, arguing for their right to know information about their genes and bodies, but the great majority also showed a strong desire to receive all whole exome sequencing results. The fact that a few participants voiced that they did not want to receive all results suggests some variability in individuals’ thresholds for genomic information and perhaps the need to let individuals personally consent to receiving particular results. It is still unclear how the recent ACMG recommendations will be carried out in clinical practice, yet this study supports that most patients who consent to genomic sequencing desire all information included in the ACMG’s “minimum list” and beyond. Based on the opinions of patients in the current study, pretest genetic counseling for whole exome or genome sequencing should provide direct and clear information about which results patients have control over choosing to receive and which they do not.

Most health care professionals believe in “genetic exceptionalism,” or treating genetic information differently from other medical information due to its unique implications (Evans, Burke, & Khoury, 2010). This is an important idea when educating patients on large-scale genome tests such as whole exome sequencing. Some participants in this study made comparisons between whole exome sequencing results and other medical information. The parallels these participants made between
genomic and other medical information, what has been coined as “reverse genetic
exceptionalism,” reveal that providers meeting with individuals prior to initiation of
whole exome sequencing need to underscore the differences of genomic information
(Evans et al., 2010). While most participants in this study recognized the apparent
magnitude difference in whole exome sequencing data compared to their previous
experience testing for a handful of genes associated with Lynch syndrome, it is
imperative that pretest counseling sessions divulge the possible implications that
could result from receiving whole exome sequencing data in detail, ensuring adequate
anticipatory guidance and self-reflection for patients.

**Limitations**

This study had several limitations. From a demographic standpoint, participants represented a small sample size from the same general region, and were
generally well educated, middle-aged, and white. All participants had previously
participated in genetic counseling and Lynch syndrome genetic testing, and therefore
may be more knowledgeable about genetics, consent, and test results than the general
population. Participants may have been more likely to want whole exome sequencing
results due to a wish to determine a genetic cause for their clinical Lynch syndrome
diagnosis or to learn more about their condition. Also, participants generally had a
positive outlook on receiving health information, which may be related to their prior
experiences with cancer and high level of perceived self-efficacy and high level of
health literacy. Given the small, homogeneous sample in this study, generalizability
may be limited. It is not possible to make any firm conclusions as to whether the
views of this group are representative of all individuals diagnosed with uninformative negative Lynch syndrome genetic test results or representative of the general population.

Recruitment of the interviewees may also have been biased in that only those interested in the topic and open about voicing their opinions were likely to participate. All of the interviewees were referred by the genetic counselor with whom they had previous contact, and these individuals may have been chosen because of their positive experience with genetic counseling, thus favorably inclining their views toward receiving genetic information.

**Future Research**

Future studies on this subject should include a larger sample size and incorporate individuals from diverse ethnic backgrounds, varied education and socioeconomic levels, and a range of genetic experience levels. Patients, providers, and policy makers should be consulted in determining recommendations for follow-up and updates from whole exome and genome sequencing. Based on the somewhat recent utilization of whole exome sequencing in clinical practice, it is not yet known whether learning of one’s whole exome sequencing results will have positive, negative, or no effect on motivation to engage in lifestyle and medical management changes, family communication, or emotional burden. Patients undergoing clinical whole exome sequencing should be followed long-term to track health behavior changes and better understand the enduring psychological impact of receiving whole exome sequencing results. Such longitudinal studies will be imperative to deduce the
most effective procedures for integrating whole exome and genome testing into clinical practices. Should whole exome or genome sequencing become first-tier genetic tests, studies should be conducted on how individuals without prior genetic testing experiences feel regarding genomic testing and the types of results it may provide.
CONCLUSION

The implications that come from the volume and complexity of clinical data generated from whole exome sequencing need to continue to be sincerely considered from multiple patient and individual perspectives. Learning about the preferences of patients who were previously clinically diagnosed with Lynch syndrome, but who received uninformative negative Lynch syndrome genetic results through traditional molecular testing methods can be useful for clinicians. For example, such knowledge can help clinicians consent patients to whole exome sequencing and report whole exome sequencing results. Given the complexity and ethical framework this new technology poses, a client-centered approach is even more necessary during pre- and post-genomic sequence counseling in order to effectively communicate the possible implications of this new technology and consent patients in an empathetic and sensitive manner.
REFERENCES


ACMG Board of Directors. (2012). Points to consider in the clinical application of genomic sequencing. Genetics in Medicine, 14(8), 759-761. doi: 10.1038/gim.2012.74


Evans, J. P., Burke, W., & Khoury, M. (2010). The rules remain the same for genomic medicine: The case against “reverse genetic exceptionalism.” *Genetics in Medicine, 12*(6). doi: 10.1097/GIM.0b013e3181deb308


discordance for return of incidental findings from clinical sequencing.

Genetics in Medicine, 14(4), 405-410.


APPENDIX
APPENDIX A

INTERVIEW GUIDE

I. Demographics

1) What is your age?

2) What is the highest grade or level of school that you have completed?

3) What is your current occupation?

4) What ethnicity do you consider yourself as?

5) Have you had any additional genetic testing since your genetic counselor last met with you in clinic?

II. Background Information

A new genetic test called whole exome sequencing was recently made available. We are conducting a research project in which we interview patients who have had uninformative genetic testing for Lynch syndrome about what they would like to learn from this new genetic testing technology. I am now going to give you some background information about this new genetic test called whole exome sequencing and ask you some questions about the information. If you want me to repeat or explain anything, please stop me and let me know.

Clinical exome sequencing is a new genetic test that can help identify changes in a person’s genes, which may be causative or predictive of many genetic conditions. This new technology may enable us to identify genetic mutations in the Lynch
syndrome genes that the traditional genetic testing techniques missed. Whereas previous genetic tests analyze one or a small group of related genes, whole exome sequencing will analyze the important regions of thousands of genes at the same time. While whole exome sequencing may allow us to identify new mutations that cause Lynch syndrome, it may also allow us to discover new genes and diagnose new genetic conditions that are not related to hereditary cancer.

1) Before this study, had you previously heard of whole exome sequencing?

[IF YES]: Tell me about what you know about exome sequencing.

Where did you hear about exome sequencing?

2) Do you have any questions about whole exome sequencing before we begin?

3) Since consenting to this project, have you done any research on your own about whole exome sequencing?

III. Interview Questions

Now I will ask you some questions related to the different types of information that whole exome sequencing may reveal. I ask you to please answer as completely as possible and feel free to extend your answers as needed.

4) Whole exome sequencing may reveal whether you carry a mutation in a gene that increases your risk of developing certain diseases in which symptoms usually don’t begin until later in life, such as Alzheimer’s disease or Huntington disease. Would you want to be informed if you had a genetic mutation that put you at risk for a later-onset disease?
- How would you feel about knowing you might get a later onset disease being that you are only [X] years old?

- Can you explain your reasoning for wanting/not wanting to know if you were at increased risk for a later-onset disease?

- How would you use the information?

- What would you do differently?

- Do you have any concerns about knowing such information?

- Do you think there would be any downsides to knowing this information?

5) Whole exome sequencing may reveal whether you carry a mutation in a gene that increases your risk of developing a disease for which there is currently no available treatment. Would you want to know if you were at risk for such a disease when there was nothing you could do to change the course of the disease?

- Can you explain your reasoning for wanting/not wanting to know if you were at increased risk for one of these diseases for which there is no treatment?

- How might you imagine knowing you will get a disease that is not treatable be different from your experience with Lynch syndrome (i.e. since colonoscopies are rather preventative and effective)?

- How would you use that information?

- Do you have any concerns about knowing such information?
6) Whole exome sequencing may reveal whether you are a carrier for a recessively inherited genetic disease, such as cystic fibrosis or Tay-Sachs disease. This means that you yourself would not be affected with the disease, but you are at risk for passing this mutation on to your children. If your partner is also a carrier of the same genetic mutation, there is a 25% or one in four chance of your child being affected with that significant disease. Would you want to know if you were a known carrier for a genetic disease through whole exome sequencing?

   - Can you explain your reasoning for wanting/not wanting to know if you were a carrier for a genetic disease?

7) Whole exome sequencing may reveal whether you have a mutation in a gene that increases your risk of developing cancer other than those related to Lynch syndrome. Would you want to know if you had a genetically increased risk of developing additional types of cancers in your lifetime?

   - Can you explain your reasoning for wanting/not wanting to know if you were at increased risk for other cancers?

   - How do you think you might use this information?

   - How much of an increased risk would there have to be for you to change your lifestyle/medical management?

8) Whole exome sequencing may reveal whether you have a mutation in a gene that increases your risk of developing common diseases such as diabetes, obesity, asthma, coronary artery disease, etc. Would you want to be informed
if you carried a genetic mutation that increased your risk of developing one or more of these common diseases?

- Can you explain your reasoning for wanting/not wanting to know if you were at increased risk for a common disease?

9) Whole exome sequencing may detect changes in your genes, called variants, which experts are not sure how to interpret. For example, these variants may be found later to be benign (representing normal variation among individuals) or may be disease causing, but as of today, are of unknown significance. Would you want to know about these variants of unknown significance in your genes through whole exome sequencing?

- Can you explain your reasoning for wanting/not wanting to know if you carried a variant?

- What would you do with that information?

10) If whole exome sequencing revealed a variant of unknown significance in one of your genes, would you want to be contacted in the future if the variant was reclassified as disease-causing?

- What about if it was reclassified as benign?

- Who, in your opinion, do you think should be responsible for contacting you about any potential changes in interpretation of the variants?

- How would you want to be contacted?

11) Results obtained from whole exome sequencing may not only reveal information about your genes, but also information about the genes of close
genetic relatives, such as your siblings and children. If whole exome sequencing were to discover genetic information that may impact your family members, would you inform them?

- Can you explain your reasoning for wanting/not wanting to inform your family members?
- How would you inform your family members?
- Are there certain types of genetic information you might withhold from your family members? Please explain.

12) Right now, the way that these tests are being used, only your ordering clinician would receive all of the test results, and would then relay to you only the information that he or she decides is medically necessary (i.e. the clinician would only give you information you could act upon and he or she may see information in your results that they might not share with you). How do you feel about that?

- Would you yourself want to have access to the actual test results?

[IF YES]: Why?
[IF NO]: Why not?

13) In the future, if the results from your whole exome sequencing test could exist in a protected online website that you could have access to, would you want to access your results in that way?

[IF YES]: Why?
[IF NO]: Why not?
14) If an outside company offered this test and you could order this on your own and pay out of pocket, might you consider paying for this test to learn this information about your genetic makeup?

[IF YES]: Why?

15) If you were to personally undergo whole exome sequencing, which of the following results would you choose to receive:

a. All possible results
b. Only the results predicted to be causative or related to your particular medical condition
c. Only the results your doctor deems “clinically relevant” to your medical care
d. No results
e. Other: _________________

16) If you were to undergo whole exome sequencing how would you prefer to receive the results? For example…

a. In-person
b. Over-the-telephone
c. Letter
d. Email
e. Other: _________________

17) Who would you prefer to inform you of your whole exome sequencing results? For example…. 
a. Primary care physician
b. Medical geneticist
c. Genetic counselor
d. Exome sequencing laboratory
e. Other: _________

18) Would you want the results from whole exome sequencing to be shared with any of your other health providers?
   [IF YES]: With which providers?
   What is your reasoning for sharing your results with others?
   [IF NO]: Can you explain your reasoning for not wanting to share your results with other health providers?

19) Is there anyone else you feel should have access to the results of your whole exome sequencing test?
   [IF YES]: With whom? Why?
   [IF NO]: Can you explain your reasoning for not wanting to share your results?

20) Do you have any concerns about whole exome sequencing that we have not yet addressed?

21) Finally, do you have any questions for me?