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Much Ado about Nothing: a Qualitative Study of the Experiences of an Average-Risk Population Receiving Results of Exome Sequencing

Shannon Rego[1,3], **Orit Dagan-Rosenfeld**[1], **Stephanie A Bivona**[1], **Michael P Snyder**[1], and **Kelly E Ormond**[1,2]

[1]Department of Genetics, Stanford University School of Medicine, Stanford, CA 94305, USA

[2]Stanford University Center for Biomedical Ethics, Stanford University School of Medicine, Stanford, CA 94305, USA

[3]Institute for Human Genetics, University of California—San Francisco, San Francisco, CA 94143, USA

Abstract

The increasing availability of exome sequencing to the general ("healthy") population raises questions about the implications of genomic testing for individuals without suspected Mendelian diseases. Little is known about this population's motivations for undergoing exome sequencing, their expectations, reactions, and perceptions of utility. In order to address these questions, we conducted in-depth semi-structured interviews with twelve participants recruited from a longitudinal multi-omics profiling study that included exome sequencing. Participants were interviewed after receiving exome results, which included Mendelian disease-associated pathogenic and likely pathogenic variants, pharmacogenetic variants, and risk assessments for multifactorial diseases such as type two diabetes. The primary motivation driving participation in exome sequencing was personal curiosity. While they reported feeling validation and relief, participants were frequently underwhelmed by the results and described having expected more from exome sequencing. All participants reported discussing the results with at least some family, friends, and healthcare providers. Participants' recollection of the results returned to them was sometimes incorrect or incomplete, in many cases aligning with their perceptions of their health risks when entering the study. These results underscore the need for different genetic counseling approaches for generally healthy patients undergoing exome sequencing, in particular the need to provide anticipatory guidance to moderate participants' expectations. They also provide a preview of potential challenges clinicians may face as genomic sequencing continues to scale up in the general population despite a lack of full understanding of its impact.

Corresponding author kormond@stanford.edu.

Author Contributions

All authors contributed to the study design. S.B. conducted interviews with participants and contributed to manuscript preparation. O.D. and S.R. contributed to coding, data analysis and manuscript preparation. K.O. developed the interview guide (with SR), coded interviews and contributed to manuscript preparation.

Conflict of Interest

M.P.S. is a founder and member of the science advisory board of Personalis, SensOmics and Qbio and a science advisory board member of Genapsys. S.R. is a consultant for Qbio.

Keywords

Whole Exome Sequencing; Genomic Sequencing; Patient Perspectives; Perceived Utility

Introduction

Whole-genome and whole-exome sequencing (hereafter referred to as exome sequencing) are quickly becoming commonplace tests in clinical and research settings (Manolio et al., 2015; Manolio et al., 2013), and will increase in prevalence as the cost of sequencing and its interpretation drops (Manolio, 2016) and coverage by healthcare payers increases. In 2018 most germline exome sequencing is performed in order to identify the cause of suspected Mendelian disease, either as a clinical test or as part of a research protocol in countries with more limited access to clinical exome sequencing. Increasingly, however, healthy individuals are also undergoing exome sequencing as part of research studies (Linderman, Nielsen, & Green, 2016; Vassy et al., 2017) direct-to-consumer testing (Phillips, 2016) or through labs offering an exome "screening" test that can be ordered by physicians on behalf of patients without a suspected genetic disorder (Illumina, 2017; Williams, 2017). These tests are increasingly sought in the general population, outpacing our understanding of the implications for the individuals tested, for healthcare providers, and for society in general.

Previous research efforts have been devoted to understanding the goals, motivations, and preferences of individuals and families with rare genetic diseases with regards to exome sequencing. This research has addressed attitudes towards the informed consent process, perceived risks and benefits of exome sequencing, and the disclosure of incidental/secondary findings utilizing both qualitative and quantitative methodologies (Appelbaum et al., 2014; Bergner et al., 2014; Clift et al., 2015; Krabbenborg et al., 2016; McGowan, Glinka, Highland, Asaad, & Sharp, 2013; Oberg et al., 2015; Sapp et al., 2014; Shahmirzadi et al., 2014; Tabor et al., 2012; Yu, Crouch, Jamal, Bamshad, & Tabor, 2014; Yu, Crouch, Jamal, Tabor, & Bamshad, 2013). This research now guides healthcare providers in their efforts to obtain informed consent for exome sequencing, allowing them to proactively address patients' questions, concerns and misconceptions, understand patients' preferences regarding the return of results, and anticipate ways in which patients may need support after receiving results.

However, there is only limited research specific to generally healthy patients, research participants, and consumers undergoing exome sequencing, and much of the early research in this area utilized physicians and scientists as research subjects (Lindor et al., 2015; Sanderson et al., 2015), which can make it challenging to extrapolate results to the general population. Existing research has demonstrated that healthy individuals have a variety of motivations that are different from those of individuals undergoing testing for the purposes of identifying the cause of a suspected genetic disease, including curiosity, an interest in learning general health information, contributing to research, self-exploration, and interest in ancestry information (Facio et al., 2013; Sanderson et al., 2016). Healthy individuals also weigh the risks and benefits of exome sequencing differently than individuals with serious medical conditions, who are more likely to view the potential diagnostic benefits of exome

sequencing as outweighing risks such as privacy breaches, insurance discrimination, and psychological implications of unexpected results (McGowan et al., 2013; Robinson et al., 2016). To this point, most studies of exome sequencing in healthy patients did not return results to patients (or had not done so yet when they explored participants' viewpoints), such that exploration of their preferences has been largely hypothetical. To our knowledge, only two published studies have utilized in-depth interviews to explore healthy participants' opinions and views *after* receiving genome results, and they found that most participants had positive reactions to the experience of receiving their results and most did not experience psychological distress (Lewis et al., 2016; Sanderson et al., 2017). These findings were also supported by quantitative research done on the MedSeq cohort, which included both healthy adults and adults diagnosed with cardiac disease (Roberts et al., 2018). This type of exploration is vital to improving our understanding participants' experiences receiving genome results, including how the results did or did not match their expectations, whether they found the results useful, and whether the results led to any positive or negative psychological impacts such as relief or anxiety.

To this end, we designed a study in which in-depth semi-structured interviews were conducted with generally healthy research participants who have received various types of exome results, including Mendelian disease-associated pathogenic and likely pathogenic variants, pharmacogenetic variants, and risk assessments for multifactorial conditions. As exome sequencing becomes more and more commonplace for healthy individuals, this type of information will help to inform clinicians' approaches to consenting and providing anticipatory guidance to patients and participants to receive results.

Methods

Design

The use of exome sequencing to study healthy individuals in a research setting is fairly new, and limited research has been done to explore their motivations and experiences. As qualitative data is ideal to richly define subjects' views complex matters, we conducted semi-structured, in-depth qualitative interviews meant to explore participants' viewpoints on the return of exome results. This study was approved by the Stanford University Institutional Review Board, and all participants provided written informed consent.

Participant Recruitment

Adult participants were recruited from the Integrated Personal Omics Profiling (iPOP) project—an ongoing longitudinal study at Stanford University in which generally healthy individuals provide blood, urine and stool samples at regular intervals for the purposes of multi-omics profiling, including microbiome, transcriptome, proteome, metabolome, and exome sequencing, among others (Chen et al., 2012). The cohort was enriched for individuals with pre-diabetes. Participants were recruited for the iPOP study through a combination of FM radio and internet radio advertisements, approaching participants already enrolled in other Stanford studies, and word of mouth. Exome results were the first results participants received, and at the time these interviews were conducted participants had not yet been offered the option to receive the results of other omics assays.

As part of the consent process for the multi-omics study, participants were given the option of selecting whether they wanted to receive actionable genomic results only, or any genomic findings with medical relevance. Actionable results were defined as likely pathogenic or pathogenic variants in genes associated with diseases that are moderately to highly penetrant, the identification of which was likely to result in altered medical management in the form of treatment, screening, or preventative measures, as described in professional society guidelines, for example, National Comprehensive Cancer Network guidelines for detection, prevention and risk reduction for various types of familial cancer syndromes (National Comprehensive Cancer Network, 2017). The following types of results were available to participants: 1) pathogenic or likely pathogenic variants in all OMIM linked Mendelian disease genes that included adequate gene-phenotype information (including carrier status for recessive diseases and variants in genes associated with dominant or X-linked disease), 2) pharmacogenetic variants, and 3) risk assessments for multifactorial diseases based on multiple genetic loci.

The details of the Mendelian variant analysis have been previously published (Rego et al., 2018). Briefly, we filtered for rare loss of function variants and variants appearing in HGMD that were in one of the more than 3,600 genes associated with human disease in the Online Mendelian Inheritance in Man (OMIM) database (Hamosh, Scott, Amberger, Bocchini, & McKusick, 2005). We also assessed all coding variants in the ACMG list of 59 genes for which they recommend returning secondary findings. Variants that passed the filtering process were then classified by two experienced genetic counselors according to ACMG guidelines for the classification of sequence variants (Richards et al., 2015). Variants of uncertain significance (VUS) were occasionally reported to participants and discussed if they were relevant to a health condition the participant already had. In such cases the study's genetic counselors emphasized the uncertainty surrounding these variants.

We assessed participants' exome data for common SNPs with pharmacogenetic annotations that reached a level 1A classification in the PharmGKB database (Whirl-Carrillo et al., 2012). Level 1A variants are those with the highest level of validation.

We also returned results for approximately 40 multifactorial conditions, including type two diabetes, coronary artery disease, and obesity, among many others. Participants received a detailed version of their risk assessment for type two diabetes and a summary of their risk assessments for the other conditions (see supplemental figure 1 for an example of a multifactorial risk assessment).

Participants' exome results were returned by genetic counselors (SR, ODR), typically in person, and sometimes included other study team members in addition to one or both genetic counselors, including physicians (ie a medical geneticist, neurologist or endocrinologist), scientists, and students. The results discussions took approximately 30–90 minutes, and included education about the difference between rare variants in Mendelian genes and risk assessments for multifactorial conditions. Some participants brought friends or family members to the results session.

As of July 2017, participants who had received exome sequencing results from the multi-omics study a minimum of three months prior (N=31) were considered eligible for the current study and were invited via email (up to 2 times) to participate in the current study.

Interview Guide

The interview guide was developed by a team of 3 genetic counselors, 2 of whom had provided the bulk of the consent and disclosure process for exome sequencing results in the multi-omics project (SR, ODR), and one who has previously done qualitative research in this area but was uninvolved in the exome component of the multi-omics study (KO). The interview guide was intended to broadly assess the following: 1) participants' reasons for participating in the multi-omics profiling study; 2) perceptions of the risks and benefits of exome sequencing; 3) expectations for results and 4) reaction to the results. In order to contextualize participants' reaction to their results, the guide included questions probing for what participants remembered about their results. First participants were asked an open-ended question about what they learned from the results. The interviewer then followed up with questions about specific types of results, for example, "What do you remember about your pharmacogenetic results?" and "Do you remember being told you were a carrier for any recessive diseases?"

Procedures

The interview guide was piloted on an initial participant, and no major changes were made to the guide. All interviews were conducted by a single interviewer who was uninvolved in the multi-omics study and unaware of the participants results or experience (SB), and they were audio-recorded and transcribed verbatim.

In addition to the interview questions, participants were asked to answer demographic questions including highest level of education completed, type of employment (if employed), whether they had a previous background in genetics, and other questions designed to enhance the study team's understanding of the participants' frame of reference with regards to their results.

Finally, participants consented to release the genomic results that were reported to them as part of the omics study, allowing the study team to pair the interview and results, thereby assessing participants' recollection of the information that was returned to them, as well as their understanding of the significance of that information.

Data Analysis

The interview transcripts were analyzed using standard thematic analysis techniques adapted from grounded theory to identify themes that emerged from the transcripts (Miles, Huberman, & Saldana, 2014). Transcripts were read and an initial code list was developed by a member of the study team who was uninvolved with the multi-omics study or interviewing (KO). The preliminary code list was discussed and validated by the entire research team. New codes were continuously added, including inductive and in vivo codes derived from the transcripts, and were discussed by the study team for consensus. One member of the team (KO) coded all transcripts using the software package Dedoose version

8.0.31, and two other members of the study team each coded three transcripts for agreement, after which discrepancies were discussed and resolved. Themes were selected for discussion primarily based on prevalence, but less prevalent themes will be presented to demonstrate the range of participants' experiences or if the theme had potential significance for clinicians who may work with healthy patients undergoing exome sequencing in the future.

Results

Participant Population

Out of 31 participants approached, 18 initially agreed to be interviewed and 12 completed interviews (participation rate of 39%) before data saturation occurred. The cohort (see Table I) was primarily Caucasian (75%), were highly educated (all participants had attended at least some college), included eight males and four females, and represented a wide range of ages (from 45 to 74 years old). Seven of the participants had at least one biological child. Three participants were diabetic and eight were pre-diabetic. All had either a personal history of diabetes or pre-diabetes or a family history, and five explicitly mentioned their family history in the interview.

All but one of the participants consented to receive all available results (Table I). Multifactorial disease results were returned to all but one participant (11/12), specifically including three that indicated increased risk for type two diabetes. Pharmacogenetic results were returned to all participants (12/12). Eight of 12 participants were informed they were a carrier of at least one autosomal recessive condition. Four participants received results that included variants in dominantly inherited disease genes. Two were explanatory for personal/family health history (*HNF1A*, monogenic diabetes; and *PROC*, Protein C deficiency), while the other two (*SLC7A9*, cystinuria; and *SDHB*, hereditary paraganglioma and pheochromocytoma) were unexpected results.

Curiosity and self-perceived ability to cope drive participation

The most prevalent reason for participating in the multi-omics study and receiving exome results was the desire to learn more about themselves and their health risks, often with the intent to be proactive if a significant disease risk was identified. For some participants their interest reflected a general curiosity about health information and genetics, particularly for one participant who was adopted and did not have any family health history; for others it was focused on diseases for which they had a personal or family history, with cancer and heart disease representing the most common examples cited.

> "Any time you have the ability to get more information about your health, about yourself, whether it be somebody doing an MRI of your neck to maybe find out if there's anything wrong there to taking blood tests to find out your cholesterol level, well this is just another test that can tell you more about yourself. That's what I think about whole genome testing."
>
> (Participant 3, male in his 50s)

> "…I actually wanted to be sequenced. I thought it would be useful particularly because I've got type 2 Diabetes and I wanted to see what the genetic underpinnings of that were for me and maybe for anybody else."
>
> (Participant 6, male in his 70s)

Participants also frequently described a desire to contribute to medical science and an interest in sharing their genetic information with family members as motivations for participation.

> "Many people in many years past have actually contributed to research and I've benefited from that research so it's my turn to do a little medical research that might benefit people in the future."
>
> (Participant 3, male in his 50s)

When asked about risks or downsides they considered prior to participating in exome sequencing, most participants said they did not perceive there to be any significant downsides to participating. Several participants articulated their thought process regarding the risk of emotional distress around receiving results, and specifically commented that they perceived they would be able to handle the results, in some cases in relationship to their career (e.g. nursing) or background (e.g. engineer, scientist).

> "…that's a downside that I'm capable of managing just because of the way I think and operate and the way I'm wired. I think I'm able to process and handle even the worst information and I just…I think that there is benefit in knowing."
>
> (Participant 7, female in her 40s)

Exome sequencing results were underwhelming to participants

There was a sense of relief articulated by several participants, particularly those participants who did not receive surprising or unexpected results. In fact, a majority of participants reported expecting more than they received from their exome results, despite the fact that most participants also stated that they did not have clear expectations of what their results would include when entering the study. One of the most frequent suggestions participants offered was to improve the consent and disclosure process for genomic sequencing to better prepare them for the types and amount of results they would (or would not) receive, so that they would not be disappointed at disclosure. Seven of the twelve participants described this sentiment:

> "I think I received the information I expected, but I expected more."
>
> (Participant 3, male in his 50s)

> "Maybe, like I said, I did get what I was expecting to, but I thought there would be a lot more other things, and I don't know what those other things would be."
>
> (Participant 9, female in her 60s)

Some participants described the need to set expectations for those undergoing this type of testing to mitigate potential feelings of disappointment.

> "Yeah, because I think some people are going to think, "…they're so good they can tell me how old I'm going to be (when I die)." … Now, I'm just putting out there. I don't know if that's anywhere in the realm, but I'm just saying some of those crazy assumptions might be out there…I think to set the stage of what the current science is and potentially what the current science might be in the future. Like I said before in popular culture, we do have this lot of science fiction and people make claims. The Internet has a lot of… it's going to press now a lot. It's fake news. In the internet you can see things that looks legit that are total BS."
>
> (Participant 10, male in his 50s)

One participants' disappointment seemed to be influenced by their prior experience with DTC testing, which she felt was more comprehensive than the exome sequencing done through the iPOP.

> "As I said, I felt like the iPOP information was actually less comprehensive and presented in a less appealing and useable fashion than 23andMe information."
>
> (Participant 1, female in her 60s)

While a majority of participants were underwhelmed by their results, there were a few notable exceptions. Several participants expressed feelings of validation or closure when their results had a potential or definitive role in a health condition they already had.

> "… It makes total sense. It actually just even brought a little closure for me and understanding more about my condition, and then they also… they were great. They gave me some articles to read that helped me understand it better and understand this and implications surrounding it. So, I felt very supported and then I was able to have an intelligent conversation with my endocrinologist at my last appointment, which went really well."
>
> (Participant 7, female in her 40s with a personal and family history of diabetes, and a pathogenic *HNF1A* variant discovered)

One participant described his excitement at having a possible genetic explanation for his medical history, but also the challenges such information can pose to family members.

> "…when I found about the protein C deficiency thing, I was really excited to have a cause for why I have this problem. I actually invited my son, who was available at the time, to sit in on it, so he actually heard the whole results as we were sitting there getting them from (the genetic counselor) I said, 'Wow, I'm really glad to know that that's why I have this problem,' and he said, 'Well, that may be easy for you, dad, but not so easy for me because I may now have it since it's a dominant passed thing.' That was an observation by having him there where he then had to mentally deal with it."
>
> (Participant 2, male in his 70s)

Multifactorial results also sometimes resonated with participants who had personal histories of the conditions included in the risk assessments.

> "Basically, the results confirmed what I… they were good because I didn't have any risk factors, like I said. It confirmed my suspicions about the obesity. But it also explained that there's the environmental factors probably weighs as much or more and I'll just be conscious of it. I really didn't get any negative information. That was good. It was all positive."
>
> (Participant 10, male in his 50s who received a multifactorial result suggesting increased genetic risk for obesity, and who mentioned his ongoing weight struggle several times over the course of the interview).

Very few participants reported making any changes to their lifestyle or health care due to their results, though a few described an intention to lead a healthier lifestyle at least in part due to a risk that was elucidated by the multifactorial risk assessments.

> "I was already doing all the things that we showed any impacts on, so it really didn't change it much. I guess, the fact that type two diabetes was slightly higher risk made me think about that a little harder, so maybe I'm trying a little harder to keep away from carbohydrates and stuff."
>
> (Participant 2, male in his 70s)

Participants discussed exome sequencing with family, friends and healthcare providers

Participants did discuss their intention to participate in exome sequencing and their results with family, friends and healthcare providers. In most cases, participants described having these conversations with family and friends because they thought the sequencing was interesting or 'cool'.

> "I told a number of people [about his intent to undergo exome sequencing] because I thought it was neat, including my daughters."
>
> (Participant 6, male in his 70s)

All participants reported discussing their results with family and/or friends, in some cases to convey health risks to family members, and in others because they found the results interesting or wanted help interpreting the results. Most participants (7 out of 12) reported that they either shared their results with their physician or intended to share the results. Those who did not share results with their physician and did not intend to described feeling that there was nothing in their results that their physician needed to know, or that they did not feel their physician would have time to deal with the results or would not know what to do with them.

Participant recollection of results

Several participants remembered the details of their genomic sequencing results incorrectly, though these instances of misremembering usually had no significant consequences. For example, 7 of 12 participants had carrier results for recessive conditions returned to them, but only 2 of the 7 recalled receiving this information. Similarly, all 12 participants had pharmacogenetic results returned to them, but only 7 of the 12 recalled receiving this

information. Participants seemed particularly likely to remember results that related to conditions that were already known to be in the family.

> "For example, both my wife and I have a higher disposition for, I think it was arthritis, at least on her side. It was interesting when we had the results of the studies, it started to make a lot of sense… Her grandmother had a lot of arthritis issues."
>
> (Participant 8, male in his 60s whose wife also participated in the study)

Notably, one participant whose results included a likely pathogenic *SDHB* mutation (and who was advised in the results session of an increased cancer risk and referred to cancer genetics clinic for follow up) did not recall receiving this result, nor did this participant share results with his family or physician.

> "It isn't anything new. Nothing. Again, because I've done the 23&Me and they didn't show much either. I didn't have any expectations to find anything dramatic in there."
>
> (Participant 4, male in his 60s)

Many participants also lumped their genomic sequencing results together with previously obtained DTC results (e.g. 23&Me), frequently misunderstanding or misremembering the differences in what each examined and reported.

> "I think I've tried looking at one item here and I had to go into several databases on the internet there to translate the sequence. I think they mentioned in the article into something that I could actually search on it in the database that I got. Oh, I take that back. That was in the 23&Me information because I haven't gotten the information yet…"
>
> (Participant 4, male in his 60s)

Discussion

Exome sequencing and other genomic sequencing options are increasingly available to the general population, but there is limited research exploring the motivations, preferences, expectations and perceptions of this group. This type of research is necessary to provide guidance for physicians, genetic counselors, and other healthcare providers who will increasingly be asked to provide pre- and post-test genetic counseling to patients undergoing genomic testing in the absence of a suspected Mendelian genetic disease, as we still lack deep insight into how generally healthy persons approach and respond to receiving results from a predictive genetic testing, particularly genomic testing, which offers a much broader range of possible results than other forms of testing that have been studied previously.

Currently, most individuals undergoing exome sequencing do so in a clinical setting in order to obtain a molecular diagnosis for a suspected genetic condition. However, motivations in generally healthy populations are not the same. In our population, however, the motivations our participants described include curiosity, a desire to know more about their health risks, and altruism. These motivations mirror previous studies involving individuals participating

in biobanking projects, undergoing DTC testing, and participating in other types of genetic research (Beskow & Dean, 2008; Facio et al., 2011; Haeusermann et al., 2017; Ormond, Cirino, Helenowski, Chisholm, & Wolf, 2009; Sanderson et al., 2016). Interestingly, one of the participants in this study was adopted and described a desire to fill in gaps in personal health risk information due to lack of family history as a major motivation for participating, a sentiment that has been described previously and may result in more adopted individuals pursuing genomic testing as a screening test (Casas, 2018).

While not quantified, participants in this study did not report anxiety or negative psychosocial implications due to receiving genomic sequencing results and few behavioral changes were implemented. This finding is analogous to that of Sanderson and Lewis in similar previous studies with the HealthSeq and ClinSeq cohorts (Lewis et al., 2016; Sanderson et al., 2017), as well as previously described findings with individuals receiving low-risk DTC genomic results (Bloss, Schork, & Topol, 2011; McBride, Koehly, Sanderson, & Kaphingst, 2010). This lack of anxiety may be the result of a self-selective bias in the early-adopter participants who agree to participate in studies exploring genomic sequencing. Indeed, our participants described a self-perceived ability to cope with potential repercussions of undergoing exome sequencing, primarily the potential for receiving unexpected information about disease risks. This self-selection sentiment has been described previously in parents of children with suspected genetic diseases who have expressed a self-perceived ability to handle secondary findings because of the ordeal they have already been through living with their child's condition (Sapp et al, 2014).

Interestingly, our participants' recall of results was often inaccurate or limited. In most cases, these participants had not received results that had significant and immediately relevant health implications, which may be the reason for misremembering. For example, many participants did not recall learning carrier status for recessive conditions or pharmacogenomic results and recommendations. While we were unable to assess the actual cognitive reasons for this disparity in recall versus returned results, there are a number of possible explanations that are consistent with prior literature. One reason is that perhaps the manner of post-test results disclosure did not allow participants to accurately understand the results being conveyed to them. For example, multiple types of results were disclosed to participants all at one time, including rare Mendelian results, pharmacogenetics results, and multifactorial results. This could potentially have led to information overload for some participants. It is also possible participants felt uncomfortable telling the genetic counselors disclosing results that they did not understand.

Second, it is possible the participants understood the results initially but simply have poor recall, which could happen for a variety of reasons. First, one could postulate that without an 'anchor' of relevance, the genomic information is not moved into longer term processing or recalled in the future. In diagnostic testing, that anchor is the specific medical condition in the individual or family. Participants seemed more likely to remember results--particularly complex disease risk results--that aligned with diseases for which they had reported a personal or family history. As participants received multifactorial disease risk assessments for approximately 40 conditions, it is not reasonable to expect they would remember the details of all of them. However, when asked about these results in the interviews participants

tended to describe their risk for conditions they or family members had (for example, diabetes, since our population was enriched for this in personal and family history), but often did not mention conditions for which their risk assessments showed larger increases or decreases in risk over the general population. However, as we had differing levels of family and personal medical history for different participants we do not know the extent of this correlation. This hypothesis, which aligns with the Health Belief model of behavior developed by Hochbaum, Rosenstock and Kegels (Rosenstock, 1974), is also supported by a previous study by Graves and colleagues, which suggests that patients who perceive the severity of their disease risk to be higher are more likely to inform their physician(s) of their results (Graves et al., 2014). Finally, it is also possible that the language used in the interviewer prompts assessing results recall were not clear to participants and that this explains participant misremembering at least in part.

In one case a participant did not recall a result that did have significant health implications. The participant's results included a pathogenic *SDHB* variant, putting him at a significant lifetime risk for cancer—a risk that was discussed at length by the two genetic counselors present at his return of results meeting, as well as in follow-up communications prompting the participant to be seen in cancer genetics clinic. This misremembering is concerning, as the participant may not receive screening that could potentially be life-saving and presumably did not discuss the result with his family. Multiple explanations for any reaction that interferes with acceptance of results such as these have been proposed, including denial, as well as Lubinsky's "mimics of denial"--disbelief, deferral, and dismissal (Lubinsky, 1994). While it is not possible to tell from such a small cohort what the reason for this scenario is or how common it is among patients who receive secondary findings with significant health implications, it may be that this problem will become more common as patients increasingly undergo genomic sequencing and receive results that relate to diseases for which they do not have the anchor of a personal or family history.

Most participants were disappointed with their results and described "expecting more," a reaction that we hypothesize is exacerbated by a lengthy consent process that emphasizes unusual events (such as identifying a mutation causing high cancer risk) and media hype around genomics. A recent study of the MedSeq cohort also found that patients expected a higher level of benefit from their genome results than was actually achieved, suggesting a need to moderate patients' expectations (Roberts et al., 2018). This finding aligned with our experience of returning exome sequencing results to the larger iPOP cohort of approximately 70 individuals, many of whom expressed this same sentiment of expecting more from their results. Most participants who felt this way struggled to describe what they expected, other than that they expected more information. The genetic counselors for the iPOP study were consenting new participants and concurrently returning results to existing participants, and as this theme began to emerge they began attempting to moderate expectations during the consent process by describing what typical results look like. It remains to be seen how successful this approach was, and further research will be needed to clarify how best to prepare these types of participants for their results.

As the demand for exome sequencing as a screening tool in healthy populations will continue to grow and will actively be performed in large international cohorts such as All of

Us (United States) and the 100,000 Genomes project (UK), this work may suggest approaches for providing patients with anticipatory guidance before the return of results. We feel that our participants would have benefited from a more extensive conversation about the results that are most typically returned to patients with less emphasis on unusual scenarios, such as identifying a pathogenic variant in a gene that causes high cancer risk. It would also have been helpful for participants to better understand that their results would probably not indicate changes to their medical care. For patients concerned about experiencing anxiety because of their results, they may be reassured by the evidence that participants typically have not had regret about their results. Additionally, as our results suggest that participants may have limited or inaccurate recall of their results, clinicians may want to consider approaches to prioritize important information and confirm patient understanding with methods such as teach-back. Some participants had done DTC testing such as 23&Me prior to undergoing exome sequencing as part of the iPOP study. As patients' prior experiences with genetic testing influence their reactions to future testing, it may be helpful for clinicians to ask patients undergoing genomic screening what previous genetic testing they have had and how they felt about the results. This could also provide an opportunity to educate patients about the differences between SNP-based DTC testing and genomic sequencing. Some participants in this study requested and received their raw sequencing data, and as other studies suggest that participants often want raw data for the purposes of pursuing heath risk assessments on third party websites, this also presents an important opportunity for anticipatory guidance (Metcalfe et al., 2018).

Clinicians and researchers working in genomics still have much to learn about the best approaches to discussing genomic tests such as exome sequencing with generally healthy patients, and further research is needed to clarify the effectiveness of various approaches. For example, further studies could explore the correlation between different approaches to the informed consent process and patient satisfaction after receiving results, which could provide valuable insight into the best ways to manage patient expectations. More research is also needed to better understand what generally healthy patients really remember and act upon from genomic screening tests. It remains to be seen if the participant we described earlier who did not recall his *SDHB* variant or the resulting follow-up recommendations was an anomaly, or whether such situations will be more common among patients undergoing genomic screening who lack personal or family medical history relevant to their results.

Study Limitations

Our study had several limitations. First, our participant population, while not atypical of the San Francisco Bay area or those who choose to participate as early adopters in exome or multi-omics research, is likely not representative of the general population, particularly with regards to their high education levels. Second, there is the possibility that our interview participants may have represented a subset of those participants who had stronger positive or negative feelings about their experience of receiving exome results, or a more significant interest in genomics than those who chose not to participate.

Conclusions

Understanding the impact of genomic sequencing on healthy populations is necessary to inform guidance for healthcare providers who work with patients undergoing exome sequencing and other broad genomic tests in the absence of a traditional indication. Our findings suggest limited risk for post-test stress or anxiety, but also that participants may not accurately remember their results, which may result in missed opportunities for screening and family members not being informed of their risk. We also found that participants expected more from the results of exome sequencing, leading to a sense of disappointment and suggesting a need for pre-test counseling to include expectation-setting.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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Table I:

Participant Demographics and Results Returned

ID	Age Bracket	Gender	Ethnicity/Race	Education	Biological Children	Types of Results Opted to Receive	Multifactorial Disease Risks[a]	Pharmaco- genetics[a]	Mendelian Results: Carrier Statuses[a]	Mendelian Results: Dominant Conditions[a]
1	60s	F	C	Doctoral	0	All	Y	Y	Y	N
2	70s	M	C	Masters	2	Actionable only	Y	Y	N	Y
3	50s	M	C	Masters	0	All	Y	Y	Y	Y
4	60s	M	A	Bachelors	0	All	Y	Y	Y	Y
5	60s	M	C	Bachelors	2	All	Y	Y	Y	N
6	70s	M	C	Medical Degree	2	All	Y	Y	N	N
7	40s	F	C	Masters	3	All	Y	Y	Y	Y
8	60s	M	A	Bachelors	0	All	Y	Y	Y	N
9	60s	F	H	Some college	0	All	Y	Y	N	N
10	50s	M	C	Masters	2	All	Y	Y	N	N
11	60s	M	C	Bachelors	2	All	Y	Y	Y	N
12	50s	F	C	Some College	1	All	N	Y	Y	N

[a]These columns represent the types of results that were returned to each participant